FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPTHLAMIC DRUGS ADVISORY COMMITTEE

Tuesday, July 19, 2016

8:00 a.m. to 4:01 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jennifer Shepherd, RPh

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Michael Bigby, MD

(Chairperson)

Associate Professor of Dermatology

Harvard Medical School and

Beth Israel Deaconess Medical Center

Boston, Massachusetts

Ken Katz, MD, MSc, MCSE

Dermatologist

Kaiser Permanente

San Francisco, California

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Marla B. Sultan, MD, MBA

(Industry Representative)

Global Clinical Lead, Clinical Development

Pfizer, Inc.

New York, New York

TEMPORARY MEMBERS (Voting)

Bonnie H. Arkus, RN

(Acting Consumer Representative)

President, Women's Heart Foundation

Hamilton Township, New Jersey

Warren B. Bilker, PhD

Professor of Biostatistics

Department of Biostatistics and Epidemiology

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Michael J. Blaha, MD, MPH
Director of Clinical Research and Assistant Professor
Johns Hopkins Ciccarone Center for Prevention of Heart Disease
Baltimore, Maryland

Erica Brittain, PhD
Mathematical Statistician and Deputy Branch Chief
Biostatistics Research Branch
National Institute of Allergy and Infectious Disease (NIAID)
National Institutes of Health (NIH)
Bethesda, Maryland

John J. DiGiovanna, MD
Senior Research Physician
DNA Repair Section
Dermatology Branch
Center for Cancer Research
National Cancer Institute, NIH
Bethesda, Maryland

Lynn A. Drake, MD

Lecturer

Harvard Medical School

Department of Dermatology

Massachusetts General Hospital

Boston, Massachusetts

Michael R. Irwin, MD

Cousins Distinguished Professor of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Distinguished Professor of Psychology, UCLA College of Letters and Sciences

Director, Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience

Director, Mindful Awareness Research Center

Los Angeles, California

Francis E. Lotrich, MD, PhD

Associate Professor of Psychiatry

University of Pittsburgh Medical Center

Pittsburgh, Pennsylvania

Stephen R. Marder, MD

Professor and Director, Section on Psychosis

Semel Institute for Neuroscience at UCLA

Los Angeles, California

Elaine H. Morrato, DrPH, MPH

Associate Dean for Public Health Practice

Associate Professor Department of Health Systems

Management and Policy

Colorado School of Public Health

University of Colorado Anschutz Medical Campus

Aurora, Colorado

Matthew V. Rudorfer, MD

Chief, Somatic Treatments and Psychopharmacology Program
Division of Services and Intervention Research
National Institute of Mental Health (NIMH), NIH
Bethesda, Maryland

Elizabeth Smith

(Patient Representative)

Burke, Virginia

Ming T. Tan, PhD

Professor & Chair
Department of Biostatistics, Bioinformatics & Biomathematics
Georgetown University
Washington, District of Columbia

Consuelo Walss-Bass, PhD
Associate Professor
Department of Psychiatry and Behavioral Sciences
McGovern Medical School
University of Texas Health Science Center at Houston
Houston, Texas

David D. Waters, MD
Professor Emeritus,
Division of Cardiology,
San Francisco General Hospital
Department of Medicine
University of California, San Francisco
San Francisco, California

Julie M. Zito, PhD
Professor of Pharmacy and Psychiatry
University of Maryland, Baltimore
Pharmaceutical Health Services Department
Baltimore, Maryland

FDA PARTICIPANTS (Non-Voting)

Amy G. Egan, MD, MPH

Deputy Director

Office of Drug Evaluation III (ODE-III)

Office of New Drugs (OND), CDER, FDA

Kendall A. Marcus, MD

Director

Division of Dermatology and Dental Products

(DDDP)

ODE-III, OND, CDER, FD

Gary Chiang , MD, MPH

Medical Officer

DDDP, ODE-III, OND, CDER, FDA

Cynthia L. LaCivita, PharmD

Director

Division of Risk Management (DRISK), Office of

Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

Simone P. Pinheiro, ScD, MSc

Deputy Director (Acting)

Division of Epidemiology I, Office of

Pharmacovigilance and Epidemiology (OPE)

OSE, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

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. BIGBY: Good morning. I would first like to remind everyone to please silence your cell phone, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Andrea Fischer. If you are present, please stand, way in the back there on the left.

My name is Michael Bigby. I am the chairperson for the Dermatologic and Ophthalmologic Drugs Advisory Committee. I will now call this meeting of the Dermatology and Ophthalmic Drugs Advisory Committee to order. We will start by going around the table and introducing ourselves. Let's start down on the far right.

DR. SULTAN: Marla Sultan, industry representative.

DR. WATERS: David Waters, clinical cardiologist, University of California San

Francisco.

DR. WALSS-BASS: Consuelo Walss-Bass, department of psychiatry at the UT Medical Center in Houston.

DR. ZITO: Julie Zito, pharmacoepidemiology, pharmaceutical health services department, University of Maryland.

MS. SMITH: Elizabeth Smith, patient rep.

MS. ARKUS: Bonnie Arkus, consumer rep.

DR. TAN: Ming Tan, professor of biostatistics, Georgetown University.

DR. DIGIOVANNA: John DiGiovanna. I am a dermatologist at the National Cancer Institute.

DR. DRAKE: Lynn Drake, dermatologist, Massachusetts General Hospital, Harvard Medical School.

DR. KATZ: Ken Katz, dermatologist, Kaiser Permanente in San Francisco, California.

DR. MORRATO: Good morning. Elaine Morrato, associate dean for public health practice and epidemiologist in the department of health systems, management and policy at the Colorado School of

Public Health.

DR. BIGBY: I am Michael Bigby, dermatologist, Harvard Medical School and Beth Israel Deaconess Medical Center.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. BILKER: Warren Bilker, professor of biostatistics, University of Pennsylvania.

DR. BRITTAIN: Erica Brittain. I am a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

DR. MARDER: Steve Marder from the Semel Institute for Neuroscience at UCLA.

DR. RUDORFER: Matt Rudorfer, psychiatrist, National Institute of Mental Health.

DR. IRWIN: Michael Irwin, professor of psychiatry, UCLA.

DR. LOTRICH: Frank Lotrich, psychiatrist, University of Pittsburgh.

DR. PINHEIRO: Simone Pinheiro, acting deputy, Division of Epidemiology I, OSC CDER.

DR. LACIVITA: Cynthia LaCivita, Division of

Risk Management.

DR. CHIANG: Gary Chiang, dermatology and dental products, medical officer.

DR. MARCUS: Kendall Marcus, director, Division of Dermatology and Dental Products.

DR. EGAN: Good morning. Amy Egan, deputy director, Office of Drug Evaluation III.

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

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

meeting.

We are aware that members of the media are anxious to speak with 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 topics during breaks or at lunch. Thank you.

Now I will pass it Lieutenant Commander Jennifer Shepherd who will read the Conflict of Interest statement.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

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

Related to the discussions of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 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 the discussion of biologics license application 761032, brodalumab injection, a human monoclonal antibody submitted by Valeant Pharmaceuticals, Luxembourg SARL, proposed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

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 they have made concerning the product at issue.

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

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. BIGBY: We will now proceed with Dr. Marcus' introductory remarks.

FDA Introductory Remarks - Kendall Marcus

DR. MARCUS: Good morning. I would like to welcome members of the advisory committee, Valeant, and the audience. Today we will be talking about the product submitted, a marketing application for the treatment of psoriasis.

Psoriasis is a chronic immune-mediated inflammatory condition that is also associated with serious comorbidities. About 7 and a half million people in the United States are affected by psoriasis.

In addition to phototherapy, there are currently 10 products that are approved for the treatment of psoriasis. As you can see, they are all associated with potentially serious adverse events that range from serious infections to malignancy to hepatotoxicity. In addition, individual patients may have varying responses to treatment where one product will work very

effectively for one patient and not work for another. So there is still an unmet medical need for patients with psoriasis.

Today, as already mentioned, we will be talking about brodalumab. It is a human monoclonal antibody that is an IL-17 receptor antagonist. There are a number of specific safety issues that were under review in this marketing application due to the mechanism of action of the product. In my introductory remarks, I am going to focus on suicidal ideation and behavior, one of the focuses of today's advisory committee. I would like to provide important context and background for members of the audience and the advisory committee in order that we can have a productive discussion on this issue.

Various studies have demonstrated higher rates of depression, anxiety, and suicidal behavior in psoriasis patients, and the incidence of these have been found to directly correlate with the severity of skin manifestations, the presence and the severity of psoriatic arthritis, and the

impacts that both of these manifestations have on patients' ability to work and maintain employment.

We learned from our recent psoriasis patient-focused drug development meeting in March that psoriasis has significant impacts on patients' career choices and employment, their ability to have healthy social contacts and engage in intimacy with partners. It can even have significant impacts on reproductive choices, and we heard from several people participating in the meeting that they chose or their children chose not to have children because of the impacts of psoriasis on their families' lives. Even when successfully treated, patients live in fear of relapse of their disease.

In the psoriasis development program, 34 subjects were observed to have 39 suicidal ideation and behavior events. In particular, 6 completed suicides were observed, and this raised concerns about a potential association of brodalumab with these events.

For the purposes of our discussion today and

for the purposes of data analysis, suicidal ideation and behavior is defined as any event of suicidal ideation, preparatory action towards suicide, which is termed "suicidal behavior," suicide attempts, and completed suicide.

The 6 subjects that committed suicide ranged in age from 39 to 57; 5 of the 6 were males. The events occurred anywhere from 97 to 952 days after receiving the first dose of brodalumab, and the event occurred anywhere from 7 days to 58 days after the last dose of brodalumab. Remarkably and of some concern, only 2 of the 6 subjects who completed suicide had known histories of depression.

There are significant challenges in clinical trials in ascertainment, signal detection, and cross-study comparisons of these events. There can be cultural and personal stigma towards reporting depression, anxiety, or suicidality. The population level incidence of suicide can change over time. It also differs across countries. About 40 percent of the patients enrolled in the

brodalumab development program were enrolled at U.S. sites, but U.S. subjects represented slightly over 50 percent of the suicidal behavior events.

Ascertainment methods can differ from trial to trial. These can range from passive reporting of events by trial subjects to retrospective adjudication of suicidal behavior events in order to accurately assess the occurrence of suicidal behavior to active ascertainment methods, and I will touch on these further in a moment.

The size and duration of development programs can differ based on whether the indication being evaluated represents an initial indication that is being submitted with the first marketing application or whether it is being submitted as a supplemental application. And finally, significant differences in enrollment criteria can make cross-study comparisons challenging.

Once a completed suicide was reported and one additional suicidal behavior event was identified, tools were implemented during the brodalumab clinical trials in order to inform

investigators and trial subjects of these events and to undertake active ascertainment of depression and suicidal behavior.

These self-rating scales for depression and suicide were implemented in the brodalumab clinical trials following the identification of the suicide and one other suicidal event. The Patient Health Questionnaire is a validated 8-item assessment tool designed to assess for symptoms and signs of depression, and the Electronic Columbia Suicide Severity Rating Scale is a validated instrument designed to detect the severity and frequency of suicidal behavior.

In addition to prospectively ascertaining suicidal behavior, the Electronic Columbia Suicide Severity Rating Scale in the brodalumab clinical trials also ascertained a history of lifetime and on-study suicidal behavior. If patients met a certain threshold of concern on these assessment tools, they were referred to a mental health professional and/or discontinued from the investigational product.

I would like to briefly describe the Columbia Classification Algorithm. It is a data analysis method for assessing suicidal behavior in clinical trials. Electronic text strings are searched in databases for terms that may indicate suicidal behavior, and narratives are reviewed and classified for suicidal behavior.

This method was first used in the review of clinical trial data for psychiatric indications in 2004, and recently, it has been utilized in data analysis of multiple biologics product applications for psoriasis. I have listed the ones in which C-CASA adjudication of suicidal behavior was undertaken.

This is a classification scheme for C-CASA. You can see that events are classified as suicidal, indeterminate, or non-suicidal.

This slide provides important examples of why adjudication is needed in order to accurately ascertain suicidal behavior. In one example, an unadjudicated adverse event was labeled as an abdominal hernia. This subject had experienced

eventration after a laparotomy due to an abdominal wound caused by a self-inflicted gunshot, and this event was adjudicated as a suicide attempt.

In the last example labeled as a suicide attempt, the subject explained that they hit their head on the wall because it felt like their thoughts were about to explode, and that adverse event was adjudicated as non-suicidal.

Finally, I would like to make the point that the rates of suicide can change significantly over time. In these CDC statistics looking at suicide rates from the period of 1999 to 2014, I have highlighted the 45- to 64-year-old age cohorts, which represents the majority demographic of patients enrolled in the psoriasis development program.

Please note that the scales are different on the left. We have suicide rates for females, and you can see that there has been about a 40 percent increase in the rate of suicide in females in this age group over the period from 1999 to 2014. Similarly, there has been a 33 percent increase in

the rate of suicide in men in the same age group.

Today, we will be discussing the adequacy of the safety evaluations for suicidal ideation and behavior. We will also be discussing the evaluation for major adverse cardiovascular events or MACE, and we will be asking for your input on the overall benefit-risk profile of brodalumab as well as your input on risk management strategies.

Finally, if you believe that this product should be approved for marketing, we will be asking you to comment on the necessity for any postmarketing studies or clinical trials.

These are the questions that we are posing to you today. We will ask you to discuss if the safety data for brodalumab suggests a signal for suicidal behavior or major adverse cardiovascular events. We will be asking you to vote on the overall risk-benefit assessment of brodalumab and on risk management strategies. And finally, we will be asking you to talk about postmarketing clinical studies and clinical trials.

One of the issues that has been raised

frequently during the review of this application is the potential of a monoclonal antibody that does not cross the blood-brain barrier in impacting suicidal behavior. In that context, we have invited a speaker today to talk about potential interactions between inflammation, cytokines, and suicidal behavior.

At this time, I would like to invite Dr. Ebrahim Haroon, our speaker, to come to the podium to provide his talk.

Guest Speaker Presentation - Ebrahim Haroon

DR. HAROON: I just want to begin by thanking Ms. Shepherd and Kendall Marcus for giving me this opportunity. I also want to congratulate everyone from Valeant Pharmaceuticals who put in a lot of time and effort and emotion and the whole difficulty just to get these things done. And at the same time, I also want to congratulate the FDA staff for analyzing this.

My name is Ebrahim Haroon, and I am an associate director of the behavioral immunology program. I am a clinical psychiatrist. I deal

with suicides day in and day out. There is a lot of psychiatrists on the panel, but for the lay public and the press and non-psychiatrists, I am just going to run you through some general information first.

As part of this presentation, I am going to start with talking about the clinical aspects of suicidology that we use, very briefly, and then quickly transition to the biomarkers that are associated with suicide, a one-slide overview. Then I am going to move to the association between inflammation, cytokines, and suicidal behavior. I am going to finish up with our own experiences on cytokine blockade and suicidal symptoms.

As you can see from this slide, it is a very complicated business, and I think there is a very detailed presentation at a later stage, so I am going to skip quickly through this. Basically, the suicidal assessment, as we teach our residents, involves at least three major pillars. One is the severity of the continuum of suicidal ideation, ranging from just ideation, planning behaviors, all

the way to actual acting upon it. But the big issue is the intent, the strategic objective. Is it to kill oneself, does one want oneself dead, or is it to make a difference in the environment?

A lot of the scales, if you see, focus heavily on these behavioral parameters, but this is just one of the three variables. This is probably a little bit more because, as you know, the suicidal ideation prediction is a forecasting. It is like weather. It is a forecasting business. What you are forecasting is the odds of someone acting out or doing something very, very dangerous to oneself.

The odds of that kind of acting out increases, if you look at it, in terms of certain risk factors like psychiatric disorders, especially major depression. If you look at most psychiatric disorders, they are impulsive. There are some symptoms where most of the symptoms are loss of mastery or the pleasure or hope, loss of sleep, generally, and also some level of family history, some modeling of suicidal behaviors in the past.

I want to focus on the precipitants stressors, and this is where I think the rubber meets the road. This is probably the most difficult, and this is where the scales really miss out because interpersonal stressors like acute breaks, acute loss of control over one's environment, can precipitate acute suicidal behaviors, to transition people from just thinking to acting.

Also, one of the things you will see is that the medical disorders, especially moderate to severe medical disorder like, say, psoriasis, probably in addition to the inflammatory aspects, there is probably a large amount of humiliation. There is a large amount of sensitivity to these things.

There is a huge psychosocial element in this, which both of the scales miss, but I guess we got what we got. I am not going to find fault in the scales. All I am going to say is that the whole behavior is a very complex thing.

The third pillar is the protective factors,

meaning if you have better support systems, if you have resources. And then we combine these three things to develop a clinical risk profile, meaning if someone has a high risk, moderate, or low protective factors, and has already demonstrated a desire to act out in way or the other, previous history of suicide a lot of times, then we hospitalize them.

If the patient has had moderate to severe levels of risk, several of the risk factors I showed you with some level of protective factors, but only has ideation, no plans, no activity in the past, they are struggling with this, then we try to manage them with the intensive outpatient management.

Thirdly, if the patient has very good social supports in spite of the high risk and has never acted on it, and has a very high threshold for manifesting any of these behaviors, we manage them as an outpatient.

Now, a brief review of the suicidal biomarkers -- I am sorry. This is a very busy

slide, but I am going to just not focus on everything. But primarily, being psychiatrists, our focus is on treating suicide. You will see that the most important thing that I can see is that a lot of these things are driven by neurotransmitters, and the main neurotransmitters that are implicated are serotonin and chloramine. Serotonin because of the large volume of work done by the Columbia group on serotonin receptor changes, a lot of the genetic polymorphisms that also revolve around serotonin transporters and put in genes.

There are also a few other markers that are being studied now in terms of the brain-imaging markers, in terms of the electrophysiology, but I am going to keep the inflammatory markers for the new few slides.

Now, the biggest problem in understanding suicidology -- and I think we had a big session at ISCTIM regarding this. The big problem is it is very difficult because our knowledge is limited by the poor quality of suicidal assessment in all

studies, not just in -- in any study. I don't think it has been done well.

The ideal scenario would be that I would have a biomarker that I can assess in the blood or in the brain that would tell me that this patient is at risk, very easy. That is what a lot of folks try to get. But in suicide, we haven't been able to really accomplish that. Part of it is the biology of the disease, but part of it is also some of the design issues.

For instance, you can see that we have still not decided on whether we need -- I mean, many of these biomarkers will need to be done at the baseline, at the endpoint, multiple time points. There is also state versus trait where individuals show certain biological changes when they are symptomatic and they are asymptomatic. Like in bipolar when they are admitted, they have a different profile.

A lot of these things are still a major issue with our research, and I think we are trying to work through that. We had a big workshop at

ISCTIM. We are trying to come up with some answers for these things. These are very difficult things to do.

I am going to focus on inflammation here because that is the primary focus here. As you can see, suicidal behavior has been associated with inflammatory markers, especially increasing inflammatory activation as we see from the plasma markers.

Now, let me take first the clinical evidence. As you can see, in rheumatoid arthritis, the incidence of suicidal ideation is about 11 percent, and it is probably three times higher in SLE. I think this discrepancy is probably because SLE has more of a neuropsychiatric component to it than rheumatoid arthritis. Maybe rheumatoid also does, but definitely there is a higher -- the greater the brain involvement, there seems to be a higher level of suicidality.

In both these conditions, both rheumatoid and in the SLE data, if you closely look at it, the presence of depression was the single major

predictor of suicidal ideations and suicidal behavior. By and large, identifying depression becomes a critical factor, and I will explain that a little bit later.

Now, this is about multiple sclerosis. Here, we moved away from the body. We are going into the brain, a classic neuroinflammatory disease. You will see that the risk of suicidality is almost to twice when you look across studies. It is almost twice as much as what you would see in the general population.

Also, the last study, unfortunately, this is a series of case reports, so I am not able to quote data on this, but a lot of these patients who are treated with cytokine-based therapies like interferon beta for treatment of MS had increased suicidal ideation; again, in the context of depression.

Now, what about suicidal behavior and cytokines, or for that matter, inflammatory markers, in patients with depression? I don't have time because I only have 15 minutes to review this,

so I am just going to summarize the results from a recent meta-analysis.

As you can see, the interesting thing is -- I'm sorry. I should have mentioned this. First, the left-hand panel is suicidal patients versus non-suicidal depression, meaning all these patients are depressed, but the comparison is between suicide and non-suicidal depressives, whereas the right-hand side panel shows the comparison between suicidal depressed patients and so-called healthy or relatively psychiatrically symptom diagnosis-free patients.

As you can see, the meta-analytic study shows -- and I was not very impressed with the first panel, if you look at it. I am not very terribly impressed with the effect sizes that I see in this, so the plasma cytokines, whereas there is some evidence of separation from, as you can see. Some of these are well beyond the midline.

It appears like suicidal depressives seem to be significantly different from healthy controls, but suicidal depressives don't seem to really

differentiate that much out from other depressed patients, meaning is the effect just depression? I don't know, but that is at least what the plasma data states from this study.

Here, we are going into the same study, but here, they have used -- here, we have data on the CSF cytokines, and we have cytokine expression in the post-mortem brains. As you can see, the CSF cytokines again are very variable. There are only two studies. It is very limited. But the CSF studies are very variable on this front.

Now, if you take the post-mortem brain, there is actually a lot of consistency. You will see that TNF alpha, IL-6, even IL-1 beta, they all seem to show greater expression in post-mortem brains of people who committed suicide. The comparison group here is so-called healthy subjects who died of other natural causes.

The post-mortem brain expression studies seem to lend support to the association between inflammatory activation in the brain at the cellular level and at the molecular level and the

behavior.

Now, the problem with this data again, to go back, this is again a suicidal depressed versus healthy or non-depressed - suicidal depressed versus so-called healthy controls. So this is again probably more indicative of the depression itself rather than suicidality because we still haven't been able to identify one biomarker that will tell us who is suicidal and not.

I am going to switch gears here and turn to our own data, and this is probably the only infusion trial that we did. We used a TNF alpha blocker here. What we did was -- the hypothesis behind this study was if you block the peripheral inflammation, does it change the level of depression? Again, this is a depression study.

We took 60 patients who are treatment refractory depression. We divided them so they were -- we used a double-blind randomized design and with a 50 percent chance of either getting infliximab or placebo. And all the patients received infusions at baseline, at 2 weeks, and at

6 weeks. So this is a 3-infusion study. During all of these time points, patients had behavioral ratings, inflammatory marker assessments.

This is the results. If you closely observe, the results show that, first of all, as a group, infliximab treatment did not really help depression, meaning if you take the total groups into account, the placebo and the infliximab had equal rates of symptomatic improvement.

When you separate them out into high and low inflammation based on a median split here, the groups with a higher level of inflammation showed a better response or a robust response to infliximab, shown in the red here, while the groups with the relatively lower inflammation showed a lower magnitude of response to infliximab, meaning in some ways, they appear to have not only not gotten better, but at one point, they actually seem to have gotten worse as the treatment proceeds.

As you can see at the very end, between the 6 and the 8 week, the symptomatic ratings actually increased.

This shows the response rates of cytokine antagonism and the effects of cytokine antagonism on depressive symptoms. This is response rates at the end of 12 weeks. And you will see here, the red box represents infliximab, and the blue box represents placebo.

As a whole group, you will see that there is no difference in the response rates. But if you take them, if you split them into high and low inflammation, you will see that the rates of response is quite high in the high inflammation group for infliximab, whereas in the low inflammation group, the rates are not that high. And in fact, they are less than what you would expect for a given treatment; whereas the placebo, if you will closely watch, actually, they show great response in the low inflammation or relatively the lower inflammation group, and the placebo response in the high inflammation group is lesser.

Actually, one of the interesting findings from this study we thought was that definitely for

the patients in high inflammation, the placebo responses diminish. And that is a big thing for a world of depression, for people who work in this field. But nevertheless, the point is well made that the effect of cytokine antagonism is probably more relevant in patients who show high inflammation.

This is the last slide on here. What we are trying to show is that if you take the infliximab responders, cytokine antagonism responders, we tried to see a symptomatic analysis of what symptoms got better with cytokine antagonism. As you can see, very interestingly, there is psychic anxiety, which you would have expected; psychomotor retardation; work and activities, which kind of closely go with psychomotor retardation; but more interestingly, suicide was one of the few symptoms that actually got better with cytokine antagonism in this sample.

In conclusion, one of the things -- again, I just made a very brief presentation. I will be happy to give more details if anyone wants this at

a later stage. But basically, suicidal behavior has been associated with inflammatory activation. It's hypothesized, but the association is probably unclear whether it's a primary association between the behavior and the biomarker or whether it's because suicide occurs more in depression and depressed patients show a higher level of inflammation, so we see a higher inflammation.

There is also a problem. We are not very sure and most of the studies have not told us whether the inflammatory activation moves patients from just thinking about it to acting on it. This is always a problem that we are not very clear.

The association probably may be directly mediated by the cytokine effects. There is a lot of hypothesis, how peripheral cytokine activation leads to brain changes. But one thing that is consistently agreed upon is that the peripheral inflammatory changes appears to have a CNS response. We have studied it using connectivity. Dr. Irwin's group has studied using FMRI. There is consistent data that says that peripheral

inflammatory activation does have CNS changes. It is associated with CNS response. The question is how does cytokine influence the brain.

Now, there are several theories that are floated: cytokines can change -- serotonin can change tryptophan metabolism to create a lot of these substances, glutamate-like substances called kynurenines. It can directly alter glutamate. It can directly alter dopamine and serotonin. So people are still trying to figure that out.

Cytokine antagonism seems to benefit patients with high baseline inflammation, and cytokine antagonism given to patients with low baseline inflammation is still very questionable. And maybe I don't know because if you look at the MS data, for instance, cytokine antagonism actually can make things worse.

One of the things is it varies, and I think the baseline markers are very important. But the biggest caveat here, I have to be very clear, this is specific for depressed patients. Again, we are not experts on psoriasis. This is specific for

depressed subjects. But a lot of the cytokine TNF antagonist data seems to have come out of psoriasis trials.

I wanted to thank you for your attention, and I will be happy to answer any questions at a later stage either directly or by email. Thanks.

Clarifying Questions

DR. BIGBY: Does anybody on the panel have a clarifying question for Dr. Haroon?

DR. BRITTAIN: I am not sure you showed us any sample sizes on that case of what looked like an interaction with the baseline inflammation level a few slides back.

DR. HAROON: The one with the graph you mean?

DR. BRITTAIN: Yes. I just didn't know is this a small sample or if it is really statistically significant or what.

DR. HAROON: It was statistically significant, but the samples were smaller. I cannot exactly give you the number, but it is a subsample with a very high level of inflammation

because it is about 5 grams per liter CRP concentrations.

I am not convinced because this was a median split, and this is what happens when you do these things. But the problem is we were not sure that someone between 3 to 4 -- say, 5 milligrams is high, but what about someone who has 3 to 5? Are they really low? I am not sure they're low.

But this was just a small analysis of a small sample that we did. We are following it up with more detail. In fact, we just got scored well on a follow-up study to that.

DR. BIGBY: I will just remind the panel, please state your name before you ask the questions.

DR. TAN: Ming Tan. I was going to ask you, why did you choose 5 milligram per liter?

DR. HAROON: In fact, it was based on the study from rheumatoid arthritis. It was based on what was given by other specialties and what was the easiest to administer. There was a lot of concerns from our IRB as to the dosing that could

be given for these things, and then we settled on 5-milligrams based on the data that was tying it, all those studies that had been done in this field that we used.

DR. IRWIN: Michael Irwin, UCLA. Thanks, Ebrahim.

Could you speak to the issue related to inflammation and suicidal and impulsive behavior that is occurring independent or without the presence of ongoing depression or significant depressive symptoms?

DR. HAROON: It is a very good -- in fact, I think we should be studying more of those things. There is one -- I think very recently I saw one or two papers. There was one with a CSF study of cytokines where I think it was done by the Chicago group at UC where they showed that the patients who had higher CSF inflammatory markers like IL-6 showed a greater level of impulsivity on the Barratt Impulsivity Scale.

The question would be, again, how would that translate into suicidal marker? I think it is a

very good question. I think that a lot of psychiatry-related suicide [indiscernible] are very impulsive if you look at it. Some of them are very well planned, but a bunch of them are non-planned. They are just quick. There is a stress, and they quickly act on it. But I think the CSF inflammatory markers have been shown, at least with impulsivity, not impulsive suicides.

Thank you.

DR. BIGBY: There is one more question.

DR. HAROON: Oh, sorry.

DR. KATZ: Thank you. Ken Katz.

Do you know, did inflammation rates improve with improvements of symptomatology in terms of depression? So did CRP levels fall? Did they correlate with improvements in depression scales?

DR. HAROON: Yes. In this sample, the CRP levels declined very quickly within the first 2 weeks.

DR. KATZ: Differently in people who had improvements in depression symptoms compared with those who didn't?

DR. HAROON: No. The CRP, it was very strongly correlated with the depression, meaning the reduction in CRP was associated with reduction in severity of depressive symptoms.

The time scales probably were different, and that is what we are trying to study, meaning it appears like the CRP appears to decline first, and depression appears to follow suit, meaning they don't have the same -- if you look at it, they are not overlapping time scales. In fact, that is one of the reasons why we think there is a CNS plasticity issue involved even though you reduced the peripheral inflammation very quickly with these antagonists. I don't know how fast that affects the brain, and maybe it is something that future research funding should do as well.

But one thing I do want to before I leave, I want to tell you that the IL-17 is a completely new thing, and I haven't seen many studies on depression with IL-17. But who knows, some of them are in progress.

DR. MORRATO: One more. Sorry. Elaine

Morrato. I am wondering in the Remicade study for that particular drug, is there any evidence of direct CNS effects of that drug? Do you know?

DR. HAROON: The drug is not known to penetrate CNS very well. I don't think it does.

DR. MORRATO: Okay.

DR. HAROON: The evidence of direct penetration of the medication itself is not --

DR. MORRATO: In other words, we could summarize from your findings that while there may not be evidence of direct effect on CNS, there is indirect evidence. Is that a way of summarizing?

DR. HAROON: Yes, yes. That is a very big area of study. In fact, several of us are here who work on this thing in the same area because there are so many pathways that have been hypothesized, but one thing that is unquestionable is that the brain responds to peripheral inflammatory activation.

DR. MORRATO: I just wanted to make sure I interpreted what you presented nicely --

DR. HAROON: Yes, you did.

DR. MORRATO: Thank you.

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

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

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

speaking.

We will now proceed with the sponsor's presentation.

Applicant Presentation - Tage Ramakrishna

DR. RAMAKRISHNA: Good morning. My name is Tage Ramakrishna. I am the chief medical officer of Valeant Pharmaceuticals, the sponsor of this biologic license application. I would like to thank the FDA and the advisory committee panel for allowing us the privilege of presenting the data for brodalumab.

Brodalumab is a monoclonal antibody antagonist of the IL-17 receptor. Brodalumab has been recently approved by the PDMA in Japan as a first-line treatment for patients with moderate to severe plaque psoriasis. There are no restrictions with regards to dosing or patient selection on the Japanese label for brodalumab.

Brodalumab at a dose of 210 milligrams administered subcutaneously biweekly should be approved for use in adult patients with moderate to severe plaque psoriasis who are candidates for

phototherapy or systemic therapy. Brodalumab meets a clear medical need where other therapies have failed.

Over the next few slides, I would like to give you an overview of why we have concluded that brodalumab will make a unique and important contribution to the effective treatment of these patients.

There are three key points that I would like to establish in this introduction, points that we will elaborate upon in subsequent segments of our presentation. First, brodalumab has demonstrated durable efficacy in skin clearance. Over 50 percent of patients in clinical studies had complete clearance, a PASI 100 score, within 1 year of treatment with brodalumab. PASI 100, representing complete clearance of psoriasis, has demonstrated for patients to be a much more clinically meaningful endpoint than PASI 75.

Complete clearance is the most important goal of any therapeutic in psoriasis. It is the key determinant of quality of life. No other agent

in this indication has demonstrated complete clearance greater than brodalumab.

Second, we would like to emphasize that the efficacy of brodalumab has been thoroughly investigated in three large phase 3 studies for our U.S. regulatory filing. The safety database we are presenting is from over 4,000 patients. This has allowed a thorough evaluation of the potential risks associated with brodalumab.

Finally, brodalumab has a well differentiated mechanism of action. Although there are other approved agents that target the cytokines that initiate and perpetuate psoriasis, brodalumab is the first biologic that targets the IL-17 receptor. Receptor targeting is hypothesized to be the key to rapid onset and durability of brodalumab's treatment effect.

At the March 17, 2016 FDA public meeting on patient-focused drug development for psoriasis, patients reiterated the need for new therapies to achieve complete clearance. Brodalumab offers an option to achieve this important goal.

Brodalumab has a unique mechanism of action. Psoriasis is characterized by a cascade of inflammatory cytokines and in particular, with activation of the IL-17 signaling axis and the localized overexpression of IL-17 family members. A growing understanding of the importance of this pathway in autoimmune pathologies has led to the development of agents that target it with greater specificity.

From top to bottom of this graphic, we show agents that are progressively more tightly focused on pathways relevant to psoriasis pathology from the very broad immunosuppression of TNF alpha inhibitors to specific targeting of IL-17. Brodalumab, however, is the first agent that binds the IL-17 receptor preventing signaling through the key receptor subunit IL-17RA.

Blocking the receptor has two critical implications that may differentiate the activity of brodalumab. First, currently approved agents target only IL-17A. IL-17A, however, is only one member of the IL-17 family of cytokines. Second,

the IL-17 receptor is expressed in keratinocytes. Therefore, brodalumab is the only product active at the site of psoriatic lesions themselves.

Brodalumab has undergone a long and thorough development cycle for us in psoriasis. The antibody was first discovered in 2003, and preclinical development culminated in the filing of the initial IND, which was filed by Amgen in 2008.

Pivotal phase 3 clinical studies were launched by Amgen in 2012. Starting in 2013, AstraZeneca partnered with Amgen. Amgen made a business decision to pull out of the brodalumab development program in 2015. At that time, all patients had completed the controlled portion of the phase 3 program and were in the open label on controlled extensions. It was then taken over by AstraZeneca. Valeant is currently the largest dermatology company in the U.S. with the broadest development pipeline.

After a thorough review of the data and consultation with key opinion leaders in dermatology and psychiatry who were excited about

the possibility of bringing brodalumab to their patients, we chose to partner with AstraZeneca to develop and commercialize brodalumab. Subsequently, Valeant approached AstraZeneca in 2015 and initiated a collaboration.

Through 10 phase 1, 3 phase 2, and 4 phase 3 trials conducted worldwide, over 5,600 psoriasis patients have been enrolled in studies of brodalumab with over 5,000 completing treatment per protocol. The safety database is one of the largest compiled for any product in psoriasis. We are convinced that the data compiled through the exhaustive development program demonstrates a favorable risk-benefit for the use of brodalumab in patients with moderate to severe psoriasis.

I will briefly discuss this forest plot, which demonstrates the benefits and risks of brodalumab as compared with ustekinumab in a double-blind, controlled, 52-week period. As you can see, the benefits across all efficacy outcomes measures that are important to patients, healthcare providers, and health authorities were superior to

ustekinumab.

When examining all safety topics of interest, including MACE and SIB events, there is no difference from ustekinumab with the exception of non-serious fungal infections, which is consistent with the IL-17 mechanism. In the upcoming presentations, we will present the results of efficacy as well as detailed analysis of MACE and SIB observations in the brodalumab program.

Patients have made it clear. There is an urgent need for a treatment like brodalumab. Plaque psoriasis is incompletely treated with currently approved agents. Plaque clearance is typically incomplete. Currently approved products lose effectiveness over time, and no currently approved product is effective in every patient. Patients with moderate to severe plaque psoriasis require options not provided by therapies currently available.

To that end, I would like to show an example of brodalumab's overwhelming strong efficacy. Complete skin clearance is an important treatment

goal in psoriasis that has both measurable and clinically meaningful benefits. The greatest improvements in patient-reported outcomes are seen in patients achieving total skin clearance.

Brodalumab has expanded the definition of efficacy in psoriasis by conducting studies with a predetermined complete clearance endpoint of PASI 100. Measured by PASI scores, brodalumab demonstrated statistically significant and clinically superior efficacy compared to ustekinumab, considered the gold standard during the brodalumab program.

The impact of improved outcomes cannot be underestimated in the psoriasis population, and as Dr. Lebwohl will highlight in his medical landscape presentation, there is a significant difference in the psychological wellbeing between patients who achieve complete clearance and those who do not.

This morning, our presentation will be organized into the sections shown here. To begin, I would like to introduce Dr. Mark Lebwohl to present the medical landscape.

Applicant Presentation - Mark Lebwohl

DR. LEBWOHL: Thank you very much.

My name is Mark Lebwohl. I am the chairman of dermatology at Mount Sinai in New York. I am not being paid by Valeant, though they are paying my trip here. My conflict of interest is that I was the lead investigator on this trial when it was sponsored by Amgen.

My department receives research funding from most of the companies with psoriasis products, and we receive much more funding from Valeant's competitors than from Valeant. But I am testifying here today because it was very important to me that this extraordinary drug be approved for our patients.

The title of my talk is "Do We Need More Psoriasis Therapies?" And I thought I would start with a photograph of this patient, whom I have taken care of for many years and who ended up enrolling in our brodalumab trial.

In 2002, I saw this patient, and I will never forget something that she said to me. She

said she was thinking of committing suicide, but she was a religious woman and she was worried that if she committed suicide, she'd go to hell, and hell would be worse than having psoriasis.

I ended up admitting her to the hospital because I was worried about her committing suicide. She went on to fail every approved drug that we gave her for psoriasis and some unapproved treatments. Nothing worked for her.

When the IL-17 blocking drugs came out a few years ago, all of them showed incredible results, but the brodalumab phase 2 results were better than any we had ever seen. Nearly 2 out of 3 patients achieved PASI 100. Not 75 percent improvement; they were completely clear. So even though I had access to many of the new drugs, I encouraged many of my most difficult to treat patients to enroll in the brodalumab trial, including the patient I just showed you.

This is what she looked like after a few months on brodalumab. Here is a before and after. She achieved PASI 100, not one dot of psoriasis

left. Last summer when the trial was discontinued, her psoriasis remained clear for several months and then gradually recurred. So we started her on one of the new anti-IL-17 drugs, which have been remarkably effective for psoriasis. Here she is after approximately 4 months on that drug. These are recent photos.

I can show you many similar stories of current therapies not working. This gentleman with severe psoriasis tried many of the available treatments at the time. He had relative contraindications to oral therapies because his obesity increases the toxicity of those drugs, but like many other obese patients with psoriasis, we end up using drugs that perhaps we should be more cautious about because we don't have enough choices. You can imagine all of the difficulties he's had with social interactions and keeping a job because of his psoriasis.

I can show you many similar patients. Despite all the treatments we have, many of us see patients every day with severe psoriasis that is

just not managed well. I could spend hours showing you photos of these.

We know that myocardial infarctions are increased in patients with psoriasis. In this study, patients at the age of 30 with severe psoriasis had more than a threefold increase in myocardial infarctions. And you will hear much more about the increase in depression and suicide in patients with psoriasis. Psoriasis experts are used to seeing patients with comorbidities because they are so common in our patients.

The stigma associated with psoriasis is something we don't often speak about. In this study, it was found to be one of the 10 most embarrassing diseases, and the impact of that comes out in every survey that is taken.

This was a huge survey that was published recently. Nearly 140,000 households were called by randomized telephoning, and of that group, 3,426 patients were identified and agreed to be surveyed. Look at the impact of psoriasis on employment. It interferes with getting a job, keeping a job,

choice of career, career advancement, and working full-time.

This is another survey, and what was reported here is that patients with moderate to severe psoriasis are much more often absent from work and have much lower work productivity because of their disease. Low household income defined as less than $30,000 was markedly more common in patients with moderate to severe psoriasis compared to those with mild psoriasis.

In this survey, the impact of psoriasis was compared to the impact of various other diseases. The survey is divided into physical questions that address physical components and questions that address mental components of day-to-day living. On that survey, psoriasis scored worse than cancer, hypertension, depression, myocardial infarction, and a host of severe diseases. Only congestive heart failure impacted physical functioning worse than psoriasis.

In terms of the questions addressing the mental component of the quality of life, psoriasis

did worse again than diabetes, congestive heart failure, cancer. Only chronic lung disease and depression had more of an impact on the mental component of the disease.

This is a list of all the approved treatments for psoriasis, and many of them certainly improve the lives of our patients, but they all have drawbacks. With phototherapy with both UVB and PUVA, there are many treatment visits required. PUVA has fallen out of favor to large degree because of the association with non-melanoma skin cancer and malignant melanoma.

Acitretin is teratogenic. We virtually never use it in women of childbearing potential, and as monotherapy, it simply isn't that effective. Methotrexate is toxic to the bone marrow and to the liver. Cyclosporine, the guidelines for cyclosporine say it shouldn't be used for more than a year because after a year, 100 percent of patients who had kidney biopsies showed kidney damage.

Apremilast, the most recently introduced

oral drug, is associated with diarrhea and has certainly helped many of our patients, but the PASI 75 scores at 16 weeks are only 28 to 33 percent. So we could use better efficacy than that.

Biologic therapies represent major breakthroughs in the treatment of psoriasis. Their drawbacks are first and foremost their expense. Many patients don't like injections, and the TNF blockers specifically have warnings about heart failure, connective tissue disease, demyelinating diseases, infection, and malignancy.

Many of the drugs lose effectiveness over time, creating a real need for new drugs. This is a recent publication from the Journal of Investigative Dermatology, and you can see that all of the biologics available at that time ultimately lose some efficacy or patients stop taking them because of loss of efficacy or because of side effects.

The green line is etanercept. That actually had the least treatment survival over the 96 months

of study here. The one that has the least loss of benefit is only out to 5 years, and that is ustekinumab. And there is still more than a 20 percent loss of patients using that drug. And the reasons for discontinuing using them, the biggest reason is lack of efficacy. The second biggest reason is adverse events.

In brodalumab, we have a molecule that is much more targeted than many of our psoriasis therapies. This is a drawing published in the New England Journal of Medicine, which shows the soup of cytokines and cells that lead to the development of psoriasis. And here is how cyclosporine works. It blocks the whole thing.

Here is how TNF blockers work. They are much more selective but still block a good portion of the immune system. Ustekinumab is even more selective, blocking only IL-12 and IL-23, and secukinumab and ixekinumab, the most recently approved drug for psoriasis, block IL-17A.

Brodalumab is the further downstream in this scheme. It blocks the receptor for the IL-17s.

And unlike cyclosporine in which we see an increase in malignancies and infection, we know exactly what IL-17 deficiency does because there are people born with deficiencies in IL-17, and we can create knockout mice for IL-17.

What they get are yeast infections. They get chronic mucocutaneous candidiasis. They don't get more heart attacks and more malignancies than anyone else. They get yeast infections and some tinea infections. Individuals born with mutations in the receptor for IL-17 also get chronic mucocutaneous candidiasis.

I am going to close with photos of two patients, the first, a PASI 100 responder, whom I've shown you, and the second, a PASI 75 responder. The patient had awful psoriasis at baseline and is much better but could still be quite self-conscious with this extent of disease.

The difference between PASI 100 and PASI 75 improvement in the Patient's Symptom Index, the PSI, which is a measure of 8 psoriasis specific patient-reported outcomes, is dramatic. If you

look at the DLQI, which is a measure of quality of life, again, the difference between PASI 100 and PASI 75 is substantial.

Why do we need a new drug? Patients are dissatisfied with the current treatments available, and despite all of the really good treatments we currently have, which work for some, they don't work for all patients.

As an example, this patient, whom I saw two weeks ago, has failed many of our treatments. And in this photo, he's been on one of the new anti-IL-17 drugs for 6 months.

I now have several patients who have failed those drugs, which shouldn't be a surprise. In clinical trials, there has not been a single drug that has achieved PASI 75 in 90 percent of patients. And not even 50 percent achieve PASI 100 during the controlled portion of these drugs.

So there will still be thousands of psoriasis patients who will not achieve adequate clearance with the current drugs out there, and patients like this may fail one drug and respond to

a similar drug for reasons we don't know.

Psoriasis still has a measured impact on quality of life for many patients, and we need something better for patients like these, and I see patients like these every day in my office. In brodalumab, we have a drug that brings more patients to PASI 100 than any drug before it, so that for patients like these, we still need more therapies like brodalumab.

By complete coincidence, yesterday morning, I saw a patient from our brodalumab trial who is not doing well on one of the new anti-IL-17 drugs. I told him I was coming here today, and I told him about the suicides. And to my surprise -- and he actually gave me permission to use his name and tell his story. His name is Dr. Alec Miller, and I've been calling him Dr. Miller for years, not knowing what he does. He said, "I'm a suicidologist."

If you PubMed his name with suicide, you will find many references on that subject. He's a clinical professor of psychiatry at Albert Einstein

College of Medicine and a suicide expert. He has performed research on suicide, published numerous articles and books on the subject.

I told him details of the suicides in the patients who had been in our trial, and he expressed great skepticism on the association with suicide. I asked him to send me an email about that, and he wouldn't because he hadn't reviewed all of the data. But he did send me an email, and I would like to quote from his email.

"As your patient, I had received numerous medications over the past 20 years or so with mixed results. The best medicine I had ever taken for my psoriasis and psoriatic arthritis was brodalumab. I was 100 percent clear from skin plaques and had never felt happier with regard to my body and my quality of life.

"I had no suicidal ideation and no depressive symptoms whatsoever during the entire trial, which was several years. In fact, I was significantly saddened and worried about the abrupt discontinuation of this trial and the potential

resurgence of my symptoms.

"I have since been placed on other FDA-approved medicines with not the same clinical benefits. I believe it was a huge mistake to discontinue such an efficacious treatment, and I feel that that dermatological patients of the world have been deprived of the most effective treatment I have ever known.

"My hope is that brodalumab is reintroduced to patients as I am confident this medicine will improve the medical and psychological health of innumerable patients in the future."

That is why we need brodalumab. Thank you.

Applicant Presentation - RK Pillai

DR. PILLAI: Good morning. My name is R.K. Pillai, and I head up the dermatology development efforts for Valeant.

I will now review the robust efficacy data for brodalumab in psoriasis. Efficacy of brodalumab has been established in 4 controlled clinical studies, 1 phase 2 study, and 3 pivotal phase 3 studies.

The key highlights for the 210 dose include rapid onset of action as early as 2 weeks; achievement of PASI 100 or complete clearance in majority of patients within a year; superiority over ustekinumab or Stelara, the gold standard for psoriasis treatment at the time of study initiation. This was confirmed in two head-to-head studies.

The initial excitement for brodalumab efficacy stems from the phase 2 results where over 60 percent of patients on 210 dose achieved PASI 100 within 12 weeks. These results were better than both approved biologics and other development programs targeting psoriasis at the time.

Three large multicenter placebo- and comparator-controlled studies in over 4300 patients were conducted. Two doses of brodalumab, a 210 milligram and 140 milligram, were evaluated. All phase 3 studies had a 1-year control period followed by the open-label, long-term extension.

For AMAGINE-2 and 3, they were identical, 52-week comparator-controlled studies using

ustekinumab as the active control. The inclusion criteria for these studies were generally similar to most biologic psoriasis studies. Most of the exclusion criteria were also similar to other biologic studies with the following exceptions: Unlike other programs, patients with a history of substance abuse, depression, suicidality, or other psychiatric conditions were not specifically excluded, making the study population more representative of the real world.

Key baseline demographics and patient characteristics were consistent across the three studies. They were also consistent within the treatment arms for each study. The patient population was primarily Caucasian male with a mean age of 45 years, mean duration of disease of 18 years. About 40 percent of patients had severe disease involvement.

We will now go over the key design elements of the pivotal studies, starting with the 12-week placebo-controlled period.

All phase 3 studies had a similar design for

the 12-week randomized double-blind placebo-controlled period. In the 52-week blinded comparator controlling period for AMAGINE-2 and 3, different brodalumab regimens were evaluated. What we want to focus here is that through week 52, more and more patients moved to brodalumab 210 dose, as shown in the bottom of the slide, such that 88 percent of patients were exposed to the 210 dose by week 52.

Similar to AMAGINE-2 and 3, for AMAGINE-1 in the long-term period, progressively, more patients moved to brodalumab 210 dose, as shown in the bottom of the slide, such that 87 percent of all patients were on the 210 dose at week 52.

For AMAGINE-1, 2, and 3, all primary efficacy endpoints were met, and these were met with high statistical significance. Of note, brodalumab program evaluated PASI 100 as the predetermined primary efficacy endpoint compared to ustekinumab in two replicate studies.

I would now like to go over the key efficacy results for the 210 milligram biweekly dose at both

12 weeks and 52-week control period that has generated substantial excitement.

Brodalumab demonstrated a rapid onset of action. In AMAGINE-2 and 3, brodalumab differentiated from ustekinumab as early as 2 weeks, and the 210 dose shown by the top line remained differentiated through week 12.

A higher proportion of patients, 37 to 44 percent, achieved complete clearance of PASI 100 with the 210 dose compared to all other treatment arms. More importantly, twice as many patients responded to the 210 dose compared to ustekinumab in 2 replicate well-controlled studies. This differentiation with ustekinumab was maintained through 52 weeks.

For each of the two studies, AMAGINE-2 and 3, brodalumab 210 demonstrated superiority over ustekinumab. This figure represents an integrated summary of the two randomized well-controlled studies for PASI 100 over 52 weeks.

Over 50 percent of patients on brodalumab 210 were completely clear of plaque psoriasis

within 52 weeks. These results were well reflected in the patients' quality of life. In all three studies, the DLQI response for patients on brodalumab 210 dose was better than ustekinumab, placebo, and the 140 dose at 12 weeks.

As we have heard, the patients have clearly expressed their desire to have access to new therapies that offer complete clearance. The importance of PASI 100 must be underscored.

This graph clearly demonstrates that achieving PASI 100 translates to a high level of patient satisfaction. For brodalumab 210 patients, 61 percent of PASI 100 responders had a DLQI score of zero at week 12. In contrast, only 34 percent of patients with a PASI response just shy of PASI 100 had a DLQI score of zero.

For patients with a response between PASI 75 and 90, the patient satisfaction was even lower. This defense was maintained at week 52, as shown by the bars on the right.

In conclusion, robust efficacy of brodalumab 210 has been demonstrated. What

differentiates brodalumab are the following features: Patients on brodalumab saw treatment benefit as early as 2 weeks into treatment. Brodalumab differentiated from ustekinumab as early as 2 weeks and demonstrated superiority through 52 weeks in two replicate studies. More than half the patients on the brodalumab 210 dose achieved complete clearance within 52 weeks that resulted in high patient satisfaction.

I will now invite Dr. Robert Israel to discuss the safety of brodalumab.

Applicant Presentation - Robert Israel

DR. ISRAEL: Good morning. I am Bob Israel, vice president of clinical and medical affairs at Valeant. I thank the committee for allowing me to present the brodalumab safety program.

The brodalumab program is a very large program that allows for a robust analysis of both safety and efficacy in patients with moderate to severe psoriasis. In the phase 2 and 3 psoriasis programs, there were 4,464 patients who had been exposed to brodalumab of whom 92 percent received

at least 1 dose of brodalumab 210 milligrams due to the designs of the studies. Of these, more than three-quarters had greater than 1-year exposure, and over 2,000 patients have been exposed to brodalumab for 2 years or more.

In our discussion of the safety data, exposure-adjusted rates are used primarily for the 12- and 52-week data. Exposure-adjusted rates count the time from the first dose to the last dose of brodalumab plus one dosing interval. In terms of total exposure, 76 percent of exposure-adjusted patient-years were on brodalumab 210 milligrams.

As we review the general safety and specific safety topics, we will provide data for the 12-week period, the 52-week period, and the long-term period. As you can see, the 12-week period portion of the study is the placebo-controlled portion, and no change of dose or rescue were allowed. Therefore, the 12-week period provides the most objective comparison between treatment groups.

Out to 52 weeks, the study remained double-blind with ustekinumab as the control arm.

After 52 weeks, all patients were on brodalumab, and there was no control arm.

The design of the studies resulted in variable dosing after 12 weeks. However, constant dosing groups for brodalumab at 140 milligrams and brodalumab at 210 milligrams are shown in this slide during the 12-week and 52-week pools. And the all-brodalumab column accounts for all brodalumab-treated patients who received at least one dose of brodalumab.

In the long-term pool, the overall 140 milligrams or overall 210 milligram categories include patients who have received at least 75 percent of the planned respective dose.

For all adverse events and serious adverse events, rates were similar between brodalumab and placebo or ustekinumab. No significant differences were seen between the brodalumab 140 milligrams and 210 milligram doses.

In the 52-week pool, event incidence rates were comparable across ustekinumab and brodalumab arms. No increase in rates in the long-term

extension and no evidence of a dose effect for brodalumab were seen.

The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Headache and arthralgia were slightly more frequent and considered to be adverse drug reactions.

For serious adverse events, rates were similar overall between placebo, ustekinumab, and brodalumab in both the 12-week and 52-week pools. In the 12-week pool, cellulitis, appendicitis, gastroenteritis, and acute pancreatitis were the most common. In the 52-week pool, cellulitis, myocardial infarction, and cholelithiasis were most common.

There were 25 fatal events in the study, 23 on brodalumab for a rate of 0.3 per 100 patient-years and 2 on ustekinumab for a rate of 0.4 per 100 patient-years. For this, we used follow-up adjusted to capture all events. Follow-up adjusted counts all events through the entire follow-up period regardless of when they occurred.

Using data through the end of the study, the standardized mortality ratio, or SMR, which compares mortality rates to a general population, was calculated as 0.53. Since the SMR is below 1.0, there is no indication that brodalumab is associated with an increase in mortality.

Following a comprehensive review of the safety data, there are known risks associated with brodalumab. These include exacerbation of existing Crohn's disease; infection, specifically fungal infection; and neutropenia, consistent with other agents, which target the IL-17 pathway and discussed in detail in the sponsor's briefing document.

I will now discuss MACE, an adverse event of interest, which was monitored because of the increased prevalence in the psoriasis population.

Cardiovascular disease is a known comorbidity in psoriasis patients who often have increased risk factors, including obesity, hypertension, smoking, type 2 diabetes, dyslipidemia, and a cardiovascular history.

In a systematic review and meta-analysis by Armstrong et al. in 2013, published in the journal of the American Heart Association, myocardial infarction rates were found to be higher by 70 percent, stroke by almost 60 percent, and cardiovascular mortality by 40 percent compared to background populations.

It should be noted that there were minimal exclusion criteria in the brodalumab studies with regards to cardiovascular risk factors. The brodalumab program only excluded MI or unstable angina in the previous 12 months.

Consequently, cardiovascular risk factors were common in our study population with smokers and former smokers over 50 percent and almost half of the patients having a BMI of greater than 30. Cardiac or vascular disorders were present in about 30 percent of all groups at baseline.

Additionally, more than 80 percent of patients in the brodalumab program had one or more cardiovascular risk factors, and about half had two or more risk factors.

Cardiovascular events were evaluated by grouping all relevant reported adverse event terms for each treatment group by using the two-standard MedDRA SMQs of ischemic cerebrovascular disease and ischemic heart disease. No imbalances in the rate of these events were seen through the long term.

A MACE adjudication committee from the Duke Clinical Research Institute reviewed all potential cardiovascular disorders and all deaths. There were 3 adjudicated MACE events in the 12-week pool, 2 myocardial infarctions, and 1 stroke in the brodalumab 140 milligram treatment arm.

It should be noted that there was one MACE adjudicated event of myocardial infarction in the placebo arm, referred to in the FDA briefing document, that was subsequently treated with brodalumab without further problem.

The exposure-adjusted rates for MACE events was 0.4 per 100 patient-years in the ustekinumab arm and 0.6 per 100 patient-years in the brodalumab arm for 52 weeks, and 0.5 or 100 patient-years for the brodalumab in the long-term pool. In the

follow-up adjusted, the rates are 0.4 per 100 patient-years and 0.7 per 100 patient-years for ustekinumab and brodalumab respectively.

An analysis of time to event to MACE was also performed from study baseline for all patients receiving a dose of brodalumab through the end of the study to analyze the cumulative probability of the incidence of MACE across the study population. The rate of adjudicated MACE events remained constant over the full-time course and showed no notable trends.

This figure from the FDA briefing document showed comparative MACE rates for brodalumab and other programs for psoriasis. The brodalumab rate falls within the confidence intervals of other agents.

A number of factors have been assessed in order to evaluate MACE causality. The direct evidence was based on relatively few events and showed a somewhat higher rate in brodalumab patients. However, confidence intervals overlap.

There was no temporal pattern or association

in the phase 3 trials, and time-to-event analysis shows constant occurrence over the time of the study. No dose trend in MACE events was seen between the 140-milligram and 210-milligram doses, and no effect was observed with any dose in nonclinical studies.

The evidence does not support a link between the mechanism of action of brodalumab and adverse cardiac events. There is no evidence of adverse events on glucose, lipids, blood pressure, or EKGs. And there was consistency in the findings overall. A broad grouping of cardiovascular and cerebrovascular adverse event terms showed no imbalance between brodalumab and ustekinumab in controlled study periods.

Other molecules that target the IL-17 signaling pathway such as secukinumab and ixekinumab have not been associated with adverse cardiovascular events and have MACE rates similar to brodalumab. And lastly, the MACE events are nonspecific in that they are strongly associated with identified cardiovascular risk factors.

This slide shows a forest plot of the safety parameters we have discussed. The control data from these large studies demonstrates that in the 12- and 52-week study periods, the safety profile of brodalumab 210 milligrams was similar to that of ustekinumab with the exception of non-serious fungal infections.

In conclusion, in the phase 2 and 3 psoriasis programs, there were a total of 4,464 patients who have been exposed to brodalumab, and over 3,000 patients have received brodalumab 210 milligrams for greater than 1 year. With over 8300 patient-years of exposure, we conclude that the safety profile of brodalumab is consistent with the known effects of agents that target the IL-17 pathway.

Risks associated with the exacerbation of Crohn's disease, infection, and neutropenia are manageable and are described in the proposed label. Analysis of MACE data does not support a causal association with brodalumab.

We will now move on to discussion of

suicidal ideation and behavior in the brodalumab program by Dr. Marangell.

Applicant Presentation – Lauren Marangell

DR. MARANGELL: Thank you very much. Good morning. My name is Lauren Marangell. I am a practicing psychiatrist. Earlier in my career, I was a professor of psychiatry at Baylor College of Medicine. I was also an executive at Eli Lilly for a shorter period of time.

My subspecialty is depression and bipolar disorders. I have published on medications and suicidality. I have served on the FDA psychiatry advisory board committee, including the 2004 evaluation of antidepressants in SIB. I am being paid for my time here today as well as transportation. I have no financial interest in the outcome of this committee meeting.

SIB is a composite term. I was going to go through a bunch of definitions, but you have already heard those, so let me simply make a methods point. If you rely on spontaneous report, you will capture most completed suicides, and you

will capture most serious suicide attempts, patients who need medical treatment. And that's reported back to the investigator or told to the investigator.

You often will not capture ideation, milder attempts, the patient who took three sleeping pills instead of one, which would be an attempt but a less lethal attempt. So when you are comparing across programs, it is incredibly important to make sure that you are comparing apples to apples because the methods will have a tremendous impact on the rates.

Next slide, please. You have also already heard about risk factors. Depression is certainly a significant risk factor, perhaps the most important for patients who ultimately commit suicide. As that is my specialty, I have a tremendous investment in people with depression being adequately diagnosed and treated and subsequently reducing suicide risk.

There is an interaction between all these risk factors and life stressors. These are data

from the CDC. I also want to note that people commit suicide who don't have any of these risk factors. I live in Houston, Texas. You may know that that is an oil town. You may know that the price of oil has dropped dramatically.

I have a number of patients who have lost their fortunes, and their fortunes are their entire identity. They don't have depression, and they are scaring me tremendously because they have told me, "If this bank loan doesn't go through and get extended and I'm going to lose my house, I would prefer not to live."

It is a decision they have made, and frankly, I wish they had depression because I could treat that. I can't treat their life circumstances. I am not saying that that is what is happened in the entirely in the brodalumab program, but I do think it is an important background point to keep in mind.

You have read in the briefing book that psoriasis is associated with increased risk factors. I do want to emphasize the point that

this program did not have a specific exclusion for patients at risk. I have done a lot of depression trials throughout my career, and even in depression trials, we exclude patients who we view as being at risk for suicide or suicidal attempts, actively. Almost every registration trial you'll see, unless it is a study, which is unusual, that is trying to look at suicide as an attempt, will exclude these folks.

This study did not, and when we look through some of the case reports -- and we can go into that if you like -- these folks are really tremendously different than what you would usually see in a typical registration trial. These include people who have heroin addiction, who are abusing methamphetamine. This is really quite a different population.

Next slide, please. This is baseline psychiatric comorbidity. This is reliant on medical history, and it is not a standard skid that is looking for all diagnoses. So you would imagine that this is an underestimate. But what you are

seeing here is that approximately 17 percent of patients had baseline psychiatric disorders by medical history.

In one of the phase 3 studies, AMAGINE-1, there was the specific measurement called the HADS. The HADS stands for the Hospital and Anxiety Depression Scale. It is a very standard tool that is used internationally. Per the HADS, 23 percent of patients had moderate to severe depression and anxiety at baseline.

Before going any further, I need to acknowledge some historical facts about the program. The psoriasis phase 3 program began enrolling in 2012. Over the course of 2013, there was 1 completed suicide, an overdose that may have been a suicide attempt, and 3 attempts in 1 person within the psoriasis program.

There was no clinical hold and no determination of causality, but additional safety measures were put into place. One of these was implementation of the eC-SSRS, which was administered monthly, and you have already heard a

definition of that scale and how it is used.

Over the course of the following year, 50,000 eC-SS forms were completed. However, most patients in the psoriasis trials, the data that you are looking at, were already in the extension phase. So when you look at longer term data compared to the placebo in the 52 week, that methodology is important to keep in mind.

Today, our task is to evaluate in a systematic and objective fashion whether or not the data have a signal or not. And I am going to try and walk you through this in a way that I went through when I was thinking about what do these data mean because it is a very complicated dataset.

Shown here is the 12-week placebo-controlled data. This is in the psoriasis program. There was a single subject on brodalumab 210 with 2 attempts during this period. These data were collected with standard AE reporting as are all the other biologic programs that you have seen. There has been a comment that the SIB rates may actually be higher than shown because there was not a prospective

assessment during the controlled period.

This is the placebo-controlled pooled data in psoriatic arthritis. This trial started later in time than the psoriasis trials so that when the C-SSRS was implemented, this trial was at the beginning. So 79 percent of patients were able to have baseline data, and as per the other studies, this was also done monthly to capture new events or new onset events.

As you can see, there was a single patient with suicidal ideation in the brodalumab arm. If there was a drug effect with brodalumab, it should be evident in this study. It is placebo controlled, and it has prospective assessment with the eC-SSRS, and there's not a signal.

These are treatment-emergent incidences of clusters of MedDRA PT terms in the 12-week period. We have grouped all psychiatric and all neurology clusters, partly to compare across other agents. However, all PT terms that were treatment emergent are included here.

One difference that you might note between

some of these tables and some of the tables in the FDA briefing book is that we have looked at treatment emergent. So if somebody had headache at baseline and they continued to have headache, that is not treatment emergent. If they didn't have headache at baseline and they develop it, that, of course, would be treatment emergent.

You will note that these rates are very low, and I think it is worth emphasizing that the 12-week placebo controlled data, in my mind, this is a large dataset. The psoriasis study, there were over 800 patients on placebo and over 3,000 on brodalumab. In the psoriatic arthritis trial, there are over 300 patients on placebo and over 600 on brodalumab.

This is the HADS again. I mentioned this was used a priori in AMAGINE-1. Here you see statistically significant improvement in both depression and anxiety with both doses of brodalumab compared to no change on placebo.

This was one of the first things that I wanted to see when I was looking at this dataset

because I was wondering if maybe there is something in depression that is perhaps leading to SIB events. Then from here you say, okay, well, this is nice. There is no mean effect. Is there a subgroup that is getting worse, and maybe that is the problem.

We looked at that, and here you see the patients who worsened. Worsening was the standard definition of moving from a score of less than 8 to greater than 8, so not clinically significant to clinically significant, plus a 2-point change was the most restrictive definition.

As you can see, there were more worsenings with placebo, shown in gray, compared to brodalumab, shown in purple. We have also looked at the patients who worsened, and there were no SIB events among those patients.

In clinical practice as well as clinical teaching, we think about drug-related psychiatric events when they occur close in time to when you start the drug. Following up on that, we have reviewed medications that we are aware of with the

suggestion of a SIB association.

We have been unable to find a drug with a signal where that signal is not evident in the first 12 weeks. Now, it may not peak in the first 12 weeks. It may not stop after 12 weeks, but it is evident in 12 weeks.

The other thing that you see, which also makes sense clinically, is you don't see SIB in isolation. When SIB occurs, so drug-related SIB, you typically see this as a cluster of neuropsychiatric symptoms. So you don't see that the rates of neuropsych adverse events are the same in the drug causing SIB as they are in placebo. There is not a single instance of that. And again, medically that makes sense that there should be a relationship.

The brodalumab program, the neuropsychiatric events are infrequent, and they're comparable to comparators during the drug-controlled periods. And they don't increase in the long run. And I'll show you that data.

These are the data from the 52-week pool

combining all psoriasis studies. Again, this is randomized double-blind study with an active comparator. Note that you are now seeing rates instead of percents because this was the a priori outcome for the 52-week and longer term data for SIB and other safety outcomes.

The rates are higher in the ustekinumab group, particularly considering that the brodalumab rate includes an intentional self-harm without suicidal intent as well as 1 completed suicide that was later ruled indeterminate by an external review.

Overall, these data do not suggest a differential drug effect, but before I move on to the next slide, we have stratified this analysis, much as the FDA did in their briefing book, looking at patients who start off with and without a history of depression or with or without a suicide risk. And there is no question that there is a higher rate of SIB in the patients who have baseline risk factors. However, the same exact increase is seen in the active comparator with

ustekinumab.

I can also show you very similar data from other drug classes that show the same thing. That's a backup slide. If you would like to see it, feel free to ask about it.

Next slide, please. Here you see treatment-emergent neuropsychiatric disorders up to 52 weeks. This is any age during the 52-week period that is cumulative, so it is not just the 52-week slice. It is anything that happened in the 52 weeks. Again, you see very low rates and no imbalance between groups.

When you look at long-term neuropsychiatric events, so this is beyond 52 weeks, we have placed the 52 weeks side by side so you can see the comparison. We actually see that with increased exposure to brodalumab, the rates decrease.

Now, you are looking at cumulative SIB events in the psoriasis program compared to 52 weeks. So this is the long-term now. So there is no active comparator, and this is the timeframe when the eC-SSRS is implemented; dramatically

higher rates. This makes us think that this is likely ascertainment bias and not some late onset biological effect that doesn't happen until after 52 weeks.

Again, if this was late onset SIB, you would expect at least neuropsychiatric adverse events to go up, too, and they don't. As I showed you two slides ago, they actually are going down.

We will discuss completed suicides next. Of the 4 completed suicides in the psoriasis program, as you have heard from the earlier presentations, all are male, age range 39 to 59. Time from the first dose of brodalumab ranged from 97 to 845 days. All had either risk factors or stressors.

Recall that 1 of the 4 suicides in the psoriasis program was possibly an accidental overdose. As you have seen in the briefing book, there was also 1 completed suicide in the RA program and 1 in the psoriatic arthritis program.

Why did these occur? I obviously can't tell you for sure, but I do have some alternative

explanations from it being a drug effect. One is this was a higher risk population. I believe that, and I hope I have shown you data that make a compelling argument for that.

There was also a disproportionate randomization and rescue to brodalumab. So patients who weren't doing well were systematically shifted to the active drug. There was also substantial exposure to brodalumab in the long term.

Another explanation is simply variability. Variability in this program may wind up on the higher end of the spectrum than other drugs have to date due to random factors that aren't associated with the drug. Towards that end, I would like to show you some examples of how variable the SIB data are across programs, all the while keeping in mind that we do believe that this program had higher risk patients than other programs. We are not making a drug-to-drug comparison. The point is just to show you variability.

Here you see one completed suicide on

placebo in the apremilast program. This gives a rate for complete suicides on placebo that is similar to the brodalumab rate. You also see one completed suicide in the secukinumab program during screening, so not drug effects but pointing to that these SIB events occur in this population.

There were 10 attempts in the ixekinumab program. On page 34 of the FDA briefing book, you see variability across a number of programs. That same table shows three programs that have higher rates of suicide attempts than brodalumab.

The point is that SIB occurs in all of these programs. There is tremendous variation. My interpretation of this is that it is a random occurrence in patients that are high risk and not necessarily a drug effect.

This slide speaks to time to event. These are Kaplan-Meier curves for both brodalumab and ustekinumab from baseline to 52 weeks based on the randomized double-blind data. There is no differential signal between the drugs out to 52 weeks.

Regarding biological plausibility, there is no CNS toxicity in the preclinical studies. While some pro-inflammatory cytokines have been convincingly linked to depression, IL-17 is not one of them.

In addition, blockade of IL-17 receptor prevents any downstream effects. So there is not cytokine-to-cytokine stimulation. Everything goes through the receptor. Dr. Trager will discuss this in more detail in the following presentation.

Starting to summarize, the study design, including a lack of exclusion criteria for SIB, the disproportionate randomization to brodalumab, the crossover in rescue periods, as well as the implementation of the eC-SSRS when most patients were in the open-label extension makes this a tremendously difficult dataset to interpret.

However, there is a robust body of direct evidence to look at. This includes large placebo-controlled studies that showed no SIB signal and extremely low rates of psychiatric treatment-emergent events. If there was a drug

effect, the placebo-controlled trial in psoriatic arthritis, which included prospective assessment of SIB, should have picked up a signal. As I have shown you for other agents, that signal is shown in the first 12 weeks.

The 52-week SIB data are comparable to the active comparator, again, so a randomized double-blind trial. AE events for neuropsych are exactly the same. SIB rates, if anything, are higher with the comparator.

The only temporal pattern that is discerned is in the uncontrolled period after 52 weeks where psychiatric events remain stable but SIB rates increase in a timeframe that overlaps with the implementation of a tool that specifically asks about SIB events, suggesting ascertainment bias.

Finally, it is highly improbable that SIB events would occur in the absence of other neuropsychiatric events, particularly with no differential signal in 15 weeks of controlled data.

Thank you very much for your time. I would like to turn it over to Dr. Trager.

Applicant Presentation - James Trager

DR. TRAGER: Good morning. My name is James Trager. I am vice president of research with Valeant, and I would like to discuss IL-17 signaling and safety.

In its briefing document, FDA emphasizes the fact that serum IL-17 levels are elevated upon treatment with brodalumab and has expressed some concern then of potential biological consequences of interactions of IL-17 with the central nervous system and cardiovascular atherosclerosis.

Given the brevity of that document, the agency couldn't fully explore the implications of that observation, and I would like to discuss the topic in a bit further depth.

Here is the phenomenon we are talking about. This is data from the AMAGINE-1 trial. They show that serum IL-17A levels are elevated in patients treated with brodalumab. Understand that this phenomenon is completely consistent with brodalumab's mechanism of action. Receptor binding is an important route of clearance of IL-17A. By

blocking the receptor with brodalumab, we block that method of clearance and cause some accumulation of the cytokine.

This is not a unique observation for brodalumab. Blockade of the IL-6 receptor with tocilizumab similarly elevates serum IL-6 levels. The serum levels of IL-17 rise in concern with the antibody, and they reach a new steady state by 12 weeks. That steady state persists through a year of treatment, and no reason to believe that they don't continue on as long as treatment continues.

The change we see, the fluctuation we see in the cytokine level, doesn't appear to be coordinated temporally with the observed events of SIB or MACE. So it's a blockade of the signaling that causes the cytokine levels to rise. In other words, the elevated IL-17 levels don't equate with elevated signaling.

To step back, IL-17 receptor A is expressed in many cell types, and while the effect of IL-17 may vary depending upon the cell type, typically, IL-17 would induce those target cells to express a

variety of inflammatory cytokines and chemokines. These often include IL-6, IL-8, and TNF alpha.

Blocking the IL-17 receptor with brodalumab should inhibit the induction of these cytokines regardless of serum IL-17A levels. We can demonstrate this in several ways. First bear in mind that brodalumab was developed based on its ability to block IL-17 signaling, and the 210 Q2W dose can completely block IL-17 signaling in patient's skin and blood.

In addition, in a phase 1 study in rheumatoid arthritis, serum levels of several key IL-17 inducible inflammatory factors were measured during treatment with brodalumab. I'm showing you results of that study here, and you can see the results of that treatment with brodalumab didn't increase levels of downstream cytokines IL-6, IL-8, or TNF alpha.

The gray box in each panel here shows baseline levels of those factors, and you can see that through 18 weeks of treatment, the levels of these cytokines remained within the range observed

at baseline. Similarly, no significant changes in levels of serum C reactive protein, which is a sensitive responder to inflammation in particular to IL-6 and TNF alpha, were observed in any brodalumab treatment group from 12 weeks of study up through 3 years after the start of therapy; further evidence that elevated IL-17 in the absence of a functioning receptor is unlikely to be a physiological consequence.

Our careful review of both our own data as well as the available data from the literature does not suggest a mechanistic link between brodalumab and SIB or MACE.

As Dr. Haroon has discussed, inflammation may play a role in at least a subpopulation of depressed patients. Increased levels of inflammatory cytokines and IL-6 is the one that has been reported most frequently in the blood, have been observed in the blood of patients with SIB and depression. Brodalumab, however, as I showed a moment ago, doesn't elevate the levels of these cytokines.

Moreover, the association of IL-17 itself with depression has been examined in a number of studies, and no consistent signal has emerged. In fact, most of those studies have observed no correlation whatsoever between either serum or CNS levels of IL-17 and depression, nor can we identify a route by which elevated serum IL-17 in the context of brodalumab treatment might enhance cytokine signaling to the brain.

IL-17 is too large to diffuse passively through the blood-brain barrier, and known active transport mechanisms would be blocked by the antibody as would every other proposed route of peripheral signaling to the brain.

Finally, nonclinical studies revealed no sign of the neuroinflammation that might be expected as a consequence of IL-17 elevation in the CNS, nor did controlled clinical trial data indicate neuropsychiatric effects that might be consistent with elevated inflammatory signaling.

Similarly, for MACE, neither preclinical or clinical studies demonstrate perturbation of

cardiac function. We know that atherosclerosis is closely associated with chronic inflammation, and individuals with autoimmune disorders, for example, including psoriasis, have increased incidence of atherosclerosis.

Multiple studies in both humans and animal models suggest that increased IL-17 signaling is a risk factor for MACE, potentially contributing to vascular inflammation, plaque development, and plaque instability. Brodalumab blocks that signal.

IL-17 is a subject of active investigation, and new data continue to emerge from studies in humans, animals, and in vitro models. Given what we know today and really to reiterate the overall theme, elevation of serum IL-17A levels in brodalumab-treated patients, in the absence of a functioning signaling pathway, is unlikely to promote cardiovascular inflammation.

With that, I will turn it back over to Dr. Ramakrishna.

Applicant Presentation - Tage Ramakrishna

DR. RAMAKRISHNA: In the next few slides, I

will outline Valeant's approach to risk management of brodalumab post approval. We have thought carefully about the appropriate risk management approach for brodalumab.

The data suggests that SIB observations are related to a comorbidity in psoriasis rather than the effect of brodalumab. However, due to the seriousness of the observations, Valeant is proposing elements in addition to labeling. Our plan will educate healthcare providers, patients, and caregivers involved in the treatment of psoriasis.

The proposed comprehensive risk management program includes four components: labeling in the warnings and precaution section; routine and enhanced pharmacovigilance; an enhanced communication plan designed to educate healthcare providers, patients, and caregivers on the comorbidities associated with psoriasis; and finally, participation in an independent and well-established psoriasis registry such as Corrona.

The label will be the primary tool for

education and awareness. The key elements with regards to SIB labeling are highlighted on this slide. To our knowledge, this will be the only biologic agent for psoriasis, which will describe events of SIB in the label.

Valeant will use targeted follow-up questionnaires for all cases of SIB and MACE. These questionnaires will be appended to any cases of SIB and MACE and will be entered into our global safety database.

In addition to routine monthly signal detection, Valeant will perform quarterly review and analysis of all adverse events of special interest by a safety review panel. The safety review panel will consist of independent experts, which will include psychiatrists, cardiologists, dermatologists, and other professional consultants such as the Degge Group.

Valeant's proposed enhanced communication plan is designed to proactively inform, educate, and raise the awareness of patients and healthcare providers about the comorbidities of suicidal

ideation and behavior in patients with psoriasis.

This slide provides elements of our enhanced communication plan. The medication guide will clearly highlight all potential risks in psoriasis patients with an emphasis of the comorbidity of SIB. The communication plan will include letters for healthcare providers and professional societies that include targeted messaging regarding all potential risks.

The healthcare provider fact sheet will target healthcare providers and will specifically detail the comorbidity of SIB in psoriasis patients. The patient wallet card will instruct patients on when and how to seek medical intervention.

All of the above components will provide detailed and pertinent information to patients and healthcare providers. The final aspect of the proposed comprehensive risk management program includes our planned participation in an independent psoriasis registry. The registry will have comparator cohorts, including TNF inhibitors

and two recently approved IL-17A inhibitors.

The prospective study will enable a comparison across multiple biologic psoriasis patients. We have chosen to take this proactive approach to collaborate with Corrona. Speaking with experts in dermatology, cardiology, and psychiatry who are familiar with evaluating rare signals in a highly comorbid psoriasis population, participating in an independent psoriasis registry with comparative cohorts, would provide the most valuable data in a realistic timeframe.

The Corrona registry currently involves over 120 dermatology sites across the U.S. with over 1,600 patients currently enrolled. All SAEs are reported with supporting medical records, including nonfatal SAEs such as MACE and suicide attempts.

This comprehensive risk management plan has been developed to address patient safety, which is of utmost importance to Valeant. It achieves this by the effective communication of the comorbidities related to psoriasis; dissemination of information using many methods, including direct provision to

patients, healthcare providers, and caregivers; collection of long-term longitudinal safety data obtained through a well-established and independent comparative registry, which will continually analyze and report its findings.

I will now introduce Dr. Kim Papp, who will present the benefit-risk of brodalumab.

Applicant Presentation - Kim Papp

DR. PAPP: I am Kim Papp. I' a dermatologist practicing in Waterloo, Canada. I am being paid for my time and travel to be here today and expenses, but I am not vested financially in the outcomes of these proceedings.

I was a lead investigator in the multiple ascending dose study as well as lead investigator in the phase 2 program for brodalumab in psoriasis. I'm a lead investigator in one of the phase 3 studies. I am an investigator in another study evaluating brodalumab in psoriasis, and I participate as an investigator in two of the psoriatic arthritis studies with brodalumab.

Today we have seen for the novel IL-17

receptor antagonist brodalumab. Professor Lebwohl has very poignantly illustrated the needs of psoriasis patients, patients not unlike the one shown here. I think it's important to realize that psoriasis is not just a disease of older patients, but it is actually a disease of younger patients with more than half of the psoriasis patients having their disease established before the age of 30. Professor Lebwohl has also highlighted the need for new therapies with different mechanisms of action. None of the therapies we have work for everyone, and certainly none of the therapies we have works forever.

We have also seen that brodalumab offers a unique mechanism of action that delivers an overall favorable benefit-risk profile that addresses very important gaps among currently available agents.

Brodalumab had demonstrated that it can provide complete disease control in many patients in the same way, as we shall see in a moment, it has for this patient. These patients start with extensive disease, and within a few weeks, freedom;

they are often clear.

Now, for those of you who do not have the benefit of the TV screens and you have to look at the projection, the only normal skin are the few patches that appear on the chest and shoulder. So this patient has very extensive disease.

What we have seen is that this rapid and thorough response is not unique. Four weeks following initiation of treatment with brodalumab, for this patient, 90 percent improvement. I think we can only imagine the impact that this rapid response has on these patients.

These data show that brodalumab provides meaningful efficacy resulting in psoriasis patients with totally clear psoriasis-free skin. The previous patient was not unique. We have seen that as early as 4 weeks' treatment with brodalumab results in 100 percent improvements in signs and symptoms in one-tenth of patients, indicative of its rapid onset of action.

We have seen that after 12 weeks of treatment with brodalumab, more than one-third of

patients are clear. And we have seen that continued treatment with brodalumab results in more than one-half of patients achieving totally clear skin. This high level of response is sustained throughout the year.

Put into context with one of the most widely prescribed biologic therapies on the market, brodalumab produced clearance in almost twice as many patients as ustekinumab. The results seen for this patient from baseline to 12 weeks was experienced by more than a third of patients. And equally important, the response of clear, no psoriasis is, as I said, not unusual. More than half the patients with brodalumab had achieved this complete resolution from week 26 to week 52.

Psoriasis is not unusual. When we compare these results with the currently available treatments, brodalumab achieves the highest level of total skin clearance. The high level of response seen clinically is reflected in improvement in quality of life as reported by the patients. And more pointedly, we have seen

significant reduction in depression correlates with improved psoriasis scores.

Summarizing the clinical benefit, treatment with brodalumab produced a rapid response seen as early as two weeks. The overall response resulted in durable skin clearance in more than 50 percent of patients within one year. These results were superior to ustekinumab with twice as many brodalumab patients achieving clearance, and response was maintained over the year.

Total skin clearance was also associated with improvement in quality of life outcome measures and depression scores. Brodalumab provides clinically a meaningful benefit to patients with moderate to severe psoriasis.

There are potential but I believe manageable risks: worsening of Crohn's disease, it's an uncommon event; neutropenia identified in the phase 2 programs of IL-17 blockers. In patients treated with brodalumab, cases of neutropenia were uncommon. They were sporadic, they were self-limiting, and not associated with infections.

Infections, particularly infections with candida, are recognized risks that have also been associated with other IL-17 antagonists. These can be managed through appropriate labeling.

I would like to comment on two additional areas, comorbidities associated with psoriasis. The first is MACE. Small numbers of events were observed across the program. These rates were based on relatively few MACE events and showed potentially as point estimates higher rates of MACE in brodalumab patients.

Additionally, rates observed in the program were similar to rates observed in other biologics, and the evidence does not support associated MACE with brodalumab.

The second is SIB. SIB events have also rarely been observed in the brodalumab program. No imbalance was observed across treatment groups in SIB incidence rates in the controlled treatment period, and we know that there is variability in occurrence of SIB events across other psoriasis development programs.

Evidence supporting a biologically plausible mechanism is lacking. The data do not support a causal relationship between brodalumab and SIB. And given the high background comorbidity in this patient population, an education risk management program and warning labeling statement has been proposed for the product label.

I will now review data supporting a favorable benefit-risk profile for brodalumab. This plot, which presents the benefits and risks of brodalumab in a quantitative manner, shows in the top panel a summarizing of key efficacy endpoints. Results are presented as the difference of response between brodalumab 210 milligrams dose compared to ustekinumab. Differences greater than zero favor brodalumab.

Similarly, the bottom panel summarizes safety parameters. In this panel, differences in the proportion of risk are shown with values in greater than zero reflecting risks that are observed more frequently with brodalumab in comparison to ustekinumab.

If we focus for a moment on the top panel, we see the outcome measures of efficacy, sPGA zero or 1, PASI 75, PASI 100, DLQI of zero or 1 clearly favor brodalumab.

At week 52, brodalumab demonstrates clear benefit over ustekinumab. If we consider safety, I have expanded the bottom panel and have extended the observation period through the full 52 weeks and included patients who were treated for more than 40 weeks.

We see, similar to the 12-week results, which were presented earlier, an exception to the trend, an increased incidence of non-serious fungal infections, but otherwise, no significant risk differences were observed between brodalumab 210 milligrams in comparison for the ustekinumab.

Serious infections; non-serious fungal infections, which are essentially candidiasis; neutropenia; SIB; adjusted MACE; and malignancy rates compared to a SEER database, excluding non-melanoma skin cancer, these data altogether suggest that there is no significant increase in risk

compared to ustekinumab.

I will briefly discuss using this forest plot, which demonstrates the benefits and risks of brodalumab as compared to ustekinumab in the controlled, blinded 52-week period. As you can see, the benefits across all efficacy outcome measures that are important to patients, that are important to healthcare providers, and important to health authorities were superior to ustekinumab.

Please note the difference in scale. When we look at the magnitude of the benefit, it greatly exceeds the magnitude of the risk. When we examine all of the safety topics of interest, we can see that we are able to detect a small increase of risk in fungal infections, which are mostly candida. MACE and SIB events show no difference in risk, with an upper bound indicating less than 1 percent maximum difference in proportions.

The suffering experienced by these patients is very real, so I would like to share just two vignettes, if I could, for a moment, that are as close as I am ever going to get to living with this

disease.

The first occurred several years ago when at the end of the week, I was doing what I think for most of us is the highlight of our week. I was standing in a checkout line, and three customers ahead of me, it was a young woman. I easily recognized her as having psoriasis. So I am merrily going about my business.

The cashier just instinctively reaches out to grab the card, turns over, and reflexively withdraws her hand. Clearly, she was terrified. She was terrified because of what, this strange disease. It's an infection. It's contagious. She has no idea.

But it was at that moment that I realized that all the stories, the dozens and dozens of stories that my patients had been telling me about how they were rejected from public pools, how they were threatened and told to leave public beaches, were true. I had witnessed firsthand how this rejection can occur because of fear that others who don't have psoriasis experience when they first

witness it.

The other story that a patient -- an experience that I had just a few years ago, seated next to a patient. He is a very tough, buff. He's a guy's guy. He is not well educated, but he's very well read. He's well spoken, had psoriasis for most of his adult life, was on a treatment that had actually kept him clear of his disease for the better part of the 3 years.

In the discussion -- and I am seated not even an arm's length away from him -- was that we would have to stop the treatment. He cried. This 50-year-old guy's guy, this tough guy who just 3 years before had said, "Psoriasis doesn't bother me. I'm not bothered by it. I get into my hot tub. I just scrape off the scale. I'm fine. I'm okay," he was crying. He was bawling. He had tears streaming down his face. At that moment, I realized what it means to these patients to have clear skin.

So I really believe that brodalumab will provide a very much needed opportunity for these

psoriasis patients.

While newer treatment options certainly provide improved outcomes compared to the traditional therapies, there remains significant unmet medical needs. The data provided today demonstrates that brodalumab offers a unique mechanism of action, that brodalumab delivers a favorable benefit-risk profile that addresses many important unmet medical needs among the currently available agents.

I will now ask Dr. Ramakrishna to return to provide sponsor's conclusions.

Applicant Presentation - Tage Ramakrishna

DR. RAMAKRISHAN: The committee has seen the results from our brodalumab program. Even with the available therapies today, patients with psoriasis continue to struggle. Patients have made it clear, PASI 75 is not the same as being completely free from psoriasis.

Brodalumab provides a step change from currently available therapies by providing patients with total skin clearance, a PASI 100. The

evidence from our comprehensive development program does not support a causal relationship to SIB and MACE. However, we have developed a comprehensive risk management approach.

Brodalumab should be approved so that patients suffering from psoriasis will be able to benefit from a treatment allowing them to experience a well-deserved improved quality of life.

This morning we are pleased to have external experts with us who are available to help answer questions: Dr. Lori Davis, Dr. Michele Hooper, and Dr. Lauren Marangell, Dr. Peter Kowey, Dr. Mark Lebwohl, and Dr. Kim Papp. I think you for your time this morning.

Clarifying Questions

DR. BIGBY: Thank you all for your presentations.

Time now for the panel to have a chance to ask qualifying questions. Please remember to state your name for the record, and before you speak, if you can please direct your questions to a specific

presenter. Go ahead.

DR. DRAKE: I would like to address my question to Dr. Lebwohl. I was very impressed with the remission rate. A hundred percent is almost unheard of. But how long after the study was stopped, how long did they stay in remission before they began to flare?

I know you comment on one patient, I think it was four months, but could you give me a sense of how long they are in remission?

DR. LEBWOHL: The company may actually have statistics on a withdrawal/retreatment study that they have to know that, but certainly in the experience I have with my approximately 50 patients who were on it, I would venture to guess it averaged about three months. It was a gradual return, not a flare or rebound.

DR. DRAKE: Thank you.

DR. BIGBY: Dr. Bilker?

DR. BILKER: Dr. Haroon mentioned that there is a relationship between suicidality and response, but in the assessments that were shown of the

completed suicide and the other SIB events, there was no mention of the disease course or status at the time of the event. Was consideration given to that relationship? I am just curious to know if you looked at that.

I have one other question I wanted to ask. The SMR of brodalumab compared to the general population was shown to be 0.53 with a confidence interval that didn't include 1, but that indicates that these people are better than the general population. Is there an explanation for that?

DR. RAMAKRISHNA: Sure. For the first part of your question, I will call Dr. Mark Lebwohl, who can answer that, and the second part, I can call Dr. Davis to help with the statistics.

DR. LEBWOHL: Yes. I actually have the PASI scores, which I will tell you, I do want to say of the 4 suicides in the psoriasis trials, 1 of them was a 56-year-old man who had alcohol, benzodiazepines, and opiates. The investigator did not call it a suicide. The coroner did. And then an external adjudication committee viewed it as

indeterminate. I think that many of us might not have called that an intentional suicide.

Of the other 3, 2 of them were at my site. One of them was a patient who was going to go to jail. And in hindsight, he was distraught about that, so it did not come to a surprise to us that he committed suicide.

The second one came as a huge surprise because it was an individual who was doing extremely well. He was PASI 100. And I have the PASIs for all of them. He was PASI 100. And when my staff called his family, they were not surprised. He had been severely depressed before going on brodalumab, was doing very well on the drug, and then moved where he lived. He was isolated and anxious and depressed about the move, so they were not surprised that he committed suicide at that point related to the move.

The third one, which was not at my site -- so he was PASI 100, the guy that went to jail was PASI 73, so still pretty good but not perfect. Unintentional, the overdose was PASI 100,

also.

The fourth one was PASI 100, so that means completely clear. And he was an individual who was on disability, and when his psoriasis cleared, he lost his disability. And the financial crisis we believe may have precipitated the suicide. So 3 of the 4 were PASI 100, yes.

I will say the first suicide I had as a dermatologist was a patient who cleared with cyclosporine, and I would have thought his life was going great. I am not a psychiatrist, but it seems to me that -- and certainly, in that case, patients blame a lot of their problems on psoriasis. And then when their psoriasis goes away -- I know the problem he was blaming on his psoriasis did not go away. It was marital problems.

I think that we have taken away what they are calling the cause, and they are left with normal skin, but still left with the problems that they had before they went on the drugs.

DR. RAMAKRISHAN: I can call Dr. Davis to respond to the second question.

DR. DAVIS: My name is Lori Davis. I am with QST Consultation, statistician. Valeant is paying for our statistical support.

It is true, the SMR does show a lower rate compared to the age and sex population. We have details on how it was done, but this is not unusual for a clinical trial.

DR. BIGBY: Dr. Zito?

DR. ZITO: Thank you. My question relates to CC-68. I am interested in the relative potency of the comparator with brodalumab. Siliq. I guess we could say that. Because greater efficacy could relate to a much greater dose exposure. So could you shed some light on that?

DR. RAMAKRISHNA: To respond to your question, I would call Dr. James Trager.

Could we clarify your question with regards to the exposure?

DR. ZITO: Relative potency of the drug in question to the comparator. So you have both dose and duration differences that might represent differences in potency.

DR. RAMAKRISNA: I will ask Dr. Kim Papp to speak to that then.

DR. PAPP: I was actually involved in the design of the trials at the beginning. I have also participated in the ustekinumab trials.

The reason for selecting ustekinumab as comparator is that it was the most potent, most efficacious drug at the time of development of brodalumab that was commercially available. Knowing or anticipating the results of brodalumab to be as good as they demonstrated themselves to be, it was felt that it would only be appropriate to compare what was believed to be the best to what was available and the best.

So it was not to do with relative potency or any biochemical characteristics, biomolecular characteristics. It was simply due to what agents were available.

DR. BIGBY: I think that I can help you. I think the answer to your question is they have different mechanisms of action, so while ustekinumab is a 1223 inhibitor and the drug that

we are studying here is a IL-17 antagonist, so totally different mechanism of action.

DR. ZITO: Right. I really was not relating to mechanism of action but whether we are comparing equally potent exposure. In other words, have we got equally potent exposure? It sounds like because it says on the slides something about variable dosing, I don't see numbers that would help me understand the exposure.

DR. RAMAKRISHNA: Are you talking with regards to the dosing and the exposure and the variability of the -- Mark, would you like to speak to that or R.K.? Sure. Hopefully, we can clear this up for you.

DR. PILLAI: For ustekinumab, just to be clear, we used the dosage that is recommended for ustekinumab, which is the 45 milligrams for subjects below 100 and the 90 milligrams for subjects above 100.

With respect to brodalumab, the 140 and the 210 were chosen for phase 3. During the 12-week period, they were constant. All the subjects on

140 got 140. All the subjects on 210 got 210.

After 12 weeks, when we talk about the overall mixed dosing, what has happened because of the design, they were rescue subjects, placebo were moved on to 210. Some of the subjects who had inadequate response were moved to 210.

So these are the reasons the mixed dosing came into being. We have efficacy, but the core for us was to look at the 210 dosing. Would that answer your question?

DR. ZITO: Yes.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: Thank you. My questions are with regard to clarifying your risk management program that you have --

DR. RAMAKRISHNA: Sure.

DR. MORRATO: -- Dr. Ramakrishna, and trying to understand what is really enhanced as I look at the slides and what you had in the briefing.

Let me start first with so there are three elements, and I will ask a question for each. The enhanced pharmacovigilance, this looks like you are

doing passive reporting, and when someone reports a case, you will have a questionnaire.

Am I correct in understanding that?

DR. RAMAKRISHNA: Where we have the routine pharmacovigilance is outside of the enhanced. So what we have developed for the enhanced pharmacovigilance are additional questionnaires specifically just for SIB and MACE.

DR. MORRATO: When it comes in as a case.

DR. RAMAKRISHNA: When it comes in as a case to follow up. And what we have done is we have implemented a special procedure is proposed, is that every case of SIB or MACE or anything that may be of an adverse event of special interest will then have a review period of no greater than 48 hours. Then it can precipitate into a critical action committee.

All of these will be reviewed by an external committee almost like a drug safety monitoring board is what we are proposing for any cases of SIB or MACE.

DR. MORRATO: So in terms of meeting the

criteria, you would be willing to accept FDA, that immediate reporting criteria as cases come in?

DR. RAMAKRISHNA: Yes. So we are open to that.

DR. MORRATO: Okay. The quarterly review is standard pharmacovigilance when drugs are newly approved, as I understand. So I am just trying to understand how that --

DR. RAMAKRISHNA: This is for the external review panel. It is in addition. This is --

DR. MORRATO: All right. The timing is standard. You are having an external --

DR. RAMAKRISHNA: We are going to have an external so the FDA could give -- if they would like to see external safety so it is not by the sponsor.

DR. MORRATO: Right.

DR. RAMAKRISHNA: So we are willing to have an external panel of experts evaluate what we --

DR. MORRATO: Are you planning active pharmacovigilance studies?

DR. RAMAKRISHNA: Our only study that we are

planning right now that we are in discussions with at Corrona, which is the independent registry which we --

DR. MORRATO: Okay. So not looking at any other external databases in terms of surveillance of emergency room visits or any other -- the kinds of studies that I know have limitations but have been done with anti-depressant monitoring.

DR. RAMAKRISHNA: Sure. Currently, they are not in place.

DR. MORRATO: Okay. Then you bring up the planned or proposed registry update. Can you describe what are the outcome measures that are already included in that registry?

DR. RAMAKRISHNA: For the Corrona registry? Sure. Actually, Dr. Lebwohl, who is a chair of the Corrona registry, would be a great person who can respond to the actual objectives of the Corrona.

DR. MORRATO: Great. Because I would also like to see where you stand on enrollment, because obviously, being able to get case -- getting drug use here, it looks like you already have 1600

patients. If you are going to finish at 10,000, I am just trying to understand how many patients would likely be on this drug in the registry.

DR. LEBWOHL: First of all, I have conflict because I am a consultant for Corrona, and also, I am not allowed to speak on behalf of Corrona. I am speaking as answering that question from the Valeant side.

I think Corrona is the best option for getting a comparable patient population. These are moderate to severe psoriasis patients who are being treated with systemic drugs, other biologics. Several of the other companies as part of their post-approval safety reporting mechanism have gone to Corrona to do this.

It is a similar patient population. They are capturing the most important serious adverse events, which is serious suicide attempts and suicides are captured. There are over 1600 patients. Because it is not just brodalumab and there will be a requirement for thousands of brodalumab patients, but it is also thousands of

patients on other systemic treatments in a fairly balanced way, we will have large numbers to compare. The follow-up is going to go certainly for at least 8 years and perhaps longer.

DR. MORRATO: Okay. It sounds like what you are saying is that -- you mentioned thousands of brodalumab. So there might be an expansion of the total sample size --

DR. LEBWOHL: Right.

DR. MORRATO: -- could result of your discussions with the company?

DR. LEBWOHL: Yes. As new drugs come onboard, there is a commitment made for certain numbers of patients for each drug and individually. So there will be a commitment made to a number of patients on brodalumab.

DR. MORRATO: My last real quick one is the enhanced communication components. Are there any planned directed for patients, and what is the evaluation plan that you are proposing?

DR. RAMAKRISHNA: If the drug is to be approved and prior to launch, actually, all

components, we are planning to have everything reviewed by an independent focus group that will go to patients and make sure everything will be clear, understandable with regards to any messaging. This includes the website. This includes the medication guide. This includes the patient wallet card.

Our proposals have a third party review everything so that patients and their families from a layman's perspective would be able to understand the messaging that we are trying to convey with regards to the risks.

DR. MORRATO: Are you planning on doing any postmarketing knowledge, attitude, behavior surveys to test or evaluate the effectiveness of the communication plan?

DR. RAMAKRISHNA: Yes. We have not planned those at this time.

DR. MORRATO: Thank you.

DR. BIGBY: We are going to take the questions from Dr. Blaha and Dr. Tan, then we are going to take a 15-minute break. Dr. Blaha.

DR. BLAHA: A fairly straightforward

question. Michael Blaha at Johns Hopkins at the Ciccarone Center for Prevention of Heart Disease.

Simple question I think for Dr. Trager with respect to CC-110. This is a slide showing the effects of inhibition of the IL-17 receptor, I believe, and effects on serum cytokines. A comment was made about CRP levels not being affected.

I wondering, can the data be shown for CRP if that is available? My second follow-up question, were MACE events, although I know limited, stratified by prior CV status, i.e., people who already had existing cardiovascular disease and events in follow-up?

Question about CRP and then stratification by baseline CVD status.

DR. RAMAKRISHNA: Sure. I will ask Dr. Trager to respond.

DR. TRAGER: We can take a look at slide 1. C-reactive proteins were monitored through the trial. You can see that they were through the clinical program in general actually. This is from AMAGINE-3, the 12-week pool.

You can see from the median line, the second line down, levels were fairly low at baseline. The highlighted row there shows us the change from baseline in each of these groups at 12 weeks. And again, this is basically no change.

This observation was consistent in the population no matter what time point we looked at. We really did not see a perturbation of C-reactive protein level.

DR. RAMAKRISHNA: Dr. Kowey -- we will have Dr. Israel respond to your second part of your question.

DR. ISRAEL: Thanks for the question. The observation was that patients that had prior cardiovascular history or cardiac disorders did have a higher rate of MACE, but the study was not stratified based upon that.

DR. BIGBY: We will take the question from Dr. Tan. The remainder will be -- just remember what you wanted to ask, and we will get them answered later after the FDA presentation.

Dr. Tan?

DR. TAN: This is Ming Tan. This is a question related to [indiscernible] for Dr. Papp about the duration of the remission, but I am going to ask you statistically.

Are there studies done after discontinuation of the therapy? Do you have the data on those patients, how they do in terms of the duration of the clearance?

DR. RAMAKRISHNA: Duration of the effect after discontinuation of therapy? Is that the question?

DR. TAN: Yes.

DR. PAPP: I would first like to perhaps recast the definition of recurrence because it depends very much on the definition of recurrence as defined -- or relapse as defined in the protocol. In many protocols, it may be defined as a change in severity, in other words, reflecting a percentage loss of improvement.

In the case of brodalumab, recurrence was defined as a change in the PGA, which is not necessarily a robust measure of the actual extent

of relapse. However, if we bring back the slide, slide 1, what you see here is patients who were continued on either the 2 doses, the 140 or 210, which were studied in the core programs, and you see in the gray lines the loss of response in patients who were withdrawn from treatment. And you see that clearly the response rate drops fairly rapidly. And in keeping with Dr. Lebwohl's remarks, we are looking at the order of, say, 2 to 3 months to see a median loss of response, 4 months perhaps.

DR. TAN: Those patients are still being treated.

DR. LEBWOHL: On the upper line, those on the upper graph maintained on treatment. Those on the gray lines, where we see a loss of response, we can see that the median time to loss of response is about 16 weeks, give or take.

DR. BIGBY: Okay. We will now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during breaks among yourself or with any members of

the audience. We will resume at 10:55 promptly.

(Whereupon, at 10:39 a.m., a recess was taken.)

DR. BIGBY: We will now proceed with the FDA presentations.

FDA Presentation - Gary Chiang

DR. CHIANG: Good morning. I would like to take a moment and thank the committee for taking time of their busy schedules for helping us do this important work. I would also like to thank my colleagues in the consulting divisions for their hard work and opinions on this challenging application.

We will have quite a few speakers from the FDA today, so let's begin.

This is an overview of the presentations you will hear. The focus will be on the safety signals revealed in the clinical development program of brodalumab. You will also hear from an expert panel of FDA speakers with differing perspectives and recommendations. We acknowledge that the data is not only incomplete but also inconclusive. The

presentations are meant to provide the committee with a broad perspective for utilizing the available data.

A product description for brodalumab was introduced by Dr. Marcus. Here I will briefly discuss the pharmacology of the product.

This figure is the biological therapeutic targets in the cytokine network. Brodalumab is a human monoclonal antibody produced from the Chinese hamster ovary cells. In contrast to ixekinumab and secukinumab, which are direct 17A ligand inhibitors, brodalumab has a novel mechanism of selectively binding to the cytokine receptor and blocking the biological activities of multiple cytokines in the IL-17 family. This mechanism is distinctive in the biologic scheme.

The pharmacokinetics of brodalumab is exhibited by nonlinear PK with exposures increasing in a greater than dose proportional manner and the clearance of brodalumab decreasing with the increasing dose. Age, sex, race did not significantly influence the PK of brodalumab.

However, clearance and volume, distribution increase as body weight increases.

In subjects with plaque psoriasis, 1 week following a single subcutaneous administration of 210 milligram brodalumab, the exposure of midazolam, which is a CYP3A4 substrate, was increased by 24 percent over baseline administration.

Serum levels of IL-17A were higher after receiving brodalumab treatment compared to pretreatment levels. This is consistent with the mechanism of action for brodalumab as a receptor binder. When brodalumab engages in the target IL-17RA, IL-17A fails to bind to IL-17RA with reduced subsequent receptor-mediated elimination of IL-17A, resulting in excess IL-17A levels.

The IL-17 excess has been implicated in the role of inflammation as well as atherosclerosis due to mechanisms of cytokine regulation that we do not fully understand.

Efficacy overview. This figure denotes the clinical trial design for study 103 and 104 with

active comparator ustekinumab. Note the lack of placebo arm after the induction 12-week phase. Subjects receiving study drug are re-randomized after 12 weeks to multiple maintenance doses with all placebo subjects receiving brodalumab 210 milligrams. Ustekinumab is only an active comparator in 103 and 104, which are identical studies.

This is the results of the phase 3 clinical trials in psoriasis. Generally, the efficacy is good with over 80 percent achieving primary endpoint of PASI 75 reduction and a SPGA of zero to 1 in all three clinical trials. Brodalumab 210 milligrams was also found to be statistically significant in complete clearance as measured by PASI 100 against ustekinumab.

This graph was generated to look at the comparative rates for biologics across psoriasis products. Cosentyx and Taltz are the most recent additions and act on IL-17A cytokine system.

Safety assessments. This common adverse events table describes events greater than

1 percent, which was mostly equal across the treatment arms. Headache, arthralgias, and injection site issues were the most common events. Although these common adverse events do not individually suggest any causation, the combination of events suggest an influence of like constellation of symptoms, which may suggest a relationship to drug effects.

Serious adverse events from first dose to the end of study in system organ class was most common for cardiovascular events, infections, and infestations, and suicide behavior. This table highlights some of the preferred terms under the SOCs of interest. Infections, SIB, and cardiovascular events will be discussed in more detail.

To recap the safety issue, we will briefly touch on the neutropenia, malignancies, and infections, and then focus on the safety signals in the phase 3 clinical trials due to suicide ideation and behavior as well as cardiac events.

Specific monitored risks with monoclonal

antibodies includes infections, neutropenias, malignancies, and cardiovascular, cerebrovascular adverse events. Neutropenia was recognized early as an identified risk in association with IL-17 cytokine inhibition as well as the IL-17 family of cytokines that play a role in proliferation, maturation, and chemotaxis of neutrophils affecting G-CSF production.

Although neutropenia was seen in the brodalumab program, few subjects discontinued due to neutropenia, and none were associated with serious infections. Malignancies were uncommon in the clinical trials and generally were not related to investigational drug. The most common were non-melanoma skin cancers.

Infections will be further discussed in the next slide.

The IL-17 cytokine axis play an important role in host defense against infectious pathogens, in particular extracellular pathogens of fungi. We compared the rates of serious infections across the biologics for psoriasis. The most frequent events

in the brodalumab clinical trials were nasopharyngitis and upper respiratory tract infections.

The serious infections, fatal infections, per 100 subject-years are shown in the comparison table across for all biologics indicated for psoriasis. Serious infection rates were not that different compared to IL-17 products and fall within the range when comparing biologic products across the board.

In all subjects on brodalumab, there were only 2 reported serious opportunistic infections, 1 cryptococcal meningitis and 1 coccidioimycosis. Candida infections were common but of low severity in the clinical trials.

To recap the SIB safety issues, there were 6 completed suicides that occurred in all brodalumab development programs, 4 in psoriasis and 2 in other brodalumab programs. The psoriasis completed suicides were all male and of the age between 40 and 60 years old. Subjects were followed in the phase 3 trials out to about 2 years, and then all

studies were terminated by the sponsor.

For other biological programs, ongoing pharmacovigilance data continued to be reviewed, which informs the risk-benefit calculus. For brodalumab, it has been 15 months since any subject has been exposed to any drug product once the studies were terminated by the sponsor.

The 4 completed suicide profiles are reintroduced here in this study. Several interesting messages can be taken away from this table. Recognize the lack of relationship when evaluating the suicide events from the first active dose or from the last dose given.

Three of the 4 subjects in the psoriasis trial were re-randomized to the 210 milligram dosing from placebo, and all 4 subjects that committed suicide in the psoriasis trials were male. Note, 1 suicide was later adjudicated as an overdose but is included here in our SIB evaluation. In contrast, 1 completed suicide was evaluated with multiple negative C-SSRS and PHQ-8, but the subject committed suicide by jumping off

the roof of his apartment building.

Now, Dr. Ling will go over the agency's statistical review of the SIB events.

FDA Presentation - Ling Lan

DR. LAN: Thank you, Gary.

Next, I will present and review findings from Division of Biometrics VII. We analyzed the suicidal ideation using 120-day safety update dataset. This flowchart includes the safety population for psoriasis and other indications such as psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and asthma.

The plot shows indication with at least 1 event only. It illustrates the distribution of SIBs and the completed suicides by overall brodalumab usage and by indication.

SIB incidence was defined as proportion of subjects who experienced at least 1 SIB among the total number of subjects in the same trial. It was not adjusted by exposure time here.

In total, 44 of 6,781 subjects experienced SIB. The majority of the subjects received

brodalumab. Among brodalumab users, we identified 40 SIBs, including 35 SIBs in PsO trials, 3 in the PsA trial, and 2 in the RA trial.

There were 6 completed suicides, and all in brodalumab users, 4 completed suicides occurred in PsO trial, 1 in PsO trial, 1 in PsA and 1 in RA. SIB was not detected in brodalumab users of asthma and Crohn's disease trials.

For non-brodalumab users, 4 of 538 subjects experienced SIB, 2 in ustekinumab arm of PsO trial and 2 in the asthma trial.

Our primary analysis was to estimate incidence and incidence rate of SIB in the psoriasis safety population, which pooled all psoriasis trials, including one phase 2 and three phase 3 trials.

This slide summarizes the baseline demographics and the characteristics of PsO safety population by original treatment arm. As these characteristics were similar across arms, I will emphasize brodalumab arm here.

Subjects randomized to brodalumab arm

consisted of 69 percent men, 45 years of age on average; 44 percent enrolled from the United State; 29 percent with previous biologic usage; 21 percent with history of PsA; and 18 percent with prior psychiatric disorders, including 14 percent with depression and 3 percent with suicidality at baseline.

Due to the study design, we evaluated SIB in PsO trials by study phase. During the placebo-controlled phase, the first 12 weeks, 1 subject experienced an SIB event in the brodalumab arm and none in the comparator arms. Note that exposure time in this phase was short, and few events were observed. Therefore, it was not possible to compare incidence of SIB among brodalumab and the comparator arms in this phase.

At the end of the placebo-controlled period, the majority of the placebo subjects and some ustekinumab subjects received brodalumab. During the active controlled phase, 7 SIB events occurred in the brodalumab arm and 3 SIB events in the ustekinumab arm. The incidence of SIB among

subjects exposed to brodalumab, including subjects who switched to brodalumab after receiving ustekinumab, was 0.17 percent, and the follow-up time of adjusted incidence rate was 0.2 per 100 subject-years.

This table presents the incidence and the incidence rate of SIB by overall treatment arm from randomization to end of follow-up. The overall treatment arm was determined by 75 percent or more doses of the treatment received.

In total, 35 SIB events occurred among brodalumab users, resulting in the incidence of 0.78 percent, and the time of adjusted incidence rate was 0.38 per 100 subject-years with 95 percent confidence interval from 0.27 to 0.53.

We conducted a subgroup analysis to estimate the incidence rate of SIB events among brodalumab users by the baseline depression status and the suicidality status.

Baseline depression was determined by medical history of depression and usage of anti-depressants. Brodalumab users with history of

depression had approximately a sevenfold increase in SIB incidence rate than users without history.

Baseline suicidality was determined by eC-SSRS and an additional since the study start questionnaire. The sponsor defined the suicidality as unknown if the subject had a positive eC-SSRS response from the lifetime questionnaire and a positive score for the since the study start questionnaire but did not have a medical history of suicidality.

Brodalumab users with a history of suicidality had approximately 18-fold increase in SIB incidence rate than users without history.

eC-SSRS was implemented in the midway of the study. There was less than 18 percent of the safety population received eC-SSRS evaluation by week 52. We summarized the most severe on-study eC-SSRS responses through week 52 by baseline suicidality in trials 103 and 104. Trial 102 was not included in this analysis because the eC-SSRS was implemented when all subjects had completed the 52-week treatment period.

Of note, the SIB events described in this table were based on responses of the eC-SSRS only without incorporating the investigator-reported adverse events.

It should be noted that in addition to the subjects originally randomized to brodalumab, the second column, and ustekinumab, the third column, the all subjects column includes subjects randomized to either placebo or ustekinumab and who subsequently switched to brodalumab.

During the first 52 weeks of treatment, subjects in the brodalumab arm experienced numerically most severe on-study eC-SSRS response than those in ustekinumab arm regardless how the SIB responses were categorized.

Only 474 subjects in trials 103 and 104 received a PHQ-8 during the first 52 weeks, and the maximum score was derived from the response since last contact. During the first 52 weeks of treatment, subjects in brodalumab arm had numerically fewer, minimal PHQ-8 scores and more mild PHQ-8 scores than those in ustekinumab arm.

Biometrics VII conclusion on SIB are the limited duration of placebo-controlled phase did not provide long enough exposure time to observe or compare SIB between brodalumab and placebo arms. Brodalumab users with history of suicidality had approximately 18-fold increase in SIB incidence rate than users without history.

Our next presenter is Dr. Robert Levin from the Division of Pharmacovigilance.

FDA Presentation – Robert Levin

DR. LEVIN: Suicidal ideation and behavior are complex adverse events to assess, and these are often relatively rare events in trials and in general. As a result, we assessed data and information from several sources to put the SIB events in perspective.

In addition to the SIB and neuropsychiatric AE data from the trials, we assessed the medical literature regarding psoriasis and psychiatric morbidity as well as the impact of psoriasis on patients' quality of life and personal experiences.

Psychiatric and psychological factors are

estimated to play an important role in at least 30 percent of dermatologic disorders. Patients with psoriasis have a particularly high rate of psychiatric morbidity, including depression, anxiety, suicidal ideation behavior, substance use disorders, and other psychiatric disorders.

Various authors estimate that the background rate of psychiatric disorders in the psoriasis population ranges between 30 percent and 45 percent. In a study of psoriasis patients that used formal psychiatric assessments, demonstrated that 45 percent of patients met criteria for at least one psychiatric disorder based on diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders.

As demonstrated, the rates of specific psychiatric disorders in this study were as follows: dysthymia, 29 percent, also known as chronic depression; major depression, 15 percent; alcohol use disorders, 7 percent; generalized anxiety disorder, 5 percent; and panic disorder, 2 percent. All of these are risk factors for

suicide, another SIB. In this study, 13 percent of patients had current suicidal ideation or behavior.

Reported rates of SIB in psoriasis patients ranges from 7 percent to 21 percent based on a wide variety of assessment types. A large prospective cohort study in the UK analyzed the risk of self-harm by analyzing the hospital episodes, statistics, and national record linkage database.

The investigators looked at risk ratios for self-harm across numerous psychiatric and other medical conditions. As expected, the highest risk ratios occurred for psychiatric illnesses, including depression, bipolar disorder, schizophrenia, alcohol abuse, anxiety disorders, and eating disorders. For these conditions, the risk ratios ranged from 5.7 to 9.7.

For other chronic medical conditions, psoriasis had the fourth highest risk ratio after epilepsy, asthma, and migraine. The risk ratio for psoriasis in this study was 1.6.

Another large UK cohort study of psoriasis patients using the General Practice Research

Database estimated that the hazard ratios for depression, anxiety, and SIB were 1.39, 1.31, and 1.44, respectively.

All these studies describe the various strengths, limitations, and methodological concerns. However, overall, substantial literature indicates that psoriasis patients generally have an extremely high background rate of psychiatric illness, psychological distress, and substantially impaired quality of life.

In addition, biological aspects of psoriasis may also contribute to psychiatric disorders associated with psoriasis. These include chronic inflammation as well as alterations in the hypothalamic, pituitary, adrenal axis, and changes in the sympathetic nervous system.

We analyzed all neuropsychiatric events in the placebo-controlled, ustekinumab-controlled 12-week study. Of note, the brodalumab psoriasis studies did not exclude all patients with psychiatric history, but it did exclude subjects with unstable psychiatric illness.

Typically, drugs that cause CNS and psychiatric adverse reactions tend to cause a wide spectrum of neurological, cognitive, psychiatric, and behavioral adverse reactions rather than a single type of CNS adverse event such as suicidality.

In addition, such drugs often lead to a cluster of CNS reactions within a single individual. For example, drugs associated with an increased risk of suicidality, for example, anti-depressants and anti-epileptics, can also cause a variety of neurological, cognitive, and psychiatric symptoms. Such a pattern did not occur in the brodalumab studies.

There are relatively few neuropsychiatric adverse events in the controlled phases, as demonstrated in the next few slides, and there are no significant differences between treatment groups. However, there were no prospective assessments of psychiatric symptoms, and events were likely underreported.

The majority of psychiatrics AEs occurred in

subjects with a past or current history of psychiatric illness and treatment. These disorders included depression, anxiety, bipolar disorder, schizophrenia, substance use disorders, and previous SIB. However, there were some events that did occur in subjects without a psychiatric history, and some did lead to psychiatric treatment. None resulted in discontinuation.

Most of these AEs were isolated, transient, and did not lead to discontinuation or psychiatric symptoms.

As shown in the next few slides, the rates of psychiatric AEs in the controlled trials were low, and there were no significant differences between treatment groups. The data here are presented as rates adjusted for exposure in subject-years. As illustrated here, the rates of depression, depressed mood, and anhedonia were lower in the brodalumab group compared to the placebo and ustekinumab groups.

The rates for anxiety, panic, and panic symptoms were higher in the brodalumab than placebo

group. The rates for other psychiatric AEs were quite low, as seen in this slide.

The rate for non-completed suicide attempt was 0.3 in the brodalumab group and zero in the other groups. The brodalumab rate for insomnia was slightly lower than the other groups. The brodalumab rate for libido decrease was slightly higher in brodalumab group.

Two neurological adverse events in the controlled phases did appear to be related to brodalumab treatment. These were headache and paresthesia. In fact, headache was the most common neuropsychiatric event in the brodalumab studies for all treatment groups.

Headache accounted for 83 percent of all neuropsychiatric events in the brodalumab group, 68 percent in the placebo group, and 56 percent in the ustekinumab group. Most of these events happened quite early in the study and were short-lived and did not require treatment.

The rates of these other neurological symptoms were generally low, and there are no clear

patterns among the groups. The rates for dizziness in the brodalumab group was higher than the placebo and ustekinumab group. The rates for other adverse events were quite low as well.

The following slide presents some of the controlled data regarding depression and anxiety. One of the controlled psoriasis studies, study 102, included a prospective assessment of depression and anxiety symptoms specifically in the subset of patients who had baseline moderate to severe anxiety symptoms as measured by the Hospital Anxiety and Depression Scale or HADS. The HADS is a commonly used tool in clinical studies in a variety of medical indications.

As summarized in the table, subjects in the brodalumab group generally had greater improvement in depression and anxiety symptoms compared to the placebo group.

Conclusions, we have uncertainty about whether the signal for completed suicide is a drug-related risk related to brodalumab treatment. From the available data, we cannot conclude whether

or not suicide is a drug-related risk. These populations have a highly elevated risk of psychiatric disorders and symptoms, including SIB.

The controlled data do not suggest firmly that neuropsychiatric adverse events are drug related. However, we should note that the controlled phases were relatively short, 12 weeks, and there were no prospective assessments of neuropsychiatric events in this phase.

On the other hand, in the brodalumab group in the controlled study, there was greater improvement in depressive and anxiety symptoms in a subset compared to placebo.

The neuropsychiatric events reported in the uncontrolled phases was generally similar to that in the controlled phase with the exception of the completed suicides. All the completed suicides occurred in the open-label extension phase.

Information about these cases was quite limited and is extremely challenging to assess the potential relationship between brodalumab treatment and suicide.

Recommendations. We would consider approving the brodalumab application for the treatment of psoriasis broadly, or we could consider approving brodalumab only as second-line treatment for patients with an inadequate response to other biological treatments for psoriasis.

We should clearly describe in labeling the potential risk of suicide and other neuropsychiatric events and the study results regarding these events. We could also emphasize that this is not necessarily an established drug-related risk.

We should consider potential risk mitigation strategies. For example, the use of a prospective directed assessment of suicidal ideation behavior such as the C-SSRS and others could possibly and partially mitigate the risk of SIB. One could assess patients for the presence of SIB currently at a specific time point, which could inform management of such patients.

However, such tools would probably not prevent all suicides if there is a risk. Some

patients can acutely develop SIB even after a recent negative screen, and there can be falsely negative assessments depending on factors related to the subject and the rater. Such an assessment tool would not be fully effective or reliable probably.

I would not recommend excluding patients with a history of psychiatric disorders from brodalumab treatment because it has not been established firmly that there is a drug-related risk. And also, there are a number of patients, as mentioned with psoriasis, that have significant psychiatric disorders.

Our next presenter will be Andy Mosholder from the Division of Epidemiology.

FDA Presentation - Andrew Mosholder

DR. MOSHOLDER: Thank you. What I am going to do is take the next few minutes to summarize the Division of Epidemiology's assessment of the suicide risk with brodalumab. Here, I am acknowledging my colleagues who collaborated with this effort.

First, let me point out that we faced major challenges in evaluating this risk. The SIB events, as you have been hearing, were rarely reported in the placebo-controlled portions of the trials, and monitoring with the eC-SSRS was not implemented until after the placebo-controlled phases were complete, as we have talked about.

The exposure in the controlled groups was limited, and so it became necessary to make external comparisons to other psoriasis products, as I will describe on the next slide.

This summarizes the methods. Clinical trial data on suicide, suicide attempts, and suicidal ideation was extracted from regulatory submissions of the other psoriasis products in the formed of pooled summary data. We did not have access to subject level datasets.

It is worth nothing there are a number of caveats that apply to this approach. The use of historical comparisons in general is not optimal. Data are subject to heterogeneity in patient characteristics, follow-up methods, time periods

during which the studies were conducted, and ascertainment of suicidal events.

We did not have data for a subject level meta-analysis, as I mentioned, and we also did not always have data specific to psoriasis subjects alone. With those caveats in mind, let's review the findings for the other products versus brodalumab.

This is a somewhat busy slide, so let me walk you through it. It presents the rates of suicide in the trials of recent psoriasis products with rows showing data for each individual product. Sample size and exposure in person-years are in the left columns, then we have the numbers and rates of completed suicide on the right.

Person-years or patient-years, I'll just mention by way of definition, is a cumulative measure of exposure equivalent to one person receiving treatment for a year. That could represent 2 patients receiving treatment for 6 months each and so forth.

At the top, we see the 6 completed suicides

with brodalumab that we have heard about this morning, which occurred in something over 10,000 person-years of exposure, giving a suicide rate of around 57 per 100,000 person-years. I expressed the rates per 100,000 person-years because that is the customary unit for suicide rates.

Now, one of these 6, as we have heard, was adjudicated as a suicide by the coroner but that was questioned by investigator. And also in that regard, it is worth noting that review of the suicide behavior cases showed there are a number of very serious attempts, which only by good fortune did not result in completed suicides.

Next, I have highlighted the other IL-17 products for comparison. Ixekinumab had no suicides in over 6,000 person-years of psoriasis treatment, and secukinumab had no suicides in something over 3,000 person-years, though there was a suicide during screening and suicide with placebo in a trial for another indication. But between the two, there is close to 10,000 person-years with no suicides, which stands in contract to brodalumab.

And in fact, roughly speaking, the number of completed suicides with brodalumab was around the total for the other products in combination.

Now, the sponsor provided a systematic review of suicide in psoriasis biologics trials, which here we compared our review to the brodalumab data. Looking at the right-hand column for the rate of completed suicides, in our review, we found a rate of 14 per 100,000 per year, and the sponsor's systematic review found a rate of 19 per 100,000 per year, which is pretty good agreement.

If one were to add a published source, our review would have found a rate of 17, but that is still fairly consistent. It stands in contrast to the rates observed with brodalumab in the all trials dataset and the psoriasis trials dataset.

Let's look at that comparison in more detail in a next slide.

Can we quantify the excess in suicides that we have observed if that excess is a valid observation? As a thought experiment, consider the suicide rate from the sponsor's systematic review

of phase 3 and 4 psoriasis biologics trials as the expected rate.

The observed rate with brodalumab in psoriasis was 2.3 times higher. That's 44 versus 19 per 100,000 per year. This would translate to roughly 1 excess suicide per 4,000 or so person-years of brodalumab use over the rate observed with other biologics.

If one considers the entire brodalumab dataset, the contrast is even greater with a threefold increase representing 1 excess suicide with every 2600 person-years of exposure.

Now, this is changing gears a little bit, and we have seen these data previously. This is the analysis from the sponsor of the psychiatric adverse events in the placebo-controlled portions of the trials of 12 weeks in duration. You can see that regardless of the treatment, the rates were well under 1 percent for each, even for relatively common events like depressed mood or insomnia.

Now, the reason may be that such new onset events were, in fact, infrequent, but a concern

would be that these events were not well ascertained during these trials. I will show you how that will apply to suicidal ideation in the next slide.

The sponsor conducted an analysis comparing the rate of SIB events reported during treatment before there was monitoring with the eC-SSRS versus during the trial experience with the monitoring in place, and that's shown on the right. At the top, we see completed suicides that were 3 versus 1, fairly small numbers, but the rate turned out to be numerically rather similar.

For suicidal behaviors, actually, there was a slightly higher rate observed with the monitoring, and in fact, there were attempts that subjects reported to the investigator on their eC-SSRS responses. For suicidal ideation, there was a major difference with almost 10 times the rate of suicidal ideation being reported after implementation of the monitoring. The implication is that prior to use of the eC-SSRS, the investigators had been unaware of the majority of

subjects with suicidal feelings.

I will just point out Dr. Marangell mentioned that one of the psoriasis arthritis trials was done almost entirely with the eC-SSRS monitoring and found a single event of suicidal ideation. That actually is consistent with the rate shown here of 0.59 per 100 person-years because it looked like there was about 200 person-years of exposure-years in that trial.

That said, it is also important to remember that 2 of the subjects who committed suicide, 1 shown in this table and another from a trial in a different indication, committed suicide within a matter of days after completing a negative eC-SSRS response.

This is going to be the point that has been made previously. Dr. Lan covered this in her presentation. This is the sponsor's analysis showing how profoundly past psychiatric history influences the rate of suicidal events, and this is simply to make the same point graphically. Nonetheless, it is still the case that most of the

completed suicides did not have a known psychiatric history.

Our conclusions for the SIB analysis, first, there was a several-fold higher rate of suicide in the brodalumab clinical trials compared to the combination of other psoriasis biologics. There is an insufficient number of suicidal events in the double-blind trials for meaningful comparisons. Detection of non-suicidal psychiatric adverse events may well have been incomplete.

Monitoring with the eC-SSRS greatly improves detection of suicidal ideation and perhaps even suicidal behaviors. It is unclear whether it was preventative with respect to attempts or completed suicides. And finally, past psychiatric history profoundly influenced the rate of these events among the subjects.

Our recommendations, first of all, I think there is broad agreement that the data are not adequate to establish a causal relationship to suicide. However, to the extent that we are having to give that serious consideration, one might make

the case that, in the words of the regulations, there is insufficient information about the drug to determine whether the product is safe for use.

If it is approved, restricting its use to patients without psychiatric risk factors would reduce the number of events that occur among the brodalumab users, and that would actually apply regardless of the extent of causality.

Monitoring with the eC-SSRS or a similar tool would improve detection of these events and facilitate referral. Labeling and medication guide would have a place, of course, and we are not recommending a postmarketing observational study for SIB events at this time given the limitations of the electronic database studies for measuring outcomes related to suicide.

I will stop there, and I will turn it over to Dr. Jean Kim from the Division of Psychiatry Products for her remarks. Thank you.

FDA Presentation – Jean Kim

DR. KIM: Thank you, Andy.

The Division of Psychiatry Products was

consulted to provide our input regarding psychiatric adverse events, including suicidal ideation and behavior, that were seen in these brodalumab trials and to clarify whether these events were a primary drug effect and/or whether they reflected a background occurrence of SIB events in a patient population with higher rates of psych morbidity, as we've discussed; with higher than average rates of depression and SIB.

During the trials when concern over several suicides arose in 2014, our division advised implementation of the C-SSRS screening, which the sponsor did add in the middle of the trial's maintenance phase as well as adding PHQ-8 screening in May 2014 until the trials were closed by the sponsor in May 2015. Events prior to this implementation were retrospectively adjudicated using the C-CASA scale.

Regarding the question of any primary drug effect, a comparison between study drug and placebo was performed by me using data from the three phase 3 psoriasis trials for brodalumab. Due to the

trial design, the only placebo-controlled period we could analyze was the initial 12-week induction period after which there was a re-randomization of treatment groups rendering future cross-treatment comparisons unreliable.

During this initial 12-week phase, there was only 1 SIB subject that I adjudicated who was on brodalumab compared to none on the active control ustekinumab and none on placebo. The difference was not statistically significant, although the study power was too low to say definitively.

Other limitations of this finding relate to the short duration of the placebo-controlled induction period, the overall rare incidence of SIB events, and the later use of different adjudication scales and screening for SIB event detection between C-CASA and C-SSRS. Although, at least during the 12-week phase C-CASA was consistently used.

The other concern is that C-CASA, as per the Division of Epidemiology's discussion, is less sensitive at detecting SIB events than the C-SSRS.

So perhaps fewer SIB events were picked up during this period.

For observational purposes during the rest of the trial period into the maintenance and post-study period, I detected the following SIB events. On brodalumab 6 plus 17 plus 8 for a total of 31 additional SIB subjects treated with brodalumab after the initial 12-week phase through the last safety update period on November 2015.

For our division's conclusions, again, my review of the placebo-controlled phase doesn't really show a significant association for SIB event increase between drug and placebo, but this finding's generalizability is very limited. Accordingly, based on the provided study data thus far, no definitive conclusions are available about the relationship between brodalumab and suicidality.

There are ongoing concerns about the lack of ability to make any definitive conclusions about this relationship between brodalumab and suicidality and the adequacy of our currently

available pharmacovigilance methods to detect events during the postmarketing period and whether any proposed REMS recommendations would actually be helpful in preventing suicides if the risk factors for SIB remain uncertain in this population.

Suicide is not a one-size-fit-all category. As we have discussed, there are many types of suicide and potential risk factors contributing to it, which is why it is so difficult to prevent. Some suicides occur due to impulse control or impulsivity issues or acute sudden life stressors or other factors that are virtually impossible to prevent or detect beforehand.

A REMS might not be able to mitigate those types of suicides, especially if there is some sort of impulse control effect or unusual primary drug etiology or mechanism of action for suicidal behavior.

On the other hand, some events are able to be mitigated through psychiatric intervention and detection such as successful treatment of a primary depressive or psychotic episode leading directly to

suicidal thoughts or withdrawal of a medication causing a side effect like akathisia known to increase suicidal risk.

For now we don't fully know of any possible etiology for any potential psychiatric effects of IL-17RA blockade, although I guess in the literature review, there was some association with depression postulated with IL-17A cytokines.

Our conclusions. With regard to the question of whether background psychiatric morbidity in psoriasis patients is a contributing factor to increased SIB risk, it may provide some anecdotal and historical context to know although, of course, this is not an official head-to-head comparison study or analysis, that 6 suicides as seen in the brodalumab trials is higher than we typically see in our large psych drug trials.

In our trials, the patient populations have a 100 percent psychiatric morbidity with diagnoses like major depression, schizophrenia, bipolar, all of which are well known to have some of the highest risk of SIB events.

It is also possible that closer psych monitoring and screening in these psych trials might have provided more safety despite an arguably higher risk population, but that might also point to an issue in real-life clinical management where psoriasis patients may not have as frequent or close access to psych management.

Again, there is no known effective screening scale that exists for the prevention of suicide, so it is unclear if REMS will actually prevent SIB events if there is a true drug association. At least 4 of the brodalumab subjects who committed suicide had no disclosed prior psych history, and out of 2 suicides who had been screened after C-SSRS implementation, both showed no findings during screening.

Given the lack of specific data we have, our main recommendation is for the sponsor to perform an additional active controlled parallel group study with brodalumab focusing on SIB events and psychiatric symptoms likely of a similar long-term duration of at least 52 weeks. The active control

agent should be another psoriasis drug with no known history of this type of SIB risk.

The study can use C-SSRS and PHQ-8 and similar screening tools to monitor psychiatric events and would have the same adjudication method used consistently throughout the study. This study could potentially clarify any existing relationship between brodalumab and SIB events and/or any psychiatric risk factors and/or interventions to inform a future REMS or to determine whether REMS would be helpful. We may even deem a REMS to be unnecessary if no relationship is detected.

I would recommend that this study be done premarketing, given that other safe and effective psoriasis drugs without this SIB risk are already on the market. We acknowledge that this type of study would likely have to be very large and of consideration duration due to low SIB incidence and powering issues. We would be happy to assist in designing this type of safety trial.

Now I would like to turn the floor back over to Dr. Gary Chiang, who will be switching gears

from psychiatric to cardiovascular adverse events.

FDA Presentation – Gary Chiang

DR. CHIANG: I will now go over the agency review of the major adverse cardiovascular events for the brodalumab trials. MACE was defined as cardiovascular deaths, nonfatal MI, and nonfatal stroke. And the agency defined the time limit of within 42 days after the last treatment dose, consistent with the pharmacokinetics of the brodalumab product.

MACE was adjudicated by a committee for only trials 103 and 104. A total of 23 deaths was seen in the psoriasis clinical trials. Nine were CEC adjudicated MACE deaths. Sudden deaths included cardiac disorders like arrhythmia, cardiac disease with history of previous MI and/or heart failure, any cardiac risk factors leading to cardiovascular disorders, and seizure disorders that may have contributed to sudden death.

The baseline demographic revealed that 70 percent of the phase 3 safety populations were male and in the age range of 45 to 64 years old.

One-third had some form of history of cardiac or vascular disorder.

During the induction period of the first 12 weeks, there were 3 MACE in the brodalumab arm, occur all in the 140-milligram lower dosing groups. There was no time to event or event to dose relationship that could be established.

During the 52 weeks maintenance phase, incidence of MACE events was 0.8 in the brodalumab arm compared to 0.4 in the ustekinumab arm; 25 events in all occurred in the all brodalumab and brodalumab after ustekinumab arms with the incidence rate of 0.7 and a 95 percent confidence interval of 0.4 to 1.10.

This table shows the follow-up observation time adjusted events rate per 100 subject-years of MACE through to the end of the follow-up in the psoriasis subset. An incidence rate of all brodalumab and brodalumab after ustekinumab was found to be 0.6 with 95 percent confidence interval of 0.42 to 0.76.

A comparison based on the exponent Amgen

report of all biologics in phase 3 or 4 trials found a rate of 0.43 for all MACE events and a rate of 0.299 for myocardial infarctions. This is in contrast to brodalumab psoriasis trials where we see a rate of 0.6 for MACE and 0.8 for myocardial infarctions. Therefore, the cross-comparison event rate is approximately 1.4 times higher than the reported biological treatments from the Amgen exponent reporting.

A subgroup analysis of the MACE in brodalumab users revealed that age is a significant risk factor and that any prior cerebrovascular or ischemic heart condition predisposes the subject to MACE by 9-fold. With a history of cardiac or vascular disorder, the rate is increased by 4.7-fold.

In summary, no conclusions can be made for the placebo-controlled phase of the psoriasis trial. As expected, the incidence rate of MACE was higher in brodalumab users over 65 years of age, and those with ischemic heart disease had a 9-fold increase in rate of MACE compared to those without.

Brodalumab users with histories of cardiac or vascular disorders have a 4.7-fold increase in the incidence of MACE compared to those without a history.

Our colleagues in the Division of Cardiac and Renal Products was also tasked to review the data for MACE in the brodalumab application. Their conclusions were similar to our own. The evidence of MACE in phase 3 do not suggest an elevated risk. However, due to the higher predisposed risk that psoriasis subjects have for cardiovascular and cerebrovascular events, MACE should be included in the labeling of the product.

Now Dr. Mosholder will review the epidemiological findings for MACE events across biologics.

FDA Presentation - Andrew Mosholder

DR. MOSHOLDER: Thank you. This analysis corresponds to the one previously shown for the SIB events across psoriasis products, but in this case, the outcome is MACE. So all the previous caveats apply here as well.

Without going into too much detail, brodalumab had numerically higher rates of MACE and cardiovascular death than the other products, but the difference was slight, not the discrepancy seen with suicide. Here I am showing the brodalumab rates and the other IL-17 agents.

A few words about the TNF blockers, I could not locate analysis of MACE in submissions for TNF blockers, but all are labeled for heart failure, as was mentioned earlier this morning, though that is not usually included in MACE. Also, I will just mention there was published last month a meta-analysis suggesting a reduced rate of MACE with TNF blockers, but we have not reviewed that study.

Actually, this graphic was shown by Dr. Israel earlier this morning, but this just depicts graphically the rates across the products for MACE. You see the brodalumab rate in the middle there, numerically higher than the others but really with a lot of overlap and not a lot of precision in these comparisons.

Our conclusions, as we have heard, there is

an insufficient number of MACE events in the double-blind trials for meaningful comparisons. While brodalumab had numerically the highest rates, the rates were really fairly similar across products.

Recommendations. Obviously, a cardiovascular outcome randomized-controlled trial would provide the highest quality of data but would present challenges. There are postmarketing observational study techniques that could be applied. And also, one possibility would be to explore within the existing data whether there was a correlation between levels of IL-17 and risk of MACE.

With that, I will stop, and I will turn it over to my colleague, Dr. Jasminder Kumar, from the Division of Risk Management.

FDA Presentation - Jasminder Kumar

DR. KUMAR: Thank you. Today, I will be providing an overview of risk evaluation and mitigation strategies, or REMS, and discuss the risk management options available for brodalumab.

A risk evaluation and mitigation strategy, or REMS, is a required risk management plan that uses risk mitigation strategies beyond FDA-approved labeling. FDA can require applicants to develop and comply with REMS programs if a REMS is determined necessary to ensure the benefits outweigh the risks.

A REMS can apply to a new drug application, a biologic license application, and an abbreviated new drug application. A REMS can be required pre- or post-approval and is enforceable.

A REMS can include a medication guide or a patient package insert directed towards patients, a communication plan directed towards healthcare providers, or elements to assure safe use referred to as ETASU. A REMS must include a timetable for submission of assessments to determine if the REMS is meeting its goals.

Elements to assure safe use are interventions or other actions that healthcare providers may need to take prior to prescribing or dispensing a drug to a patient. ETASU provides

safe access to a medication with known serious risks that would otherwise not be approved or would be withdrawn.

One of more of the following elements may be included as part of a REMS: certification and specialized training of prescribers of the drugs; certification of pharmacies or dispensers of the drugs; dispensing or administration of a drug in a limited setting, for example, only in hospitals; dispensation or administration only with evidence of safe use conditions, for example, pregnancy tests prior to dispensing; a requirement for patient monitoring such as for specific adverse events; and a requirement that patients be enrolled in registries.

You heard Dr. Chiang and Dr. Mosholder discuss the risk of MACE and SIB earlier. The risks currently under consideration for REMS is suicidal ideation and behavior or SIB. As a reminder, SIB is defined as a completed suicide, a suicide attempt, or a suicide behavior and suicide ideation.

If brodalumab is approved, the risk management options to address the risk of SIB can include option 1, product labeling alone, which can include a medication guide; option 2, a REMS with a communication plan, which is what the sponsor has proposed; and option 3, a REMS with one or more elements to assure safe use to meet the goals and objectives of the program. I will be going over the details of these options in the next few slides.

Option 1 addresses the risk of SIB with labeling alone. Of note, labeling negotiations are ongoing. The sponsor has proposed a medication guide and a warning and precaution, which includes evaluation of patients for the risk of SIB. The sponsor has not proposed a box warning. Additional labeling options to consider include a second-line therapy indication for patients that have tried and failed other therapies and inclusion of a box warning.

When considering the use of labeling alone to manage the risk of SIB, it is important to note

that currently no other approved products for psoriasis have SIB listed in the label as it is not an identified risk for these other products at this time.

Second-line therapy for patients that have tried and failed other psoriasis treatments may decrease the risk of SIB by limiting overall drug exposure. However, it does not eliminate the risk in an individual patient who does receive the medication.

Inclusion of a box warning may increase prescriber awareness of the risk of SIB and provide information about specific patients that may be at risk for SIB but does not provide the specific tools to identify or monitor patients at risk.

If it is determined that label alone is not sufficient to mitigate the risk, option 2 and option 3 can be considered. Option 2 uses a REMS with a communication plan to manage the risk of SIB, which has been proposed by the sponsor.

This slide shows the goals of the sponsor's proposed REMS. The goals related to the risk of

SIB include informing healthcare providers about the risk of SIB, the need to counsel patients about the risk, referral to a mental healthcare professional, and education for patients on recognizing the signs and symptoms of SIB.

The sponsor's proposal also includes a goal to manage the risk of Crohn's disease exacerbation. However, the agency believes that this risk may be adequately addressed with the proposed contraindication for use in patients with active or history of Crohn's disease.

This slide lists some of the sponsor's proposed elements as part of the communication plan, including letters and brochures for healthcare providers, a wallet card for patients, and a REMS coordinating center website.

The sponsor proposes to target providers who will likely be prescribers of brodalumab. This includes dermatology, psoriasis, rheumatology, and arthritis professional societies. The sponsor proposes to make these materials available for up to 2 years.

A REMS with a communication plan may be used to reinforce the risk as described in the PI or to support implementation of an element of the REMS. A communication plan uses materials to focus on a targeted risk message, in this case, the risk of SIB. It may be more conducive to targeting a specialized prescribing population. As previously mentioned, for brodalumab, dermatologists or other prescriber specialties that treat psoriasis patients would be the focus.

Finally, a communication plan can provide prescribers additional information about how to screen patients for the risk of SIB. While a communication plan REMS can augment the REMS messaging, it will not ensure that the prescribers have reviewed the REMS material prior to prescribing the medication. The success of the communication plan may be determined or limited by sponsor engagement.

Data shows that a wide range, 13 to 83 percent, of providers recall receiving a "Dear Healthcare Provider" letter. In addition, a

communication plan is not directed towards patients and therefore, will not ensure that patients will receive the risk messaging before being prescribed.

If it is determined that labeling and a REMS communication plan are not sufficient to ensure the benefits outweigh the risks, option 3, a REMS with ETASU, may be required. A REMS with ETASU can target prescribers, patients, and pharmacies and may include one or more elements.

In the next two slides, I will be describing a number of risk mitigation strategies that are consistent with those used in the clinical trials. Elements to ensure safe use can include the following prescriber requirements: completion of training on the risk of SIB; proper patient selection and appropriate enrollment of a patient into the REMS program; counseling a patient on the risk of SIB; use of self-rated scales to assess a patient's baseline status; and periodic monitoring, assessment, and/or documentation of a patient's results using these scales.

If a REMS with ETASU includes targeting

patients, the following patient requirements can be included: enrollment in the REMS and acknowledgement of the risk, counseling from the prescriber on the risk of SIB, completion of initial screening and periodic monitoring for SIB, and reporting of any signs and symptoms to the prescriber.

The following can be required for a REMS with ETASU that include risk messaging, focus on the pharmacy or other dispensers of the drug: obtaining certification through the designation of an authorized representative; enrollment into the REMS and training of relevant pharmacy staff, establishment of procedures to verify that dispensing is only from certified prescribers, distribution of REMS-related educational material, and providing counseling at the point of dispensation.

A REMS with ETASU to manage the risk of SIB may include some elements of risk mitigation that were used in the brodalumab clinical trials. A REMS with ETASU will ensure that prescribers are

trained, informed of proper patient selection, and understand the need to counsel, screen, and monitor patients for SIB. It may be helpful in identifying appropriate candidates for therapy, possibly minimizing drug exposure.

Option 3, a REMS with ETASU, creates assurance that pharmacists are informed of the risks and creates an opportunity for further patient counseling at the time of dispensation. The REMS with ETASU can also ensure that patients are fully informed of the risks prior to initiating therapy.

Although REMS with ETASU can provide a larger impact on how a drug is utilized compared to a non-restrictive REMS, screening of patients for SIB may decrease but will not eliminate the risk of suicide. Although screening tools were used in the clinical trials, they may need to be assessed for appropriateness in dermatology practices.

In addition, an ETASU REMS may impact patient access or delay therapy if patient can only receive a drug from a participating certified

pharmacy or if documentation of monitoring is not received in a timely manner. Also, patients may need to see the prescriber more frequently, depending on the requirements under an ETASU REMS.

In summary, the serious risks for which requires consideration for REMS for brodalumab is SIB. Each risk management option beyond labeling provides different levels of assurance that prescribers, pharmacists, and patients have been educated and understand the risks and the safe-use conditions when taking brodalumab.

Risk management options would be limited to strategies that increase awareness of the risk but may not prevent occurrence of suicide. As we heard earlier, suicides still occurred in the clinical trials despite implementation of similar risk mitigation strategies to those I described.

The committee will be asked to consider whether risk management strategies beyond labeling are necessary; and if so, what interventions would be able to ensure that the benefits outweigh the risks of SIB. Thank you.

Next we will have clarifying questions.

Clarifying Questions

DR. BIGBY: This is the opportunity for the panel to ask clarifying questions to the FDA. Please remember to identify yourself before you ask the question. I should also let you know that this will be fairly brief. We are going to stop at 12:15 for lunch and reconvene at 1:00. All outstanding questions if you have gotten your name on the list, we will try to get to them.

DR. IRWIN: Michael Irwin. I had a question. I am confused about the two recommendations. One speaker suggested that they would not exclude psychiatric patients for treatment, and the other recommendation was that they restrict use to patients without psychiatric risk factors. That has a contradiction. So which is it?

I guess one of my biggest concerns is would a recommendation be more specifically placed on those individuals that have a prior history of suicide because it seems like that was the group

that was at greatest risk.

DR. MARCUS: I will go ahead and address that question. I'm sorry. Dr. Levin, go ahead.

I was just going to provide a general comment that reviewers were allowed to express their individual opinions about their recommendations. I don't know if it's come across well, but I think that people are fairly divided on their conclusions and recommendations. Hence, one of the reasons we're here in an advisory committee today.

But I will go ahead and let the individual reviewers speak to their specific recommendations.

DR. LEVIN: Bob Levin from pharmacovigilance. Yes, I was suggesting that if approved, we do not exclude patients with a psychiatric history. The main point is that, in my opinion, and maybe this is one point of consensus, that I think we haven't proved with certainty that there is a drug-related risk or there is not. I think we really do have uncertainty.

If there was a drug-related risk and the

risk was elevated in patients with psych history, that would be a completely different story. It would be probably clearer that we could consider exclusion.

The other point is that, as we have discussed, there is a very high rate of psychiatric symptoms or disorders in this population, so it might be difficult, in some ways impractical, or it would really severely limit the access to the drug. But I think the main point is that we haven't yet established this is truly a drug-related risk.

DR. MOSHOLDER: Andy Mosholder. I will just try to articulate the logic behind what I proposed. If there is the possibility that some suicides could be causally related to treatment and we don't know, then one way of reducing the harm in the treated population would be to target patients at lower risk for suicide, which would mean excluding those with a past history of relevance. That was the logic behind that proposal.

DR. BIGBY: Dr. Brit-tain.

DR. BRITTAIN: It's Brittain.

DR. BIGBY: Brittain.

DR. BRITTAIN: Yes. I have a question on slide 65, and I also wanted to thank both the sponsor and the FDA for really nice presentations.

I just want to get confirmation. This seems to be really the only sign of a signal that you actually have in the data that is comparative at all, and of course, it is not really comparative like randomized comparative. I just wanted to dig a little bit deeper here.

First of all, I would like confirmation that that is true, if you agree with that statement. But secondly, we heard from the sponsor there is different entry criteria that were used in their trials versus other trials. But it sounds like that wouldn't be relevant to any of these actual suicide cases, none of them would have been excluded in other trials; is that true?

DR. MOSHOLDER: Let me address that first. Based on our review of the cases, I believe only one of the 6 completed suicides had a history of psychiatric illness reported at entry at the time

of screening, in other words. There was a second one in which it was determined I think posthumously, although the sponsor, of course, can provide more details, but that is my understanding of the situation.

Your first point is well taken. That is actually the case. The signal here really amounts to the discrepancy in the number of completed suicides relevant to other development programs. We did spend a lot of time looking at suicide attempts, suicidal ideation in other programs, but those data were very difficult to compare. It is really this contrast of the 6 completed suicides that were left.

This is an attempt to quantitate what people felt, which was that was a large number of suicides for one development program.

DR. BRITTAIN: One other quick question about this table. Do you know if the follow-up distribution is similar in the other studies? The person-years is kind of a blunt metric because there could be a few people who were followed for a

very long time versus a lot of people followed very short. Do you have any sense of how they compare across the studies?

DR. MOSHOLDER: I think the basic answer is no, I don't have those details. These are just summary pooled data.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: I actually had a question related to the same slide for Dr. Mosholder. It kind of builds on that, and maybe it is just further clarifying. The sponsors presented data in their slide CC-103 in which they are reporting SIB, I think, using a more broader definition, not just the completed suicides but the other events. If you look at that data, they make the observation that ixekinumab is comparable in terms of the rate, if I add up rates there.

Since I understand in looking at labeling that ixekinumab labeling doesn't mention, I don't believe, suicide risk, so therefore, why are we raising it here? I just wanted to ask on that, is it really the completed suicides are the tip of the

iceberg that is really driving it, or when you look at the total events or when you consider the broad range that fall within the bucket of SIB events, are they more comparable?

DR. MOSHOLDER: Our feeling was that the focus should be on the completed suicides, that that is the biggest discrepancy for brodalumab. If one adds the suicidal attempts and suicidal ideation, I would agree there is less of a discrepancy versus the other products. But the gist of the signal was really in the completed suicides rather than those other nonfatal events.

DR. MORRATO: Okay. That does relate to your comment earlier around the surveillance bias that might have been existing because of how those other ideation and that was actually being capture may have underestimated, in other words, events So it makes it difficult to compare, particularly on that kind of measure across trials.

DR. MOSHOLDER: Yes. One might see that there was much more suicidal ideation reported in these trials, but that, of course, is most likely a

function of the monitoring. That is why I said we decided to emphasize, as I said, the discrepancy in the number of completed suicides as being the most important thing to think about.

DR. MORRATO: Thank you.

DR. BIGBY: Dr. Zito?

DR. ZITO: I have a number of questions that relate to whether -- are we looking at a class effect of this across this whole group of drugs, is one thought I have had. Then also, in terms of the relationship to dose exposure, I don't know if there has been any work here, that I've seen, that would give you some sense of whether the exposure to dosage is the same across -- relatively speaking.

I know it is hard. I understand it is quite hard to measure, but we are relying eventually on the idea that severe psoriasis is a risk factor for suicidal events. Yet, we have not talked yet about what criteria you would be using if the drug is marketed now to assure the risk is sufficiently high to justify taking the risk.

I think I have a couple of questions there, but I would like to know more about, for example, if a registry is proposed, what will the criteria be to assure that the appropriate patients are going to take this risk, the uncertainty of risk.

DR. MARCUS: I will go ahead and take a stab at your questions as I understand them.

I think that one question you are raising is whether we are looking at a class effect, and I would say that we are really focusing this advisory committee on brodalumab. And to the extent -- no other product with one exception, and that is apremilast, is currently labeled. That is not labeled specifically for suicide. That is labeled for depression. But other products do not currently have similar labeling.

To the extent that these events are rare and attempts have been made at cross-study comparisons, we have been talking about other products, biologics, that are approved for psoriasis. But this is really focused on brodalumab. And I think that you have heard about the limitations and

problems with cross-study comparisons that made these comparisons particularly problematic for a rare event such as suicide.

In terms of potency of the products, I think that the closest that we can really get to addressing the potency issue is just to look at comparative efficacy across clinical trials.

If somebody can pull up slide 30 from our presentation. Again, there are caveats with cross-study comparisons, but I don't think that they are as problematic when you are evaluating efficacy across clinical trials as with the suicidal behavior. Here you can see three different measures of treatment success. We have PASI 75 in red, the Physician's Global Assessment of zero or 1 in black, and then the PASI 100 in blue.

Brodalumab and ixekinumab are the only two clinical development programs where PASI 100 was measured. You can see here they are roughly comparable, and the sPGA of zero or 1, you can see again, it is highest with ixekinumab and brodalumab and roughly comparable to Remicade but slightly

higher than the others.

Does that answer your question?

DR. ZITO: Okay. Thank you.

DR. MARCUS: I think that is the best we can do in terms of answering your question about potency. We really can't address that.

DR. ZITO: The other point I had would relate to some of the REMS opportunities and whether if you would suggest a registry, in what way the registry would you be seeking to assure that the people that enter the registry are people that really want to take the risks or potential risk.

So if that depends on criteria, is it all-comers according to physician suggestion to join the registry?

DR. LACIVITA: Regarding the REMS question -- this is Cynthia LaCivita. I will answer that question for you. If it is a registry that's part of the REMS, each patient would be required to be in the registry to participate in the REMS.

If it is a registry that is part of a study outside of the REMS, more than likely, that would be a requirement for a sponsor to have the registry, but participation in the registry is normally voluntary, if that helps a little bit. And we haven't really discussed specifics with regard to a registry.

DR. BIGBY: Logistically, we are going to break for lunch. When we come back, we will do the open hearing section, and we will have time I think for clarifying questions for both the sponsor and for the FDA before we address the questions.

(Whereupon, at 12:21 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

Clarifying Questions (continued)

DR. BIGBY: Can we all get seated? We are going to change a little bit of what I said before lunch. We are going to finish the clarifying questions to both the FDA and to the sponsor before we go to the open public hearing.

Dr. Katz, you are up next for the FDA question.

DR. KATZ: Thanks. It's Ken Katz. I had a question for the sponsor I hope to ask, too, which relates to slide 92 about the RA trial where the eC-SSRS was done prospectively. I am wondering if there are any exclusion criteria for psychiatric or other related comorbidities in that trial.

Then I have a question for the FDA side, which is during the presentation --

DR. BIGBY: Hold on, Ken. Just a FDA question, and then we are going to finish the FDA.

DR. KATZ: No sponsor questions now?

DR. BIGBY: No. Right. After.

DR. KATZ: Okay. So the question for the FDA is we heard a lot about the numbers, but I guess I am hoping to hear from the FDA side whether the agency thinks that there is biologic plausibility or a mechanism of action for the SIB that we saw or maybe didn't see in the trials. The sponsor pointed out why that is not likely to be the case.

Does the FDA agree, or is there an explanation for why these events might have happened, scientifically speaking?

DR. CHIANG: Hi. Gary Chiang, FDA. Can you put up our slide number 125?

Our thoughts are purely theoretical at this point. We do have some evidence that treating with brodalumab increases the IL-17 from the pharmacokinetic studies. With the increase in IL-17, we also postulated that there is a mechanism by which IL-17 can affect IL-6. And as we know, IL-6 has some neuroinflammation postulated for CNS disorders that are related to the IL-6 cytokine. So in some ways, that is just purely theoretical

from what we have been discussing internally.

DR. BIGBY: Dr. Arkus?

MS. ARKUS: I have a comment plus a question. The comment is on the registry, I wondered if FDA would consider, looking at need for patient registry, the types of side effects that are attributed to this drug aren't minimal. They're very uncomfortable, living with long-term problems such as joint pain, muscle pain, pain in the throat from the impact of fungal infections, and the like.

Perhaps a patient registry where patients could talk to one another would help patients deal with these side effects and make them less depressed from day-to-day discomforts that are actually not minimal. Then a second registry for the doctors and perhaps social workers, psychologists to be involved with the patient to track the SIBs.

Just to make note, it looked like those suicides were all I think related to finances. The drug was successful, and all of a sudden, the

patient had to find employment, and it severely impacted several of the patients. Just looking like reading between the lines, the patient that was incarcerated, I am sure it affected finances, and the other patient also was managing finances.

So that was the common theme, severe financial impact on these patients. I was just thinking two registries.

A question I also had for -- I guess I will delay. I had it for the sponsor.

DR. BIGBY: Dr. Tan, question for the FDA?

DR. TAN: My question is about these 6 completed suicides. I think it seems to me there is only one, as I heard, who could have been screened as high risk for suicide. I was wondering, is that the case, first. And then what kind of algorithm, what kind of criteria would you use to screen?

DR. MOSHOLDER: Andy Mosholder. I think you may have been referring to something I said, which was at baseline or entry into the trial, there was only 1 of the 6 subjects who went on to complete

suicide who had a history recorded of psychiatric illness. There was a second of the 6 that was discovered posthumously when they were going back over the case.

DR. TAN: Based on the history of psychiatric disorder.

DR. MOSHOLDER: Yes. That was what I was speaking to there.

DR. TAN: All right.

DR. BIGBY: Dr. Irwin?

DR. IRWIN: My question is for the FDA, and it has to do with this issue about we are bringing together depression and suicide and conflating the two. I think suicide can also be an independent disorder independent of depression and represent an impulsivity.

I am really questioning whether there is any information about impulsive behavior, and particularly impulsive aggressive behavior, viewing that we know that inflammation from Emil Coccaro's work at the University of Chicago, that inflammation can contribute to aggressive explosive

behavior, and is there evidence that there is disorders and explosive behavior outside of just suicidality.

I should say the closest I saw that in the laundry list of symptoms that you are looking at was irritability, and there were just no differences in irritability and mood swings. But that is different than -- which really happened to an effective component.

The people that have these aggressive disorders are pretty much stable, and then they explore. Certainly, alcohol or drug use can precipitate those explosions, but they also can occur just out of the blue. But if they have an underlying high level of inflammation, they are at greater risk for showing those behaviors.

DR. MARCUS: I will provide a response for the FDA, but I do invite Valeant to provide a response as well. As you said, you saw irritability listed in the list of neuropsychiatric adverse events, and there was no appreciable difference between brodalumab and I believe placebo

or ustekinumab.

I am unaware of any adverse events reported of the type of aggressive behavior that you are talking about such that it would be coded as a serious adverse event or an adverse event resulting in discontinuation. But I do invite Valeant to provide any further input on that.

DR. RAMAKRISHNA: To give a response if we have seen any of those types of events, I will call Dr. Marangell to give her opinion or Dr. Hooper. However, just for a quick overview, we did not have any type of those explosive types of irritability events come through.

DR. HOOPER: My name is Michele Hooper. I am a rheumatologist. I have expertise in patient safety, including prior experience with the brodalumab safety program. I am a paid consultant, including coverage of my travel.

The issues of impulsivity, irritability, aggression are very hard to capture from a clinical trial dataset. We rely on preferred terms.

I would like to show you what we do have, if

I can bring up slide 1. There was one event of grade 1 aggression and one event of grade 1 impulsivity that was described in the entire program. These were very low grade, and they were not associated with any event of SIB.

There were 6 patients who were documented to have events of irritability, 4 of which were grade 1 and 2 of which were grade 2. Two were not associated with SIB. In brodalumab patients, of these 4, we looked at them as carefully as we could. These were not serious adverse event so we have some limitation in what we knew.

But one patient with a suicide attempt had had a prior grade 1 adverse event of irritability that resolved some time before their SIB event, and there was one patient with a suicide attempt who had irritability during a period of alcohol withdrawal. It was noted by the intake officer.

There was one patient with suicidal ideation and low grade irritability who also had bipolar disorder, PTSD, depression, alcohol abuse, and domestic and financial stressors who had worsening

of a number of these risk factors at the time of the suicidal ideation, and that included the irritability.

Then there was one patient on ustekinumab who had a history of suicidal ideation and bipolar disorder, depression, PTSD, anxiety, mood disorder, alcohol abuse who developed suicidal ideation, which was associated with what was described as irritability, depression, and insomnia related to marital and financial stressors.

DR. BIGBY: Dr. Zito?

DR. ZITO: I have a question related to slide 102 of the FDA's slides where you are mentioning options for labeling options, and one is a second-line therapy. And I wondered if you could just help us understand what the impact would be for accessing the drug under second-line therapy and would we know about, would it be actually measurable.

DR. MARCUS: Second-line therapy would be a recommendation in labeling that the healthcare providers would take into consideration when

prescribing medications for psoriasis. It would not constitute any kind of risk mitigation strategy in that there would be no formalized process. It would simply be a recommendation in labeling.

The goal would be to reserve the drug for those most in need of the drug because they have failed other treatment options, which would shift the risk-benefit assessment for those individuals.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: Thank you. Elaine Morrato. I had a question on FDA slide 107 around considerations for the use of communication plans and noted from the speaker that the success seems to be related to sponsor's engagement.

I am wondering now that the FDA has looked at many different communication plans and evaluations, do you have any advice for us or any information on what might be minimum level or markers of engagement? I am noting that a lot of what has been proposed by the sponsor is sort of one-time events, letters, et cetera. You might say they are mass communication and not really

interpersonal engaging. So I didn't know if you had other examples. That was one.

Then the other is just to clarify my understanding. The only way that the sponsor is required to do evaluation of their communication and if it is effective is if it falls within a REMS as opposed to just normal communication activities. They are not necessarily obligated to report back to FDA. Is that correct?

DR. LACIVITA: This is Cynthia LaCivita with the Division of Risk Management. I will answer your second question first.

Depending on what the REMS requirements are, we would come to an agreement on what the assessment plan would be for assessing those requirements. Things that are done outside of the REMS would not be under our purview to require an assessment on. If they were doing a communication plan that was outside of the REMs, we would not be getting an assessment plan from them or an assessment report.

With regard to communication plans, we know

that when sponsors are actively engaged and they actually go beyond just sending out a "Dear Healthcare Provider" letter, that the results seem to be somewhat improved. Although communication plans are providing information to stakeholders, it doesn't ensure that they follow the recommendations in the communication plans.

DR. BIGBY: Dr. Katz?

DR. KATZ: Thanks. Ken Katz. I have a question about slide 80, which includes the recommendation for an additional active controlled parallel group study with brodalumab compared with another psoriasis agent. It seems to me that psychiatric outcomes in psoriasis have not been prospectively and intensively studied in an RCT like the one that is being proposed, which poses challenges to then interpreting the data.

If brodalumab does worse, it is not clear if that active agent actually improved psychiatric outcomes. How do we interpret that? If they do the same, I don't know if you can conclude that they are both better or they are both worse than

placebo.

Maybe the FDA could comment on how that would actually help us answer this question.

DR. KIM: With regard to why one with active control instead of placebo control, just from an ethical perspective, it seems like you can't deny somebody treatment for that length of time. So that is why active control would be the intermediary goal.

Then I am not sure what you are saying in terms of if it is a known agent that we know has no known suicidal --

DR. KATZ: How do we know that I guess is what I am saying. It hasn't been --

DR. KIM: Based on prior data that the other drugs that are out there don't have that risk.

DR. KATZ: But I guess they haven't been studied like prospectively and intensively on terms on psychiatric outcomes.

DR. KIM: Well, it wouldn't be as perfect as using placebo control, but it would still give you some idea, a ballpark idea.

DR. KATZ: Thanks.

DR. BIGBY: Dr. Drake?

DR. DRAKE: Lynn Drake. I have two questions for the FDA. One is slide 40. It has to do -- every time I look at that, I get confused again because it seems to me that the nonusers versus the users, the percentage is almost the same.

Could somebody explain that a little more clearly to me? I don't understand. To me, it looks like there is not a difference per se. As a matter of fact, 64 percent or .64 percent -- yes?

DR. LAN: This is Ling Lan, statistical reviewer with Office of Biostatistics --

DR. DRAKE: I'm sorry. I can't hear you. I'm sorry.

DR. LAN: My name is Ling Lan, statistical reviewer with Office of Biostatistics. This is our analysis in the general concept to show without any adjustment for the exposure time and no adjustment to trace back one exact event what has happened.

Your question, to my understanding, is the

numerical difference of the SIB incidence between the brodalumab users and non-users.

DR. DRAKE: Seems like the difference is quite small is what I was getting at.

DR. LAN: These are for all indications, and at this stage, we didn't compare any comparisons because psoriasis program was not designed and consequently not powered to compare SIB and MACE such safety event across treatment arms. Therefore, we didn't perform formal statistical testing, and these are numerical summarizations of the incidence.

DR. DRAKE: Thank you very much. Then my second question has to do with FDA slide 53, Dr. Levin. It is two of your slides, Dr. Levin. It is both 53, and it is your summary slide of 60, that I can assess that you are not convinced that there is a cause and effect here.

DR. LEVIN: I think there is uncertainty, but yes, I am not convinced that either way we can prove the hypothesis that it is drug related or not, so I think uncertainty is the key. But I

think that the controlled data do not confirm there is a drug risk. It doesn't alone support it, but it doesn't mean that -- I don't draw the conclusion that there is no chance it is a drug-related risk.

DR. DRAKE: Did you look at data that was stratified according to disease severity? Was there any correlation there?

DR. LEVIN: No, we didn't. Maybe someone else can answer that question, but I will just say some general trends. We did notice that, generally, there were trends. As patients had improved PASI, a lot of them did have decreased depressive scores.

However, one major point is that depressive symptoms other than in the one trial, study 102, there was no systematic assessment of depression. There is some studies, a small percentage, that use the PHQ-8, but overall, I would say that there was not -- other than the one study, there was really no true systematic assessment of depressive symptoms or other psychiatric symptoms.

DR. DRAKE: Because some of the data that

was presented this morning, it almost seemed like if you treated them, there was less depression. There was a slide -- I can't remember -- I have got it written down. But there was less anxiety and less depression if they were treated than if they weren't treated, which makes perfect sense --

DR. LEVIN: Yes, that's right.

DR. DRAKE: -- because as their disease -- is that an incorrect thought?

DR. LEVIN: Well, it's accurate that -- yes, in one controlled phase study, study 102, for subjects specifically -- not every subject -- for subjects that on baseline by the HADS scale had either moderate to severe depressive or anxiety symptoms, that small subset over time generally did have more improvement of depressive and anxiety symptoms. But in that analysis, it was not correlated with disease severity. That is something that we could try to look at.

I think some of the data -- we could look at that. We have some limitations, but there were some trends, though. Aside from that HADS study, I

can't give you statistical conclusion or data off the top of my mind. But generally, we did see a lot of patients who had parallel improvements in PASI score and decreased.

DR. DRAKE: On the drug, yes, so thank you. That is helpful. Then finally, it seems to me that a lot of these --

DR. BIGBY: Lynn, Lynn --

DR. DRAKE: I'm sorry?

DR. BIGBY: That is the third question. We need to --

DR. DRAKE: Am I limited, Michael?

DR. BIGBY: Well, if I add the question, you said two.

DR. DRAKE: If I am, I'll quit. No, fine, go ahead. I'll quit, although other people have had three or four questions, but Michael's picking on me.

(Laughter.)

Open Public Hearing

DR. BIGBY: We have to move on to the open public hearing.

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

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

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

preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their considerations of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairman. Thank you for your cooperation.

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

MS. BROWN: My name is Tena Brown. My travel expenses and lodging were paid for Valeant Pharmaceuticals, but I am here on my time.

I would like to start by saying I am very

grateful to be here today. This is a great opportunity for me. I am a psoriasis patient, psoriatic arthritis patient, and I have had severe psoriasis and psoriatic arthritis since I was 13 years old.

It has been my life dream to be able to be in an opportunity where I could stand in front of a group of people, share my story, share what it has been like to have a disease like psoriasis and speak to a group of people that could actually make a difference for people like myself and 7 million other people that live with psoriasis.

I'd like to get started with -- I know there is a lot of distinguished doctors and scientists here in the room today, but I would like to share that I have credentials, too. And I have a PhD in psoriasis. People ask me how I got that, and I say, "Well, I've lived with it for 46 years. I think that qualifies me as an expert."

I do. I have a positively horrible disease, and it has affected every single area of my life. I travel around the country, and I speak, and I

educate. And I talk to doctors and nurses and patients because I know what it was like growing up with this type of a disease and looking like I have leprosy since I was 13 years old. So I am extremely passionate about educating people and trying to help patients that have this disease.

People say, "What is it like living with psoriasis, Tena?" I say, "Here's a day in my life."

I wake up in the morning, and it literally almost takes me almost two hours to get up and to stretch and to move, take a hot shower and to get comfortable. I wake up every single day, and I feel like I have been run over by a Mack truck.

I have pain. I have pain in my joints. I have severe fibromyalgia from lack of sleeping. I take a lot of medications, 15 medications a day, lots of supplements.

I have developed high blood pressure as a comorbidity because of my disease so I have to watch my sleep. I have to watch the foods that I eat. And just lately in the last few months -- and

I am going to speak to that here in just a minute -- I have developed some severe anxiety issues, and you will understand why here in just a few minutes.

The physical impact, this cannot be under addressed in any way. I have had full-body psoriasis. There is not an orifice in my body, my ears, my nose, my toes, my fingers, my genital areas, my entire life that has not been affected by psoriasis. Every single day I have to treat my body. I have to treat some aspect of living with this disease.

When I was 17 years old, I went to a rheumatologist. I woke up one day, and I had a lump on my breast bone. And they rushed me to the hospital and said, "Wow, we think you have psoriatic arthritis," which I didn't know what that was. And they said, "Tena, the treatment that we are going to give you could destroy your reproductive chromosomes, but we think it could help your joints."

So they sent me to a rheumatologist, and he

said, "Hey, Tena, we think you're going to be crippled in a wheelchair in the next five years. Your disease is so progressive already." So he looked at my parents and said, "We think you should find a convalescent home to put your daughter in because her disease is going to cripple her, and in the next five years, she won't be able to walk."

It was very devastating to me. It was very upsetting to me. I am sure at that moment, that's when I decided I was going to become a patient advocate and why I wanted to help other patients.

So I have to live every single day with the fear of what this disease is doing to my joints. It's devastating. As a teenager and even into my early 20s, I had purple hair because the only treatment for scalp psoriasis was tar shampoos and a lot of tar. So I had purple hair. I am going to show you a picture here.

Last but not least, genital psoriasis, this is a huge issue for patients. A new study that I just learned said that 92 percent of psoriasis patients interviewed said that they are so

embarrassed about their genital psoriasis that they are afraid to ask their dermatologist about it, and that they wished their dermatologist or dermatology nurse would ask them about their genital psoriasis.

Imagine how your life would be if every day you woke up -- and gentlemen, if you had a problem with psoriasis in your genital area, how that would affect you, and women, if you had that. It would be very difficult for every single aspect of your life. It is very challenging. I can speak from personal experience.

This is my last hospital visit. This is me on the left. I'm laughing because I want to cry. I was in ICU in Las Vegas. I had just had a hemorrhagic stroke in February, and I brought my lunch and forgot to put the food in there.

This is me with my hair care, what I have to do every single day to put my psoriasis. And no, these did not come off an internet site. This is my behind, and this is my back, and this is my side. This is how severe my psoriasis has been. Most of my life, it has been extremely painful. It

has been embarrassing. It has been debilitating. I've been on every single medicine, treatment, protocol you can possibly imagine.

These are my toes and my fingers. The toes on the right, those are acrylic toenails. I finally gave up. Women think nothing about wearing sandals in the summer, but in Texas and Oklahoma, it is hot. I never was able to wear sandals because my toes were so ugly, so I had some acrylic toenails. And I know they cause fungus, so I had to take them off.

It's a little quality of life thing that we women have to live with. But that's the way my nails have looked for most of my life as well because of my psoriatic arthritis. It's very embarrassing. Think about just shaking someone's hand, how difficult that is.

I didn't really understand the comorbidities until a few years ago, and then I realized -- my colon ruptured on Christmas Eve, and then I was in the hospital for another week. I've had so many hospitalizations. I can't count them all.

Now, this part of my life, having to deal with my colon and those types of issues is another huge aspect of my life. I have to watch what I eat. I have to watch my exercise and eating fiber and all that good stuff, very devastating. And now part of what I share with patients, it is real important to understand the comorbidities and how they can affect patients.

The financial impact, can I just say that I would be a rich woman today if I had all the money that I had spent on my psoriasis. I am 58 years old. I've had psoriasis since I was 13. I figured kind of ballpark between what I have spent and what my family has spent, easily conservatively, well over a million dollars over the last 58 years of my life -- or 46.

It is very expensive to have this disease. I have seen probably over 100 doctors, and I didn't have health insurance. A lot of my health insurance never covered preexisting conditions until last year. I just got my first insurance. I always had to pay out of pocket for my office

visits. Fortunately, I did make a pretty mean chocolate chip cookie so I learned how to bribe some of my doctors with cookies for my visits.

The financial burden, I have lost a lot of work. As I said, seen lots and lots of doctors. It is very devastating to have to stop your life midstream. Fortunately, my parents were very supportive. I moved back home. They would take care of me. But it is a very big financial burden for the family as well. My parents suffered.

My father had psoriasis, and I inherited it from him. Every single day of my precious daddy's life, he had to suffer looking at my skin. When he died in 1992, he had never seen my skin clear. And he grieved and cried and worried so much over the suffering that I had gotten because I had inherited it from my dad. My mother had to take care of me every single night, put medicine on my hair and my scalp.

Then I had a brother; any of you that have a sibling that have ever given you a hard time. My brother denied me. He was so embarrassed of me

because of my psoriasis and how ugly I was, and I had spots all over, and I had purple hair. It wasn't pretty, you understand.

But my brother used to go to school and tell people that he was an only child because he did not want people to know I was related to him because of my psoriasis. Then as fate would have it, he developed psoriasis, too. Isn't that great?

Personal and emotional impact, this is another part. Psoriasis patients live every single day with crippling fears. As I said earlier, mine is psoriatic arthritis. Fear of what psoriasis is going to do to me next is a daily stress every single day. I never know what's going to happen to my body, the comorbidities.

I was terrorized in school, and I have often felt that living with psoriasis is like living with an inner terrorist. It is very devastating to have to wonder what is going to happen to your body next, and I have had so many different challenges.

I have been asked to leave public places. I have been asked to leave swimming pools. A few

years ago, I was in San Francisco for the AAD meeting, went to get a massage at the Hilton, and they wouldn't massage me. I had a breakout of my psoriasis, and the massage therapist said, "I am not touching you."

I tried to explain to her that I wasn't contagious, but these are things that people every single day like myself have to deal with. Being asked to leave is very embarrassing. I thought no one would ever want to date me, love me, spend time with me because nobody ever wanted to touch me because my skin was covered with sores.

I always wanted to have my own family. I think most women, if you're the type of woman that wants to have children -- I know today a lot of women don't. But I always wanted to have a big family. And I was so terrified of bringing children in the world to have to live with what I went through that I opted not to have children. That was probably one of my biggest regrets in my life that I was never able to have children because of all the trauma I had gone through. I didn't

want to give that to another child. I robbed my parents of having a grandchild and myself of having a child because of this disease.

Comorbidities, this is something that I talk to patients, and people say, "Tena, why are you a patient advocate?" I don't want anybody else to suffer like I have suffered. I literally -- who was the doctor this morning that said -- who was it, Dr. Rapp [sic], said he saw somebody right in front of him in line.

So when I see somebody that has psoriasis or something like that, I go just a little step further. I go over there, and I touch them, and I love on them. And I touch their skin because people with psoriasis or skin diseases, nobody ever wants to touch us.

So I always talk to people, and I say, "Hey, if you have psoriasis." I try to educate them, and I try to help them deal with maybe some parts of the disease that they haven't thought about. And I try to share some of my experience. I'm a real touchy-feely person because I think when I was a

child, nobody ever wanted to touch me. So I love on people now all the time. I stop people, and I try to help them.

Comorbidities. I had to reschedule a heart appointment today with a cardiologist because I have to go to have a heart monitor because they found some issues with my heart, palpitations and issues that I have had. I had to reschedule a sleep study to be here today because, as I said, I have chronic insomnia, which affects me terribly.

In February, I gave a talk and walked off the stage, and couldn't feel my face and couldn't feel my arms, didn't know what was happening. They rushed me to the hospital. I was in ICU for five days, and I have a hemorrhagic stroke.

The doctors in Vegas said, "Well, Tena, only 15 percent of people survive what you've just had." And looked up, and I said, "You know what? It's another one of the risk factors. It's a comorbidity, part of what patients have to live with."

Thank God I'm able to speak to you-all

today. Can I just tell you how grateful I am to be standing here in this room able to share my story? One of the biggest challenges from my stroke was they took me off of all my anti-inflammatories.

In the past, I have been on five different biologic drugs. I have tried just about everything there is to be on for psoriasis, and as the experts have said today and I can testify to, some drugs work for a while. Then they quick working, and then you have to change. Then you have to rotate.

It is part of the challenge of living with this disease. It is very tricky having to manage all the different aspects of it. But one of the things they did is they took me off my anti-inflammatories, which is what I was using to manage my joint pain. When they took me off of my anti-inflammatories, they all said, "You will never take another anti-inflammatory ever after having this type of stroke."

Now my big challenge is I'm having to manage my pain level with psoriatic arthritis with basic pain medicine and Tylenol. Well, after colon

surgery, we all know what happens when people have colon issues and they take pain medicine. It is very challenging. So right now, I am not treating the part of my disease that I know is the most devastating which is my joints. So that's another challenge that every single day I have to deal with.

I have developed severe anxiety. I never had the anxiety like I have had today, but now I have to worry if my blood pressure gets high, I get anxious, I could have another stroke. So managing this is something that takes an awful lot of energy every single day.

The depression, you-all have been talking a lot about depression today and drugs. Forty-four percent of psoriasis patients are depressed. They're depressed, and it is frustrating. We have emotional issues because we're embarrassed, and it is a devastating disease to live with.

These are part of the things that I think -- as far as unmet need with this disease

state, people don't know about this, the average public and patients and people that I talk to every day, that's why I stop -- and people that are overweight -- and I meet people that are overweight that have psoriasis, and I say, "Please understand, you need to read and study because you are risk for heart issues with your comorbidities." So I try to educate. Then the liver disease, taking a lot of drugs, you can have liver disease as well.

Hard choices. This is one of the big challenges for patients. You want to know patients are sad, depressed, angry, cranky? We're difficult. We are. Every dermatologist I've dealt with said, "Man, sometimes psoriasis patients can be really tricky to deal with."

Then the biologic drugs came out, and finally, there was hope for the first time. When I started doing my patient advocacy years ago, there weren't any biologic drugs. I helped the very first biologic Amevive when it was launched. There were very few treatments for patients. I am so grateful now that there are treatments that

patients can have.

Part of the challenge of living with this disease is you have to say, well, is the treatment worse, or is living with the disease worse? Like right now, my joints are not being addressed. My joints are being dissolved every single second. My back x-rays, my rheumatologist is just mortified. He said, "Tena, your back is just dissolving."

This is part of the emotional, psychological aspect, dealing with do I do the drugs, do I deal with the guaranteed damage that I am going to have to my limbs. It is part of the struggle, and that is why I am so grateful there are options for patients now, and they can't come soon enough.

Patients need hope. One of the things I always say, patients need hope. We have progressive disease, and our progressive disease needs progressive treatments. Without treatments and new treatments, patients don't have any hope. I think that is one of the biggest challenges patients have. They feel very frustrated, and they need new treatments that can help them. I think it

is critical that new drugs come to the market that can help give patients hope.

I thank you so much for listening to my story today. I waited 46 years for this moment. It is truly an honor to be able to speak to this very distinguished group of people. Thank you for hearing my story.

Clarifying Questions (continued)

DR. BIGBY: Thank you so much for coming.

We are going to move on to the clarifying questions for the sponsor. Dr. DiGiovanna?

DR. DIGIOVANNA: John DiGiovanna. I am actually glad that we had to wait this long. I have a question for Dr. Marangell, and it has to do with one of the comments that she made. Clearly, as we just heard, psoriasis is a disease that is very chronic, it is very difficult to manage, and can be all-encompassing.

You mentioned a scenario where situationally induced -- SIB, where an individual who lost a fortune lost their identity and situationally related to the suicide ideation and behavior. I

wonder if there are not disease correlates from that.

This is the first drug that I am aware of that has a high frequency of complete clearing of the disease. And generally in the past, patients that are largely improved still managed the disease they had their whole life.

The first part of my question is, are there diseases -- and may this be one of them -- where the loss of identity with sudden dramatic improvement can be associated with suicidal behaviors? The second part is, are there instruments that are effective in identifying that in patients?

DR. MARANGELL: Thank you. For your first question, that is a hypothesis. And I think one of our dermatologists spoke to that a little earlier ago. And it's akin -- sometimes you'll see this with people who go for plastic surgery. And they are expecting so much out of the outcome because they've made that into the whole problem is this body part or this thing. For psoriasis, certainly,

it is very disabling.

But yes, rapid changes that are improvement can be very stressful for people. We see that on our psychiatric rating scales for stress. Good things like getting a job promotion are considered stressful, moving into a new home. So yes, that is something that we're well aware of in psychiatry.

The second part, are there scales? Do you mean to measure stress or for applicability --

DR. DIGIOVANNA: To identify those individuals who may have that as a precipitating factor, which could be used, for example, in managing the drug.

DR. MARENGELL: It's an interesting question. I haven't really considered it in the way of a psychological scale of someone's perception and how it changes. It is an interesting question.

I don't think that necessarily we would do the eC-SSRS in clinical practice, and I can talk to you about -- well, I am a big advocate of the national effort to include greater efforts to

educate doctors and patients about depression and about treating depression. Part of that is often having scales that are available, but they need to be individualized for whatever part of the healthcare system works for them.

If you're in a medical school system, you may have an electronic medical record and one particular scale that your hospital has incorporated towards that metric. If you are in a different system, VA system or a different part of the country, there may be a different scale with the same means. So mandating one particular intervention and one particular drug I think lacks feasibility.

DR. BIGBY: Dr. Walss-Bass?

DR. WALSS-BASS: Yes, Conseulo Walss-Bass. This question is for Dr. Trager related to the IL-17 signaling molecules on figure 110. My question was, were there other molecules other than the ones mentioned here were measured. In particular, I was interested in IL-1, IL-22, IL-23, GSF or GMCSF. Also, I was wondering whether

activation of TH-17 cells was measured, and if not, are you aware of this being done in preclinical studies?

DR. TRAGER: No. The factors that you asked about specifically were not mentioned in this study. The factors that are shown here, both the major inflammatory factors, IL-6/8, TNF alpha, as well as the ones listed in the bottom bullet in the parentheses, are factors that are specifically known to be over-expressed in rheumatoid arthritis, and that is, hence, the focus.

Nor has activation of TH-17 specifically been addressed, either clinically or preclinically, in brodalumab studies. Again, given the mechanism, I wouldn't predict that we would see an activation of TH-17 cells. There is some crosstalk between IL-17 and the cells that produce it, but that again is via the receptor that would be blocked.

I guess one additional point I would point there is the basic pharmacodynamic measure for assessing biological potency assesses the ability of white blood cells to respond to IL-17 in treated

patients. Those cells would include also TH-17. And basically, there is no residual response observed there. We have completely blocked the receptor in the white blood cells.

DR. BIGBY: Dr. Brittain?

DR. BRITTAIN: I think my question was answered already, but actually, maybe I have a new one. On the enhanced pharmacovigilance, starting on slide CC-116, I guess I'm not really clear -- actually, maybe CC-121 is a better slide to look at.

The plan is to do an observational study. What would you hope to get from the observational study? Who would actually be studied in the observational study? I assume it wouldn't be every patient prescribed.

DR. RAMAKRISHAN: I would just give you an overview of where we are with the observational study on working with the Corrona. We are in active discussions with the Corrona registry. It is an independent registry.

Who participates in this independent

registry are other biologic compounds that treat psoriasis and also non-biologics, so, for example, Cosentyx, the recently approved, is part of the active registry. We cannot participate in the registry until we are approved, and actually, Corrona does -- part of the discussion is once we are approved, if it is a recommendation of the FDA that it would be beneficial to participate, then only would we have the opportunity to participate.

If I could call slide 3, what you will see here is you will see what is included in this independent registry. What we are hoping to learn is this is the best possibility for us to get data across comparator products in terms of we get to see brodalumab data against the others, for example, the IL-12 and 23.

In a timeframe, which would be as uptake happens from physicians, this would allow the most realistic data points for us to take a look at, and it is truly independent.

Mark, if you would like to comment on some of the aspects of what the data you have seen and

how you have worked with Corrona.

DR. LEBWOHL: I think this is the best opportunity to get a comparable patient group. There are patients with moderate to severe psoriasis. They've been selected out for systemic therapies, and we are going to -- so we can come out and say the TNF blockers have this rate of serious suicide attempts and suicides compared to IL-12/23 blockers, ustekinumab or IL-17 blockers or brodalumab. It will be thousands of patients.

Having said that, these are rare events. There was discussion earlier of making brodalumab second line. And that, of course, would make that a different group of patients who ended up in that.

I will say if you look at the other drugs that have been approved for psoriasis, which have documented serious adverse events, tuberculosis, clearly increased; opportunistic infections, clearly increased; certain malignancies, clearly increased; demyelinating diseases.

None of them are second line, and here is a theoretical risk of suicides that is unproven, to

make that second line. And then they enter in the registry, and it won't be an equal registry at that point. But I do think that right now, it is the best chance we have to have similar groups of patients compared to one another.

DR. BRITTAIN: How would you know -- there must be reasons why certain patients would get prescribed different drugs, and how would you take that into consideration?

DR. LEBWOHL: That certainly does happen, and that is a flaw in every registry that is out there. If you compare any registry in the world, if there is a sign that you can avoid a side effect by putting in a patient who lacks a risk factor, then a patient with that risk factor might not be included. That is going to be a flaw in every registry that exists.

DR. BIGBY: Dr. Zito?

DR. ZITO: The example that was just mentioned about the treatment for rheumatoid is really a good one, but look at the work that went into needing criteria to be eligible to be treated

with Remicade, for example. The TB, for example, was all assessed and treated, or you were excluded. It's an example of a great deal of oversight into who gets into treatment for RA.

DR. BIGBY: Dr. Drake?

DR. DRAKE: I have three questions.

(Laughter.)

DR. DRAKE: I want to ask Dr. Marangell, on slide 88, you said that -- this was really interesting to me -- and you pointed this out -- that in other trials that have looked at other biologics, they have not had specific exclusion criteria for psychiatric disorders.

Do you think that skews this? In other words, if other trials had had exclusion criteria or had enrolled these patients, would we have seen perhaps a higher incidence of SIB?

I have a second question. I have two for you.

DR. MARANGELL: Well, we can't know for sure without randomized comparison if there would be a difference, but that is our hypothesis.

May I please have slide 1? This gives you an idea of some of the other medications and what the exclusions were. They do vary.

Ixekinumab was the most robust exclusion, which included the QIDS, which is a depression rating scale with the suicidal ideation item. They screen for suicide risk as well as history of suicide attempt. Substance abuse was in apremilast, and they actually had quite high rates as well.

DR. DRAKE: I would agree that is a theoretical question. I was just curious.

When you showed slide 97, which had to do with there was no imbalance -- said these data do not support a differential drug effect, you said you had a follow-up slide to that that you would show if anybody was interested. Can you show that?

DR. MARANGELL: Yes. Absolutely. The slide I am going to show you is very similar to the slide that was taken -- that the FDA showed, and the methods are identical. The difference is that we added the ustekinumab arm to this slide.

Remember, this is a randomized controlled trial. This is the 52-week randomized trial with an active comparator that has been suggested, although it did not include the eC-SSRS.

If I could please have slide number 1. On the right, you are seeing the brodalumab data that you had seen before where patients who have yes with either depression or suicidality do indeed have higher risk, but you also see if anything, a comparable number or a higher number with ustekinumab.

I believe this supports what we have been hypothesizing, which is it is not the drug; it's the diseases that we are treating.

Let me give you another example. If I could please have slide number 2. This is from the Lamictal, lamotrigine label in their 5.4 section. And I like to look at placebo for adverse event rates because that can tell you a lot about the underlying disease. Here you see in patients treated with Lamictal with epilepsy, the rates compared to the line under that, which are the

rates with people with psychiatric disorders treated with the exact same medication. In this instance, it is placebo. It is not the medication. It is the difference in disease states.

Now, should people with depression not get this medication? I strongly disagree with that. People with depression need treatment. They need treatment for all diseases. Thank you.

DR. DRAKE: Thank you very much. And my final question goes back to Dr. Lebwohl, please. Dr. Lebwohl, I was interested in your comment about using -- it relates to whether this should be a second-tier drug -- I mean a drug only after other therapies have failed. I think I get that. That would interfere with the registry. It also takes the judgment away from the treating physician.

You're a world's expert in psoriasis. How do you feel about that?

DR. LEBWOHL: I will say it is something that has not come out in the discussions. I had the availability of all of the new drugs, which were phenomenal, but the phase 2 data for this one

was better than the other two. And my toughest patients, the ones that were hardest to treat, I put on this drug.

There was a difference in the patients who entered the trial. And I believe that that is why their PASI 100 rate went from 63 percent to 41 percent in the phase 3 trials. They just had tougher patients. And it wasn't they were heavier. They were the same size. They had the same PASI scores. But when we tried other treatments in the past, they just didn't work as well.

So this drug got stuck with patients that were different than the other drugs. They were tougher to treat, and we finally had a drug that could actually clear some of those patients who I showed you.

Out of that group of patients now, I have at least three that I know of -- I had 50 total in the study. Probably, I'm really estimating that about 10 of them have been put on other IL-17s now, that their disease has come back only because access is so hard. Of that group -- and that number is an

estimate, but I know of three that have not done well on the IL-17s even though they did great on brodalumab.

I think it is just a tougher group of patients to treat. If you make this second line, think about the logic to that. We have drugs that we know cause tuberculosis, they're not second line. They cause opportunistic infections. They're not second line. They cause demyelinating disease for sure. By the way, the rate of that exceeds the rate of suicides in this study. They're not second line. So why would we make this one second line?

DR. DRAKE: Thank you very much.

DR. BIGBY: Dr. Katz?

DR. KATZ: Ken Katz. My question from earlier about slide 92, about that RA trial and whether participants with psychiatric comorbidities were excluded from that trial.

My second question is about the registry. I think I had concerns about interpretability of the proposed RCT. The registry, it seems to me, that

the data will ultimately be uninterpretable. And the reason I think that is there is non-systematic enrollment of patients. And then if doctors are just prescribing whatever they wish -- as a dermatologist myself who does that -- a patient comes in with a history of tuberculosis, they're not likely to get a drug that is linked to a reactivation of their tuberculosis. They're going to get something else.

If this drug comes on the market and there is something in the labeling or more about SIB and they have a history of SIB, I think it is highly unlikely that they are going to get this drug as a first-line agent or second or third. So in the end, I think there is going to be a huge selection bias, and in the end, we are not going to be able to say much from these data at all.

DR. RAMAKRISHNA: I will get first to the question around slide -- you had a question around rheumatoid arthritis, right?

DR. KATZ: Right.

DR. RAMAKRISHNA: The exclusion. I will ask

Michele Hooper to discuss the exclusion criteria on that trial and second line.

DR. HOOPER: When the amendments were put in place, it included incorporating the C-SSRS and the PHQ-8 into the ongoing psoriasis studies. Additional exclusion criteria were added to those studies that were enrolling, so the asthma study and the phase 3 psoriatic arthritis study.

If I could have the slide 1, please, you can see these are patients with a history or evidence of suicidal ideation by the eC-SSRS, which would be a score of 4 or higher, would be excluded. Patients that had a history or evidence of a psychiatric disorder or substance abuse that in the opinion of the investigator would have posed a risk to patient safety or interfere with the study evaluation procedures or completion would be excluded. And patients who had severe depression based on a PHQ-8 score at screening of 15 or higher would be excluded.

DR. KATZ: What percentage of these 320 on placebo and 639 on brodalumab were subject to these

exclusion criteria? Was it all of them, or was it introduced partway into enrollment?

DR. HOOPER: It was partway; 79 percent of the patients enrolled into the phase 3 study were addressed with these exclusion criteria. I do not know what percent were screened out. That data is not in the trial master file. It resides with Amgen in a different dataset, and we just don't have that.

DR. RAMAKRISHNA: I will ask Dr. Lebwohl to respond to the second half of your registry question.

DR. LEBWOHL: I think Dr. Katz is completely right about the quality of data that you get from any registry. If a patient came to me -- knowing what we know now about even the question of suicide, if a patient came to me and I was worried about suicide in that patient, there is no way that they would be getting this drug.

I will say that this is analogous to the one other drug we have in dermatology, which is Accutane, isotretinoin, where there have been some

high profile suicides, but the causality is still unproven to this day. I am not aware that there is a registry for that, but in the warning -- and it is not a black box warning. It is a regular warning about suicide in the isotretinoin package insert.

I can tell you that every single patient that I have put on isotretinoin is spoken to about depression. Several times a year, I call their psychiatrists if they have psychiatrists. In fact, if anyone has a psychiatrist and they come to me before they go on isotretinoin, I always call the psychiatrist. It is because it is there in the warning and it has gotten a lot of attention in the press.

I think that in some ways even though the data from the registry that we collect will be tainted in that way and I think you are correct that it will be, that is how doctors take care of patients, so we avoid those bad outcomes. So in the end, if we don't put patients who are prone to suicide on this drug and they don't commit

suicides, then we have won and the patients won.

I do think that that there is no question that we already are going to influence the prescribing of brodalumab.

DR. KATZ: Clearly, but I think in doing so, we are going to limit or undermine completely the registry's ability to answer the question of whether SIB is associated with this drug or not because those people who are more prone to SIB, right, are going to be given a different drug. And you don't have that option in something like isotretinoin. That is the only drug in its class.

I think the registry can be done, but the expectation that it will answer a question like this is zero, in my opinion.

DR. LEBWOHL: Yes. I think that your comment has complete merit. I will say a randomized controlled trial, how many patients are you going to study and for how many decades before you get -- if you are going to take a rare event and you try to find an answer, it is going to be an enormous study. There may not be enough psoriasis

patients to answer that question.

DR. KATZ: I was the one who also raised the concern about that trial, that two wrongs don't make a right.

DR. BIBGY: Dr. Sultan?

DR. SULTAN: Yes. The sponsor mentioned earlier that they had received approval in Japan. Can they share the indication in Japan and if there are any conditions with that approval, or any additional pharmacovigilance associated with that, and also whether they have received approval in other regions?

DR. RAMAKRISHNA: We have received approval in Japan. The indication is for moderate to severe plaque psoriasis. There are no restrictions. There is no special pharmacovigilance plan put in place by the PDMA. And in terms of other regulatory areas, we have submitted the application in the EU, in the EMEA. It is under review currently.

DR. BIGBY: Dr. Marder.

DR. MARDER: Yes. For Dr. Ramakrishna. If

I understand your postmarketing pharmacovigilance, that there would not be any prospective systemic evaluation of suicidal ideation. Am I right about that?

DR. RAMAKRISHNA: What we have proposed in terms of the postmarketing plan, the risk management approach for brodalumab is there is no further SIB specific study planned.

DR. MARDER: There's what?

DR. RAMAKRISHNA: There's no further study planned.

DR. MARDER: There is no further study planned?

DR. RAMAKRISHNA: Correct.

DR. MARDER: So the issue about whether or not the drug is associated with SIB would go unanswered. I am sympathetic to Dr. Katz that without -- I don't know whether it needs to be done preapproval or post-approval, but without randomization and systematic evaluation, I think this -- isn't it plausible that this question would go unanswered forever about whether or not this

drug increases suicidal ideation?

DR. RAMAKRISHNA: If I could respond to that, all the data that we have for brodalumab does not support a causality, and we do not see any data that would push us towards a causality for the event of SIB.

What we have seen is what has been published in the literature and what is known with regards to psoriasis is that the underlying comorbidities were very existent, and SIB is a fact of psoriasis patients. Additionally, to power a study based on such a rare event as we have seen in this population with high comorbidities is highly impractical. As you said, it may never lead to a conclusion or a definitive outcome.

DR. MARDER: But if you considered suicidal ideation as a proxy for later suicidal behaviors, I think the power issue might be tractable.

DR. RAMAKRISHNA: Understood, but at this point, we have not planned for any specific study.

DR. BIGBY: Dr. DiGiovanna?

DR. DIGIOVANNA: John DiGiovanna. I'd like

a little more information about the Corrona registry. For example, how does it work? Is enrollment required by the patients as a condition for them to get the drug? How are the patients assessed? Are they specifically assessed by some sort of a mechanism? Who does the assessment and how often, and does this continue posttreatment? Because some of the suicides that are in question have occurred substantially after brodalumab has been discontinued.

DR. LEBWOHL: The registry is actually well in place, and it is modeled to some extent after a very successful rheumatoid arthritis registry that was run by Corrona. The NPF partnered with Corrona to establish this registry. There is a scientific advisory board.

But the bottom line is the patients are -- 120 currently investigators -- our goal is 200 -- have agreed to participate. They recruit patients. The patients are offered small compensation. It is $20 every time they are interviewed, and they are interviewed twice a year.

It would be in conjunction with their routine visits usually. It is a live interview.

That is anticipated to go on a minimum of 8 years, so they would continue to be followed for those 8 years. This is, again, well in place, and there are several pages of questions that they fill out. In my experience, it takes a little bit more time the first time that they are interviewed. It is fairly comprehensive, but then when they come in for the follow-up visits, it is actually fairly fast because often not that much has changed from one visit to the next.

DR. DIGIOVANNA: So Patients need to be solicited.

DR. LEBWOHL: Yes, that's correct.

DR. BIGBY: Dr. Arkus?

MS. ARKUS: Ms. Arkus. Thank you for the elevation. It's a question for Dr. Ramakrishna. The question I have is, does this drug have an effect, and what effect would it have, on fertility, pregnancy, and the developing fetus?

DR. RAMAKRISHNA: Sure. We have studied the

compound in preclinical development, and I will call Dr. Israel to respond to the data around that. And for further clarification, I could also call Dr. James Trager who could also respond.

DR. ISRAEL: Thank you. We have seen no safety signal in pregnancy. We have had a number of patients pregnant on the trials. No safety signal has been detected. It wasn't definitive, but there were pregnancies that have carried through to term.

MS. ARKUS: [Inaudible -- off mic.]

DR. ISRAEL: Right. And, Dr. Trager, if you want to talk about, had some preclinical data surrounding pregnancy.

DR. TRAGER: Yes. Again, so similarly in the preclinical or nonclinical program, pregnancy was assessed both in cynomolgus monkeys as well as in rats. Essentially, no signal emerged in the monkeys. The rats were indistinguishable from the controlled group by all measures of prenatal, neonatal development.

DR. BIGBY: This is Michael Bigby. I have a

question for the sponsor, but it is about FDA slide number 30. In your introductory remarks, you said that Siliq was the only drug that had PASI 100 activity. This slide shows that it and Taltz have similar PASI 100 numbers. In different slides, you had PASI 100 numbers of something like 68, then 51, and this slide it is 41.

Cosentyx, I don't think reported PASI 100 nor did ustekinumab, but they probably do have numbers. Just comments about relative PASI 100s among the drugs, especially the IL-17s.

DR. RAMAKRISHNA: Absolutely. I will call up Dr. Pillai, who did the efficacy presentation, to get an in-depth review of our PASI scores. As presented earlier, we have the PASI scores for ustekinumab, Stelara, because it was the active comparator in two of our phase 3 trials.

DR. PILLAI: Yes. What I had presented in my efficacy presentation about the 60 percent, and even Dr. Lebwohl had mentioned, was that was in the phase 2 study. So we had 63 percent PASI 100 response for the 210-milligram dose. When we moved

into the phase 3, larger, much more robust studies, the rate, as I have shown you -- can I have slide 2, please -- was close to 42 percent.

This is when we were comparing directly to ustekinumab in the AMAGINE-2 and 3. In addition, I think Dr. Papp had presented the PASI 100 comparisons -- not a comparison. These are PASI 100, which have been registered for multiple different products.

Maybe I will let Dr. -- I can bring up slide 1. This is what he had presented. Essentially, 41 is a mean for all the three studies together, and then we had the three phase 3s. Of course, these are similar numbers for the first two with what the FDA presented.

The other numbers, it was not that they were not conducted. They were not backed off the package insert. They were part of advisory committee meetings, and these data have been presented in previous. That is how these numbers were put together.

Of course, for us, just so we are clear with

respect to brodalumab, ours was the only product which had a predefined primary endpoint, and this was comparing to ustekinumab in two replicate studies. These are key points, which I know I have emphasized, but I just want to make sure that everyone understands ustekinumab, as Dr. Papp and Dr. Lebwohl expanded, they were the gold standard. They were really one of the best drugs available at that point.

DR. BIGBY: Dr. Zito?

DR. ZITO: Julie Zito. My question is to go back to the Corrona registry. I am interested to know is there a formal assessment of the severity of psoriasis to enter the registry and how much time is spent on detection of risk of SIB.

DR. LEBWOHL: Yes. It's moderate to severe psoriasis as required by the drug, and we actually do an evaluation of psoriasis severity. The two most important endpoints for what we are looking for are serious attempts and suicide, and the milder endpoints, which would be suicidal ideation, are not captured.

DR. ZITO: Just a follow-up, you said that you are assessing severity. Does that mean that the whole range of severity qualifies, or is it restricted?

DR. LEBWOHL: You would not get into the registry if you didn't have moderate to severe psoriasis at some point. The entry to get in requires that you have started on a systemic therapy within the past year. You could come in clear at the time of the evaluation. What we would try to do is record what the severity was, but the point of the registry is to look for serious adverse events over time and other questions as well.

In terms of what we are looking at here, again, things like serious suicide attempts and suicides would be captured and MACE events and other side effects.

DR. ZITO: Thank you.

DR. BIGBY: Dr. Katz, and this will be the last of the questions for the sponsor.

DR. KATZ: Thanks. Ken Katz. I wanted to

go back to that PASI 100 slide again and ask you if you could put confidence intervals around those, if those exist. Nominally, I think brodalumab looks higher. I am wondering if confidence intervals exist or numbers needed to treat to get an additional PASI 100 score compared to some of the other products on the market. It is the one that the sponsor put up recently.

DR. RAMAKRISHNA: Dr. Katz, you are referring to Valeant's side, correct --

DR. KATZ: Valeant's slide that had the --

DR. RAMAKRISHNA: -- the confidence, and it rolls around.

DR. KATZ: -- around PASI 100 scores. So one --

DR. RAMAKRISHNA: Versus the others?

DR. KATZ: That's right. And if you have numbers needed to treat to achieve that additional PASI 100 score, which I imagine is probably pretty high. I am just concerned about the claim of better PASI 100 numbers, if the data don't actually support that.

DR. PILLAI: Correct. The goal was not to claim what Dr. Ramakrishna had stated as well as Dr. Lebwohl is we have registered the highest level of PASI 100. The placebos in general in these moderate to severe psoriasis studies are in the zero to 2 percent, and it is very small. Generally, it is not the same.

So the goal was not to show -- this was not to claim that we are superior to any of the ones. We have shown that we are superior to ustekinumab in the PASI 100 in our phase 3 studies. We have not done head-to-head studies with any of these other products. But the goal was just -- yes, just pick out the PASI 100, which is our distinguishing feature for brodalumab, and we wanted to make sure the committee gets a flavor that it is one among the highest in terms of PASI 100.

DR. KATZ: Right. If you are saying it is a distinguishing feature, but to me, it is very close nominally to the ixekinumab number. If there is a confidence interval around them, I would bet they overlap. In that sense, it is maybe not that

distinguishing.

DR. RAMAKRISHNA: We don't have a slide with the confidence intervals around it. We could see if we could during a break generate and come back to you with that, Dr. Katz.

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

Dr. Marcus, will you give the charge to the committee?

Charge to the Committee - Kendall Marcus

DR. MARCUS: Risk-benefit assessments in regulatory decision-making are informed by science, medicine, policy, and judgment in accordance with the applicable legal and regulatory standards. You have heard a great deal of information this morning about the brodalumab development program and the various analyses that have been conducted by both the sponsor and the FDA as well as input from

various experts. Variations in clinical and scientific judgments among FDA experts can lead to differing individual opinions and conclusions.

We would like you to consider today the adequacy of the safety evaluation for suicidal ideation and behavior as well as major adverse cardiovascular events. We would like to hear your discussion and conclusions about the overall benefit-risk profile of brodalumab and any risk management strategies that you may take into consideration if you find that the benefit-risk assessment is favorable. Additionally, we would like to hear input about postmarketing studies and clinical trials.

I am providing information on regulations that inform our decision-making. Approval of an application can be considered after FDA determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.

FDA may consider refusal to approve an application if the application does not include

adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested.

It may refuse if the results of tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling, or if the results do not show that the drug product is safe for use under those conditions.

Additionally, if it is considered that there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in proposed labeling, FDA may consider refusal to improve an application.

When considering whether to implement a risk evaluation and mitigation strategy, FDA considers the seriousness of the disease or the condition to be treated; the size of the patient population; the expected benefit of the drug; the expected duration of treatment with that product, I should say; and

the seriousness of the known or the potential adverse events.

The questions under discussion today are whether the safety data for brodalumab suggests a signal for suicide ideation and behavior, major adverse cardiovascular events. We would like you to vote on whether the overall benefit-risk profile of brodalumab is acceptable to support approval for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

If you vote yes, we would like to note if you believe that labeling alone would be adequate to manage the risks or if you think that certain risk management options for the suicidal ideation and behavior beyond labeling should be implemented.

Finally, we would like you to discuss the need for postmarketing studies or clinical trials if you approve for approval in question number 2.

Questions to the Committee and Discussion

DR. BIGBY: Before I open the panel for discussion, I am supposed to read the question so

it goes into the record, not because you don't know what the questions are.

Discussion question 1: Discuss the safety data for brodalumab. Do the safety data suggest a signal for suicidal ideation and behavior, major adverse cardiac events? If you believe there is a safety signal for SIB or MACE, comment on possible approaches to further evaluate these signals.

Anybody would like to comment first, or we'll take -- Dr. Blaha?

DR. BLAHA: We spent a lot of time talking about SIB, but from a cardiology point of view, I will make a quick comment about MACE. As someone who is used to seeing thousands of MACE events and doing analyses in large epidemiologic studies, it certainly is hard to make judgments off a few events. But I don't see a significant safety signal for MACE. I think that is consistent with what FDA thought as well.

I will just comment on that and say I don't right now see a safety signal for MACE, but this question of whether cytokines raise or reduce risk

of cardiovascular disease is an open one. There are ongoing studies with other biologics to try to reduce events. This is an open question that could well be that this has a benefit on cardiovascular events, but I don't see any significant safety signal for MACE, in my opinion.

DR. BIGBY: Dr. Walss-Bass? I'm sorry.

DR. WATERS: David Waters. Since we're talking about cardiovascular, I agree with Dr. Blaha the patient population here has an average age of 45, which is a little bit young for cardiovascular events, but they are high in risk factors, and they have high levels of inflammatory markers so that increases their risk.

I think to do a clinical trial to look at cardiovascular events would really be impractical because you would need a huge number of patients. I think the mechanism is a bit dubious so that I would agree that there is no real increase in cardiovascular risk.

DR. BIGBY: Dr. Brittain?

DR. BRITTAIN: With respect to SIB, it looks

like, as we've talked about before, the only possible indication is the 6 suicides that were seen, the completed suicides, and that is compared to the other study drugs, nonrandomized comparisons, some suggestion maybe threefold higher. But the number is 6. So if it had been 4, would we even be here today?

I think it certainly raises a concern, but it is really nothing more than a suggestion. I don't think we can say we know for sure there isn't a problem, but I think it is just unknown what it means.

Ideally, the only way to find out would be a randomized trial. It sounds totally impractical for suicide to be the endpoint in a randomized trial. I don't know whether it would be practical to have SIB as an endpoint in a trial and whether it would be possible to possibly do that post-approval.

DR. BIGBY: Dr. Lotrich?

DR. LOTRICH: This is Frank Lotrich from Pittsburgh. I agree with the comment that

comparing the 6 suicides in a very high-risk population with much fewer suicides in the population screened to not be suicidal is comparing apples to oranges.

That said, there is a very reasonable biological plausibility for why IL-17 receptor blockade would contribute to suicide. One would be through the kynurenine pathway that was brought up earlier this morning.

It is known that IL-17 does, in fact, induce higher levels of kynurenine, and we see higher levels of IL-17 in these subjects. Given the correlation between kynurenine and the known glutamatergic effects in the brain that it has, that is one plausible biological pathway.

A second biological pathway would be simply that there are IL-17 receptors in the brain and both the receptor levels and IL-17 levels increase during inflammatory diseases. If the receptor antagonist doesn't get into the brain because it is an antibody, the increased IL-17 levels that get into the brain would presumed to be doing

something.

All of this is complete hand-waving speculation, but at least it does lend some biological plausibility to that. But I will limit my comments to that for now.

DR. BIGBY: This is Michael Bigby. The drug is clearly very efficacious. The big problem you have is that you have 6 completed suicides in a situation where in comparable studies in many other situations you don't have 6 completed suicides. And there's a lot of hand-waving about what to do with this information. No matter what we do here and what we advise, that is not going to go away.

I think that patients who take the drug and doctors who prescribe the drugs should be made aware that this occurred in clinical trials, and it is actually, I would say, a fairly big number for a randomized controlled trial.

I think that the biological plausibility is very weak, and I think there is going to be a consistency on the panel that there is no MACE signal.

Dr. Marder?

DR. MARDER: Steve Marder. I would agree that the number 6 can't be ignored. It has to be seen as a signal until it is proven otherwise. On the other hand, I think that the process for showing whether it is a signal will take a very long time.

I am going to make the argument, I guess in a subsequent question, that this might be an issue to address better post-approval than preapproval because the study that would need to be done would have to least a year. For subjects, it would require a substantial population with relatively intensive monitoring, and it was unclear how it could be powered. It would be preventing an effective medicine from getting on the market.

DR. BIGBY: Dr. Katz?

DR. KATZ: Ken Katz. I see a nominal in some cases but not statistically significant increase in suicide ideation and behavior and possibly in MACE, but it seems within the range of what has been seen, but maybe on the higher end.

From the SIB perspective, I think the biological plausibility is limited, and it doesn't seem to fit the pattern of other medicines in terms of their SIB profiles when they're concerning. I think it is a signal, but I don't really think that it should preclude moving forward with the medicine.

In terms of possible approaches to evaluation, I think that sponsor's suggestion of enhanced pharmacovigilance and enhanced communication plan are both reasonable. I think the registry is not something I would support and might even muddy the waters, so I don't favor that, and I don't favor the RCT that was proposed by a member of the agency previously for the reasons that I elaborated on before.

DR. BIGBY: Dr. Walss-Bass?

DR. WALSS-BASS: I do have concerns regarding any potential long-term effects of the elevated IL-17 measurements that were found. I do think there was a plausible biological pathway, but the IL-17 pathway has not been as extensively

studied. It is only now studied in terms of its effect on the brain.

In fact, we do know that IL-17 increases levels of other cytokines that were not measured, and that can lead to activation of TH-17 cells, which produce not only IL-17 but IL-22. IL-22 receptors are found in the blood-brain barrier, and it has been shown that they can cause leakage in the blood-brain barrier, so the TH-17 cells can enter. And those are actually how microglial cells are activated in the brain.

Another concern is that activated TH-17 cells, in fact, do have long-term memory. The fact that one of the slides that was shown that the suicide events happened variable in terms of after the last dose of treatment, I think can be consistent with this long-term memory of TH-17.

Again, this is all just hypothetical, and I am not saying that this should be a reason to not approve a drug. But I do think there are potential concerns. I don't know if there is a way to measure these further, do an immunological panel or

not.

But going on to psychiatric patients, it also concerns me because there was a lot of consistent evidence that psychiatric patients have an underlying overactive immune system as it is, so they cannot turn off when their immune system is active or stressful events, or anything that causes their immune system to then activate; that they cannot turn it off. So again, that causes concern from a long-term concern beyond what was measured here.

DR. BIGBY: Ms. Arkus?

MS. ARKUS: I agree with Dr. Blaha about the MACE events not being really clear and defined, so very difficult to put that into the mix. But as far as the suicide ideation and behavior, the suicides, as was mentioned before, two of the victims of this were actually very successful at 100 percent alleviation of their psoriasis.

The indication was, well, you look normal, so get back to work. And these people are not ready to get back to work. When specifically

stated, the woman lost her social security disability.

So I would like to see more involvement in social security and looking at ameliorating this level of involvement. That's why financial matters are critically important for these patients.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato. I just wanted to add a few thoughts to some of the comments that I agree with that others have made. As I think about this, whether or not it is a safety signal, I just have a couple things I did note.

I agree that the focus is on the completed suicides, but I find it interesting that both the FDA's and the previous sponsor's independent systematic review were yielding comparable estimates relative to what is known on the other data. That is what made me take note.

The other piece is that when you hear from the Division of Psychiatry Products that these 6 suicides, as Dr. Bigby was saying, in a development program is typically higher than what you would

normally see among psychiatric drug trials in which you have enriched patient population most at risk for these kinds of event. I take note with that.

I also note that in the trials when greater surveillance methods were incorporated, you did see an increase in rates of suicidal ideation. So that might suggest that was there some underestimation, even in this trial, around those kinds of events. Now, we can't definitively know because it wasn't prospectively analyzed.

But I just will also close because I know part of our vote is based on judgment, and I have seen other drugs in which sponsors make the argument it is all in the background rate. And that does not always pan out to be the case.

So I am just naturally skeptical when that is the argument that I hear. While the biologic plausibility hasn't been definitively shown, it hasn't been ruled out, either. So for me, with what others are saying and these points, that is why I am coming down that there is a signal that we should be considering.

DR. BIGBY: Dr. Tan?

DR. TAN: Yes, I just want to echo that. I think the completed suicides, these numbers are running low because of the -- in comparison with the background rate, I am convinced this is higher by looking at all the data. But only this psoriasis, but it was looked at in psych trials, patients, and so on.

This is a matter of how do we assess the risk-benefit ratio. What here is the problem I think is risk is difficult to manage. I think if there is any convincing way to manage the risk of SIB, that would increase my confidence for the putting forward of this drug.

DR. BIGBY: Dr. Drake?

DR. DRAKE: Yes, Lynn Drake. I tend to approach it as kind of a simple perspective, and that is what is good for the patient and a risk-benefit ratio. It seems to me from what I have heard today that the benefit from this drug has tremendous potential for these patients who are absolutely miserable. The patients that we take

care of, they're ill. People tend to think it is just skin disease. It is not just skin disease. It is skin disease, and it affects the whole body, as you've seen, including arthritis and all the comorbidities.

I think we have a drug here that is potentially, hopefully at some levels, a bit of a game changer and could really help these patients. I think the risk of it, I don't want to ignore the 6 suicides, but I agree with Erica that it is just 6. So I tend to bend a little more on that.

I think that to me this is a suggestion and not a signal, and I also think that the sponsor's suggestions about labeling, enhanced PV, and communication are actually reasonable. I would like to see this drug out and about so that we could use it on these patients who are in so much trouble.

DR. BIGBY: Dr. Zito?

DR. ZITO: Julie Zito. I do see a signal for suicides and attempts when we look at the study incidence in comparison to the pooled data for all

the others, and it is on the order of about three and a half times greater. It suggests to me -- and I am also very impressed with the effectiveness data, but I do believe we are skilled at handling a postmarketing arrangement with real teeth that would assure, either through your registry but with really appropriate access for the registry that might be involved so that we really know that the people who have failed prior treatment are the individuals that are getting access to an important drug for them.

DR. BIGBY Dr. DiGiovanna?

DR. DIGIOVANNA: John DiGiovanna. I don't see a signal for MACE, and with respect to SIB, I think at this point, it is a judgment matter which can be looked at in any one of a number of ways. To me, that means we really don't have the data to be comfortable in a unanimous way that there is a signal.

I think it is quite clear that the drug fills a strong need. It is a drug which does more than what is available, and I think it should be

available. I think it should be approved. But I like the idea of getting more data, and I like the concept of postmarketing arrangement with real teeth because I think that is probably the only way to actually get an answer to whether there really is a SIB signal or not.

DR. BIGBY: Ms. Smith?

MS. SMITH: I'm a mom. I'm not a scientist. Whether there are signals or not, that is beyond my scope. But I am concerned about the suicides. I am concerned about some of the other things leading up to it. But I am also concerned about patients. I have a 24-year-old who is on her fourth biologic for arthritis and psoriatic arthritis who's been on drugs since she was 2 years old for all of this. The patients need more. I think with proper postmarketing surveillance and everything, we can make this an option for patients.

DR. BIGBY: Dr. Irwin?

DR. IRWIN: I do not believe that there is a signal for the MACE. I do think there is a suggestion of a signal for the SIB, but I do think

there is evidence of a strong signal for those patients who have a prior history of suicide attempts for suicide risk.

I would recommend that approaches really target those particular individuals, possibly for excluding those people with a past history of suicide from these studies, and also that we evaluate very carefully that this suicide may not be behaving as, like I said, depression, but may be behaving more like an impulse disorder. That would really require much more careful scrutiny and monitoring of the suicide risk independent of simply looking at depressive symptoms.

DR. BIGBY: Dr. Drake?

DR. DRAKE: Thank you very much, Dr. Irwin. I just wanted to comment that as a dermatologist, sometimes our patients I think have suicidal tendencies because of the disease. In other words, they are so depressed. I would hate to see that patients deprived of a drug that might help alleviate those particular signs and symptoms being denied access to drug, but maybe we could do it in

consultation with good psychiatric care and oversight to make sure that we are not messing up.

But the second thing I want -- the main thing I punched my button for is I forgot to mention that I think we can go overboard with sometimes of things. I don't think this ought to be a second option. I think if the doctor thinks this is a first option and is in the best interest of the patient, that we should not force them to have tried some other option if this seems to be the best option. Thank you.

DR. IRWIN: I wish to clarify that it is not just simply suicide ideation I'm talking about. I'm talking about excluding people who have actually shown an attempt to try to kill themselves, and those are very high risk individuals --

DR. DRAKE: Oh, yes. I wouldn't disagree with you at all.

DR. IRWIN: -- across all -- and some of those have never had a depression, and those are the patients that may be actually manifesting the

suicide in this particular study.

DR. DRAKE: Can I ask you a question to follow up? If a patient has tried suicide because of their disease, would you consider -- I don't have a right or wrong answer. I am really interested in your opinion.

If you have had somebody who said I tried commit suicide because I hurt and I can't live with this disease anymore, it has destroyed my life, would you try a drug like this if you thought it might help them?

DR. IRWIN: That is a really big decision. I think the issue for me is that if I was working with a patient and would be able to carefully monitor that suicide very carefully as a clinician and really incorporate in the plan, I probably would. But I would be very concerned about how this drug is going to be delivered in the clinical setting. And it is not going to have the level of psychiatric expertise that is available for that patient in that setting. That is the concern that I would have in a postmarketing way about ruling

this drug out without that level of really very high level of psychiatric expertise that is going to monitor that suicidal risk.

DR. DRAKE: Thank you very much. I think I understand what you're saying. I will go back to my original thing, just proper labeling and make sure it is in the label and there is a clear understanding. Thank you.

DR. BIGBY: I know that the FDA likes to hear from everybody, so there are a couple people who haven't commented. Would you like to? Dr. Sultan?

DR. SULTAN: I have nothing further to add right now. Thank you.

DR. BIGBY: Dr. Bilker?

DR. BILKER: I guess I just want to say that I think brodalumab has shown high efficacy for psoriasis, and I personally think there is a slightly increased risk. But I don't think it is proven for SIB, but I think that the risk-benefit ratio here warrants approval nonetheless.

DR. BIGBY: Dr. Rudorfer?

DR. RUDORFER: Thank you. Matt Rudorfer. I like what Dr. Drake said before about a suggestion as opposed to a signal. I think that a very basic issue here that I have been struggling with is that we are used to seeing, at this level of a development program, basically efficacy data before moving on to effectiveness. I think that the dilemma here is that the previous biologics did mostly efficacy trials, and then we skipped here to effectiveness of all-comers, so we have all this noise in the data.

When I say efficacy versus effectiveness, I mean ideally ruling out comorbidities for this phase 2 to 3 trial so that we would have cleaner data to work with. I can appreciate with maybe a 45 percent rate of psychiatric comorbidities that might be difficult. But I'm also mindful of the fact that as a drug development program goes forward and one drug gets marketed, and then another and then another and then another, by the time we're at this level, maybe even the patients available to enter a clinical trial are mostly

folks who have been resistant to other drugs; are unusually complicated; or as we have seen here, have all sorts of very complex comorbidities that really make it hard to find cause and effect.

I am thinking certainly the 6 suicides are worth noting, and I think all clinicians should be aware of that. But I wouldn't see not having this drug available for folks who could benefit from it.

DR. BIGBY: The last requester was Dr. Lotrich.

DR. LOTRICH: Sure. Thank you. I guess I would second that. And the reason I come to that conclusion is guided more by the history of interferon, which started out similarly where there is this kind of a signal with maybe some suicides, followed by retrospective chart reviews that didn't really demonstrate much, followed by actual prospective assessments of emotional lability where suddenly you could start getting the signal, study it, and use that to guide therapeutic care.

With interferon, it started out with the exclusion, we're not going to treat people who have

a past history of suicidal behavior. It was eventually discovered that with good psychiatric care, you can treat just about everyone safely. The point is how do we get there to where you can get everyone who needs the good psychiatric comorbidity care needed there.

I think at this point in the absence of a lot of information, that the best way to get there truly is letting the physicians know that these 6 suicides occurred, there's a potential signal there, use that wisely, and leave it at that until further information is available.

DR. BIGBY: At the end of this discussion, I am supposed to summarize what the committee just decided.

(Laughter.)

DR. BIGBY: Sitting where you are, I find that this is the most difficult thing to do, and I hope I at least satisfy some of you.

I think we all agree that there was no MACE signal. I think for the sponsor, the fact that you had 6 completed suicides in your development

program is an unexplained issue, but it nonetheless is a problem. Whether or not it is drug related, I think there is considerable debate on the panel. But somehow clinicians and patients need to be aware of that as a fact.

Then beyond that, I think there was disagreement about the utility of having registries. Some felt that they would be helpful. Others felt that it wouldn't answer the question at hand.

I think there may be a majority in favor of evaluating patients who are high suicide risk perhaps unless they have psychiatric clearance, excluding them from the drug.

There was an interesting suggestion made to try to identify patients who would actually be more likely to be suicidal as they got much better. And then I think there is considerable debate about whether or not the proposed enhanced communications are adequate to address the issue of 6 completed suicides.

I think this is a good time to take a

15-minute break, and we will discuss the remaining three questions after, followed by voting. So 15 minutes -- actually, why don't we just plan to come back at 3:15.

(Whereupon, at 2:58 p.m., a recess was taken.)

DR. BIGBY: We're going to reconvene. Is the committee all here? I think so.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will 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 have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or wish to change your vote, you may press the corresponding

button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote for the screen into the record. Next, you will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reasons why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

The question number 2, the vote question is, is the overall benefit-risk profile of brodalumab acceptable to support approval for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy? Vote A, yes with labeling alone to manage the risk; B, yes only if the certain risk management options for SIB beyond labeling are implemented; or C, no.

(Vote taken.)

DR. BIGBY: Press the buttons again. There

are two that are unrecorded. It is not the letter you press. It is above where it is blinking. There are two that are unrecorded. It is not the letter you press. It is above where it is blinking.

CDR VO: Press the button again where it is flashing. Just keep pressing.

(Laughter.)

(Vote retaken.)

LCDR SHEPHERD: For the record, 4 voted A; 14 voted B; zero voted C.

DR. BIGBY: We will now open the question to discussion. We are going to around. Everybody has to state your name, how you voted. Please provide a rationale for your vote. If you voted for A, please describe the labeling you would recommend to manage the risk. If you voted for B, describe the interventions or tools you believe would help mitigate the risk of SIB in addition to labeling.

We will start with Dr. Waters, and we will go around.

DR. WATERS: I voted A. I almost voted B.

I think the drug is obviously efficacious. Don't think there is a cardiovascular signal. I worry about the 5 or 6 suicides, but I would think that a black box warning would be helpful in that regard.

I also strongly feel that having a registry is useful. If you follow a couple of thousand patients on the drug for 5 years and none of them are -- only 1 or 2 of them commit suicide, it shows that doctors have learned to use the drug properly and avoid the patients that are at risk.

Last comment is it is unfortunate that the control period was so short and in so few patients because you turned what is a randomized clinical trial into something that is really not very controlled.

DR. BLAHA: Mike Blaha, Hopkins. I voted yes, approve answer choice B, which I believe was consistent with what the sponsor proposed. And I'm okay with what the sponsor proposed as a plan, including the registry that we just spoke of.

I believe there is a signal or a suggestion for SIB, although I would love to see a risk

adjusted incidence. We saw a lot of unadjusted incidence. I realize the numbers are so small, but it would be great if we could adjust for risk factors for suicidal ideation because I realize these patients are enriched in risk factors.

It is difficult to compare this data, but in a registry format, if we could gather the risk factor data and provide a risk-adjusted incidence and then compare that, that would be great. I realize that that would be complicated, but I do think it would be worthwhile.

I think the benefit clearly outweighs the risk, but I was struck by -- as a cardiologist. I am not someone who treats psoriasis, but I was struck by the need for multiple efficacious drugs in this field as opposed to some of the things that I do where there is less failure of the drug to continue to work after a while.

But it seems like almost all drugs have a possibility of over time not working as well, so it sounds like multiple efficacious drugs are needed. By all means, this drugs needs to get in the hands

of physicians and patients so they can benefit from it, and I trust that prescribing physicians can learn how to use it safely.

I think this registry does have value. I am presuming the data is gathered in such a way that we can make adjusted estimates of risk that will tell us the signal hopefully over time, if this SIB is real. I think vote B, consistent with the sponsor's proposed plan, is the best way forward.

DR. WALSS-BASS: I voted yes, B. Consuelo Walss-Bass. Yes, B, similar to what Dr. Blaha just said, I think that --

DR. BIGBY: Excuse me. Can you just make sure you state your name before --

DR. WALSS-BASS: Yes, Consuelo Walss-Bass. Yes, B. I think that the benefits definitely outweigh the risks, although I do think the risks should not be ignored, and there should be a strong psychiatric assessment, follow-up of the patients with SIB assessment tools and also for depression.

I do think there is value in the registry as well. I do think that this could give us

information as to the potential risk factors for suicide for this population.

DR. ZITO: Julie Zito. I voted B, and I do think we have a responsibility to address the uncertainty that there was in the data here. That means to me that we would market with a registry plan in mind that would be pretty serious about being able to assess the individuals who come in in terms of their prior med experience and their willingness to provide information that relates to suicide attempts in the past, which is definitely a major risk factor here that we should learn about.

Also, we have had great experience with drugs like clozapine, which were really a remarkable addition to the armamentarium, but we knew in advance that there were deaths in Europe, and we came up with a really extraordinary plan to make the drug available sooner rather than later and for severe mental illness.

I think we have good experience in the past with running a registry that will enroll those that need to be enrolled so that there is no loss of

access to the drug for those who need it, but also to provide rich information going forward that would help us to know whether some of the hypothesized models that have been shared here today can really be assessed further.

Also, I am very concerned that there was really no discussion yet today around drug-drug interactions, and it is likely that in America, we have folks in this age group that are going to be on a bunch of medications concomitantly with this drug.

So let's use it as an opportunity to understand relationship to anti-depressants. For example, SSRIs are going to be likely to be the drug that people who have a history of depression are being treated with for depression. So lots of opportunities here for a well designed and well executed registry.

MS. SMITH: Elizabeth Smith. I voted yes, B. And I agree with having a registry and the black box label. But what I am not hearing from anyone is having something in English for the

patient.

All of those inserts, all the stuff we are given to read are written in medical-ease, and we need something for patients that explains the risks in language that is understood by all patients, not by just the ones with PhDs.

MS. ARKUS: Bonnie Arkus. I voted B, and again, I do believe that the patient support needs to be there. It is premature to look at these SIBs without first looking at how we are supporting patients who have devastating symptoms and burden unbelievable to live day to day. If we get that patient engaged into a community such as inspire.org or patientslikeme.com and that type of data sharing, perhaps the sponsor could reach out to either of those communities, and then the patient would be better supported in fighting this disease.

DR. TAN: Ming Tan. I also voted for B. I voted yes. I would want to have this box warning actually to allow the patients and physicians aware of the data that has been observed in the trial

that we already explained about these 6 suicides. Also, I think that a carefully designed registry can be useful but needs to be very carefully designed as to prospectively.

DR. DIGIOVANNA: John DiGiovanna. I voted for B. I think this is a potentially highly effective efficacious drug where there is a great need, and I think we have a responsibility to try to keep it available on the market if it can be used safely. I think one way to do that is to try to collect reasonable quality data that is better than the information we have so we will now whether or not there is a signal.

I think the way to do that would be with a registry that has some teeth to it, perhaps required enrollment of the patients so that a few years down the line, everyone will not be asking the same question as to whether or not there is a signal for SIB.

DR. DRAKE: Lynn Drake. I voted for A because I felt that, first of all, it needs to be available to our patients for the reasons I

outlined earlier. This is a devastating disease, and we need it in our therapeutic armamentarium.

I did not vote for B because experience tells me -- and I would hope this would not happen. I would hope the agency would use caution in any REMS or things in addition in labeling because one of the unintended consequences of over-regulating is that the insurance companies and/or other providers get spooked and won't use it, or the insurance companies won't approve it. We in effect deny patients access to the drug because of onerous regulatory or burdensome approval process to get them to use it.

So I am hoping that the agency will consider, if they consider anything in additional labeling, that it is consistent with the sponsor's proposal, which seems rational to me.

DR. KATZ: Ken Katz. I voted B. I do think as a dermatologist, I would appreciate having this additional medicine in my armamentarium for suitable patients.

In terms of the risk management, I think a

label warning regarding SIB would be prudent. I wouldn't favor a warning regarding MACE. I think the sponsor's proposed enhanced pharmacovigilance plan is reasonable as is their enhanced communication plan.

I am not in support -- I am actually recommending against the proposed registry as a way to answer the question. I think you will get data and it can be crunched. And it won't give you the truth because of the selection biases that are inherent in registries like the one that is proposed, in which patients with highest risk of SIB will likely be put on other medicines, inflating their risk of SIB and decreasing the observed risk in the brodalumab group. So I don't think that that will provide the information that the agency is seeking.

DR. MORRATO: Elaine Morrato. I also voted B. I thought the benefit-risk was strong. Psoriasis is a serious life-altering chronic condition, as we heard, and there remains significant unmet medical need.

With respect to benefit or the efficacy side, we saw evidence that many patients have had dramatic effect in using the product. It is also important to know comparative drugs have also serious life-threatening adverse event profiles themselves. How do you weigh the benefit and risk of this drug in light of how it has been weighed for others? I think it is important to be consistent as we look across drugs.

I gave some of my reasons why I still think that there is nonetheless a safety signal or something we should be caring about as we move forward in labeling. And given the life-threatening nature of the signal, suicide and death, I voted that we needed some form of risk management that would go just beyond professional labeling.

I just want to provide a couple comments on what the sponsors were saying in terms of elements. For me, overall, it is very important that the whole communication is to ensure that there is informed consent and discussion between the

prescriber and the patient so that no one down the road, a family member says if only I had known.

With that regard, medication guide, I would endorse. It is one form of patient-directed communication. I would underscore what Ms. Smith raised as concerns. I would consider expanding patient-directed information so that the communication plan is not just directed to prescribers.

I would ask that the FDA work with the sponsors so that there is some assurance of active engagement. We see many times in advisory committee meetings website, printed materials, or passive forms that are ineffective. And I would highly underscore what one of the FDA speakers said, that the effectiveness is driven by how well these materials are integrated in with the overall promotional campaign of the company. I think that is something for the FDA to follow up with.

I think it is also important that -- and this is why I see it fitting within a REMS, is that it is important to see the evaluation of the

effectiveness of the communication, did it have an effect all?

I would endorse the sponsor's -- I think what they were saying was active case reporting or 15-day reporting and review of cases. I think that is a good idea for more active pharmacovigilance.

I will save my comments on the postmarketing open registry for when we have that discussion, but other than to say I agree with Dr. Katz that there are selection biases. But I also wonder with what Dr. Waters was stating, we may not be able to know the true estimate, but we may be able to know an effective estimate of what risk is, when it is being managed in market. For me, that still provides value.

The last thing I will say is as I have gotten to look at different risk management across different drugs and therapeutic areas, one thing that this particular drug has going for it with regard to risk management is that there is demand for a new drug. There is a receptive audience that is very aware of the safety issues for this class

of biologics, so I think it will be more receptive to hearing safety information.

It is going to be prescribed among specialized prescribers and patients used to having managed this lifelong complex condition, so I believe there will be a heightened sense of working out these issues as opposed to if it was being used broadly by non-specialists.

For that reason, I think it is very important -- the sponsor briefly said that they would be developing their communication materials by running a focus group. We didn't have time to really look at the development of what they are planning, but I just would caution that sufficient time be given to actually not just slap some materials together with a focus group.

But given the uncertainty around the risk, I think there should be careful consideration of balancing over warning and scaring off patients and prescribers with the appropriate level of warning, and that will take some deliberate testing and pretesting to make sure that that risk message is

balanced appropriately.

DR. BIGBY: Michael Bigby. I voted yes with a labeling. I think that the product should be approved with a black box warning that 6 completed suicides occurred during the development program. I think that the sponsor and the FDA should come to some agreement about the clarifying clauses to that statement, but I don't think the drug should be approved without that statement being in the black box.

I think voluntary communication and voluntary registries have been proven to be and in this case will also be completely useless. The best way to make a problem go away to not look very hard for it. If there's going to be a registry, it should be mandatory.

DR. BILKER: Warren Bilker. I voted for option B. I think that this drug has been shown to have high efficacy for psoriasis, and it is critical that there be more options for treatment of psoriasis.

I believe that the risk for SIB may well be

increased -- we haven't shown it for sure, but may well be increased compared to other drugs available for psoriasis. But also, feel that the risk-benefit ratio considerations warrant approval of the drug for psoriasis.

In addition to the labeling, I feel that the risk management plan proposed by the sponsor is appropriate. That would include the enhanced communication, the enhanced pharmacovigilance, and the Corrona registry participation, which should be mandatory.

DR. BRITTAIN: Erica Brittain. I voted B. As everyone has said, there is a huge efficacy in clearing skin. And I also thought it was interesting that there was some indication of improvement with respect to depression. So it should be on the market.

We can't ignore the 6 suicides in 6,000 enrollees, which was I think where you would have expected 1 to 2 suicides given past experience. But we don't really know how to interpret this, but yet it is going to be essential, we want to ensure

that every patient and doctor makes an informed decision. As you said, you don't want down the road someone saying, "Gee, if only I had known."

I would like to see the most rigorous postmarketing study possible. I still think it is possible that you could do a randomized controlled trial with SIB as an endpoint. I don't know about what numbers you would need, but it might not be impossible. And if not, then do a mandatory registry.

DR. MARDER: Steve Marder. I voted B. Again, I think that this drug should be approved. I was persuaded by the discussion that it is an important addition to the armamentarium for treating psoriasis.

The reason why I have -- my concern about the SIB signal is that the populations that are in trials differs from the population that is in the community, even though in this case, there were no psychiatric exclusions.

I think it is an experience that drugs are more dangerous when they get out into the community

at large, and I think we need to know at some time whether or not this drug increases SIB. So when we talk a little bit later, I will again express my opinion that I think there should be a postmarketing study that has randomization.

DR. RUDORFER: Matt Rudorfer. I voted A for labeling. I do think that we need to convey to clinicians and patients our concern about SIB. I hesitate to elevate that to the level of a signal because I still think that, to a certain extent, we are dealing with apples and oranges, that the populations studied with the other drugs were different from the population we are talking about here.

On the other hand, when we talk about benefit-to-risk ratio, I certainly agree that is a very strong number, but it is also not static and needs to be individualized for every patient. I worry about scaring people away from this effective drug that I don't think we have heard data that would lead us to conclude that everyone with a history of depression, for example, should never be

on it. I think that, yes, that should raise the awareness and the vigilance of the clinician and certainly one should have a low threshold, say, for mental health consultation.

On the other hand, a couple of cases that were reported by the sponsor, if I recall correctly, showed that a couple of those 6 folks who committed suicide, or at least made a serious attempt, had reported zero on their Columbia Suicide Scale and the PHQ.

Certainly, maybe that was an extremely impulsive act, or maybe they were gaming the system and thinking, well, if I say what I really feel, they're going to take me off this effective drug.

So I would rather not have patients feel like they were afraid to tell their clinician how they are really feeling. If someone is depressed and is doing well on this drug, that maybe there is a safe and effective way of managing that without either barring them from getting the drug in the first place or yanking it away immediately. Thank you.

DR. IRWIN: Michael Irwin. I also agree that there is a really high benefit to this drug. I thought there was really compelling data also from the public about its benefit, and so I think that is really important.

There is also risk, and I think the risk of an SIB is there. I think there should be a warning. I think that the warning should emphasize that there is a potential link with past history of depression or past history of a suicide attempt. I should say past history of a suicide attempt. But I do not think that should be an exclusion criteria for the use of this drug.

I think the warning should also indicate that the suicidal ideation can occur without significant depressive or anxiety symptoms or a prodrome of those symptoms because we can see that many of the cases, that there is some benefit on depression that is occurring.

So clinicians need to be aware that this is not a suicide that is just going to occur within the setting of a depression. It might come out of

the blue, so to speak, and be impulsive.

I think a mandatory registry is a great idea. Suicide monitoring as part of that seems to be really important if we are going to gather information about the associations between this drug and ultimate suicide ideations and outcomes.

DR. LOTRICH: Frank Lotrich. I voted B, and just to be brief, you can cut and paste Dr. Morrato's comments as my own and leave it at that.

(Laughter.)

DR. BIGBY: The last question for discussion, if you voted for approval in question number 2, please comment on postmarketing studies, trials that are needed to further define the safety of brodalumab, including but not limited to the need for long-term studies to evaluate suicidality and cardiovascular events.

I think we have already done this. Do you agree?

DR. CHIANG: Some people have additional --

DR. BIGBY: Yes?

DR. PINHEIRO: This is Simone Pinheiro, Division of Epidemiology. So I'm reacting to some of the comments about the registry and difficulties in using the registry to evaluate SIB, including perhaps channeling, especially if the product is approved with labeling language, and also the comments from other members in terms of perhaps a randomized study would be helpful, but how that can be impractical if you measuring suicides.

I heard earlier about trials where one can measure behavior as a proxy for suicide. I was wondering if the committee members could comment on that.

DR. ZITO: Could you repeat your question, please?

DR. PINHEIRO: I was interested in feedback. I heard earlier comments about the possibility of considering a trial but measuring as an endpoint suicide behavior as was a proxy for suicide. I was just wanting to hear the committee members' thoughts on that, given the difficulties of the registry and the trial that measures suicide as an

endpoint.

DR. ZITO: Are you referring to pre or postmarketing?

DR. PINHEIRO: Both.

DR. BIGBY: Dr. Brittain?

DR. BRITTAIN: I believe I think I made that suggestion as well when we were going around. I don't have any idea of whether it would be feasible. I don't know the details. The other question is whether it really is getting at the real issue of the suicide in this context. So I don't know that it would, but it certainly seems worth doing and worth considering.

DR. BIGBY: Dr. Marder?

DR. MARDER: One study that I know about that was -- I don't know how similar it was, but was a comparison of clozapine and olanzapine that was done several years ago. I believe that they used suicidal ideation and behavior, and by comparing those two drugs, they found a signal. I don't think that the sample size was huge, but it did lead to the eventual labeling of clozapine for

suicidal behavior in people with schizophrenia.

It seems to me that that kind of randomized trial is plausible. Again, I don't remember the endpoints exactly.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: As I was listening to people's comments, there is maybe a couple considerations in the decision process is whether or not you need an exact point estimate of truth versus what I might call an effective point estimate of what is it we observe in practice when people are following various ranges of risk management.

I know with the LABA drugs for asthma, that was a huge debate as to what the postmarketing study was. I think the agency meted out they wanted a precise estimate, so that led to a huge trial which takes years. I know they expanded the indication, so it wasn't just deaths related to asthma but included hospitalizations and broader to help with sample size.

I think that is important to know how important is it the precise estimate versus an

effective estimate.

Then the other one, because I think some of the committee members, they might want to comment further, I heard some that said mandatory everyone versus let's have it a naturalistic cohort study that's out there. And hopefully it is done in a rigorous way, but I'm not necessarily making it mandatory.

Those are two different types of observational registry studies, and I know sometimes the registry when it is mandatory, that is starting to sound a lot more like an ETASU requirement as opposed to I would like a registry that makes sure that I have a nice distribution of all patients.

DR. MARCUS: Yes. Thank you for making that point. We have been discussing whether to bring that up, but I hope people understand a mandatory registry means that individuals will not gain access to the product unless they agree to join and participate in the registry. That could impact availability.

I am just throwing that in so that people understand the unintended -- the potential to actually restrict the access because of the requirement to enroll in the registry. The discussion we have heard is that people clearly think that there is a benefit and the product should be made available to patients. So I am just adding that to what you've said.

FEMALE SPEAKER: I just wanted to remind people, too, that these elements to assure safe use, a lot of times, we have to combine them to achieve some of these goals so if that's what -- just kind of consider that when you're thinking about that. So it wouldn't just be a registry in isolation.

DR. BIGBY: Dr. Blaha?

DR. BLAHA: I just wanted to make a methodologic comment about the idea of what I would call surrogate endpoints, use of a behavior, I guess, like in the cardiovascular world where we're markedly moving away from the idea of surrogate endpoints, of course, the idea of measuring LDL

cholesterol only or something else and saying that is good enough to say it's going to, let's say, prevent a heart attack, for example.

I would be extremely cautious just from an outsider's point of view saying a drug is associated with a behavior or a thought or something and saying that is as good as a suicide, for example. I just think that is a tremendously slippery slope.

To clarify I guess with regard to the last discussion, my vote, I found the sponsor's presentation of their pharmacovigilance program and REMS program sufficient, and my vote was for the voluntary Corrona registry that was described and not a mandatory registry. Once again, it sounds a lot more like a potential barrier to use the drug.

DR. BIGBY: Dr. Brittain?

DR. BRITTAIN: I just wanted to make a comment about the idea that in the registry we'd be accurately measuring how the drug is used and that that would be a good estimate. I understand that. I think that's a good point. But at the same time,

if after that study is concluded, it looks like, gee, there is no problem here, then they revert to -- then the process changes as a result of that, then it could be misleading.

DR. BIGBY: Dr. Drake?

DR. DRAKE: I understand the rationale behind if you're going to have a registry, it should be mandatory. I actually want to speak against the registry if it is going to be mandatory because I really am opposed to anything that creates barriers, particularly artificial barriers, to patients having access to this drug.

The second thing that is going to happen is it will spook them. And when you make life so difficult that they can't access the drug, then they don't get it. I just can't emphasize how these patients are suffering. It is like having a thousand cuts on your body all at the same time.

Nobody has actually mentioned very clearly today the pain that goes along with the disfigurement. This disease is painful, and the skin, it is like having a thousand paper cuts all

over your body in some instances.

We need to get this drug to the patients and not create a bunch of artificial barriers. Anything that is voluntary that the company wants to work out with the agency is fine, but please, I urge caution in this area.

DR. BIGBY: Dr. Katz?

DR. KATZ: Ken Katz.

So I had raised some concerns about the voluntary registry. I don't think making the registry mandatory obviates any of those concerns. You are still going to have in a postmarketing setting a population that is enrolled in a registry that has been enriched for people who are least likely to have the event of interest since it is labeling. So I don't think a mandatory registry solves the problem. It just creates more barriers to care.

I also think that you will have problems getting the truth with the registry in a postmarketing setting where people are aware of this risk of suicidal ideation and behavior because

I think people are more likely to ask about it or report it so that will inflate the estimate of SIB at the same time that the population will have less of a risk of SIB.

In the end, I think no amount of statistical adjustment will be able to correct for those two issues, and I think you will be left not knowing what the truth actually is, and it won't be helpful.

DR. BIGBY: Dr. Zito?

DR. ZITO: I have been thinking about the experience we have had with REMS and how difficult it has been to be assured of the transparency with REMS in terms of publication of information that comes from REMS. There certainly is a sense that it is taking us a good long while to be assured of anything in that regard.

Companies take a much, much longer time, and evidence doesn't emerge of a scientific nature very often. It is improving, but it is a very slow process. So there is a big deal difference between a mandatory registry and a non-mandatory registry,

and so that's one point.

I think that if you did a good job of a two-year requirement for access to the drug, with what we now know about MACE and SIB -- and I'm really only particularly with SIB very interested in completed suicides and attempts.

If we gathered just good information about that and why people stop using the medication, we would be a long way, and their current regimen when they're on of other meds, we would be further down the road of understanding whether there is a serotonergic component here to this. We could learn a great deal.

I am thinking, maybe I am naive about this, but I am thinking that this is not such a huge population if you are really going to be coming in with severe cases, and you have already got some networks going, that it would be so difficult that it wouldn't be a barrier for access over, say, two years. Then in two years, you have answered the question of whether this was not a signal, this was just noise, or it is a real phenomenon. I

would argue for that.

DR. BIGBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato. I agree with many of the points you are saying, Dr. Zito.

Just the caution, though, as Dr. Drake has said. So right now, there looks like there is about 120 dermatology sites that are involved in there. I'm not a dermatologist, so I Googled how many dermatologists are there in the U.S. Assuming this is treated primarily by dermatologists, there is about 9600 dermatologists in about 7800 practices.

So what you have is a small subset. Now, maybe they see a lot of the volume of patients. I don't know, but it does speak to unless you are going to have a dramatic change in the number enrolled sites, it is going from a small group that is interested in the science and the data collection and may not necessarily see this as a burden, but they'd like to participate in practice-based research all the way now to mandatory. I think that is the challenge going

forward, is that all or nothing, because otherwise, it does end up as a barrier.

I think in terms of the endpoints that we heard discussed, it sounds like it was only going to be measured twice a year. As you think about what are we really collecting in a twice-a-year assessment, it sounded like the assessment on suicide was not as rigorous as it could be in terms of the assessment.

So I guess the question I have is how willing would the registry group be willing to add on these extra things, too, because now they might see these as either more frequent visiting or more in-depth data collection over time, not just at baseline, might be burdensome even for these practices.

DR. BIGBY: Ms. Arkus?

MS. ARKUS: I was going to say that these patients probably just need a lot more support, that type of monitoring and support would come from a social worker, psychologist maybe twice a year, and that could be part of the registry, not

restricting patients in any way. I would surely like to see as many people have access to this drug as quickly as possible and not put any barriers in the way of that therapy being available.

Also, I don't know whether it is realistic or not, but certainly, the sponsor probably already has a list of all the medicines that each patient was taking. And the concomitant therapy could be looked at to see if there was any pattern, especially with those that have attempted suicide, succeeded in suicide or have made suicidal ideation.

DR. BIGBY: Any more comments from the FDA?

(No response.)

Adjournment

DR. BIGBY: We will now adjourn the meeting. Panel members, please take all your personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of.

Please also remember to drop off your name badges at the registration table on your way out so

they may be recycled. Thank you-all very much.

(Whereupon, at 4:01 p.m., the meeting was adjourned.)