February 3, 2020 Patient Education Call Transcription\

Becky: Welcome everyone, this call is now being recorded. I would like to thank you for being on the call with us today. Our speaker today is Dr. Annette Czernik, clinical Director of the Mount Sinai Dermatology Faculty Practice. Thank you for joining us today! The call today will discuss Clinical Trials. First let me introduce you to our speaker this evening. Dr. Annette Czernik is the Clinical Director of Mount Sinai Dermatology Faculty Practice. She has completed an Immunodermatology research fellowship under the direction of the late Jean-Claude Bystryn at NYU Medical Center. The focus of her practice and her research over the last 10 years has been investigating optimal treatments for patients with recalcitrant autoimmune blistering disease. Annette Czernik is the recipient of several notable research awards and has authored numerous peer-reviewed publications and book chapters relating to her work in pemphigus, pemphigoid and other autoimmune conditions. She has spoken at several national and international meetings and is a supporter of the International Pemphigoid and Pemphigus Foundation. Currently she is the principal investigator on several clinical trials in pemphigus and pemphigoid and routinely mentors medical students, residents and fellows interested in bullous disease. It is my pleasure to introduce Dr. Annette Czernik to answer your questions about Clinical Trials. Thank you for joining us today!

Dr. Czernik: Thank you for that introduction, it's a pleasure to be here. I am really excited I actually haven't participated in one of these calls before so I am eager to participate and it looks like there is a large number of attendees so I am excited to see that and to talk with everyone about something that I love doing which is clinical trials in the space of pemphigus and pemphigoid.

Becky: Dr. Czernik maybe you can start off and explain exactly what is a clinical trial?

Dr. Czernik: Sure, so a clinical trial is a study conducted by researchers on human subjects to test either a medical treatment or a prevention strategy. Prevention strategies include: lifestyle changes, dietary modifications or optimal health education. And a medical treatment is a drug, surgical procedure, a medical device or some other therapy that is offered to patients. So most trials in pemphigus and pemphigoid focus on medical treatments. Generally speaking prevention-based clinical trials are difficult to perform in rare conditions and most prevention-based clinical trials focus on more common, chronic illness like heart disease, hypertension and diabetes which go on for long periods of time. In severe disease especially in diseases that are rare, really all trials are difficult to perform because of setting up the design and recruitment and so our focus is really on figuring out what the best possible treatments are quickly for patients.

Becky: Great, thank you. Would you briefly explain the different phases and stages of a clinical trial?

Dr. Czernik: Sure, so phase 1 is focused on safety. So these are the phases that are broken down by the FDA. There is common terminology we use when we talk about clinical trials. So phase 1 trials really aim to find the best new dose of a drug with as few possible side effects. So the drug is usually tested on a very small group of patients and doctors start by giving very low doses of the drug to very few patients and then slowly higher doses are given. While this drug is obviously intended to help patients, really the focus of the phase 1 trials is to determine that is absolutely safe and if the drug is found to be safe it can move on to a phase 2 clinical trial. So, phase 2 clinical trials further assess the safety as well as if the drug is beginning to show signs that it is effective in treating the disease. So phase 2 trials are done on a larger group of patients compared to phase 1 trials. Patients are closely watched to see if the drug is working well however the new drug is rarely compared to the standard of care drug that's used. If the drug is found to work in the phase 2 clinical trial it can then be tested in a phase 3 clinical trial. So phase 3 clinical trials compare the drug to the standard of care drug. So these trials are used to assess the side effects but also primarily if the drug works better or just as good as the standard of care and of course the goal is to find something that works better than the standard of care. So phase 3 trials typically in pemphigus enroll around 100 or so patients, between 100 and 200. Often these trials are randomized, this means that patients are put into a treatment group called trial arms by chance. So randomization is needed to make sure that people in all trial arms are the same and it allows scientists to know that the results of the clinical trial are due to the treatment and not difference between the two groups. A computer program is used to assign patients randomly to one arm versus another. There can be more than two treatment arms in phase 3 trials. The control groups get the standard of care treatment and the other group gets the new treatment that is under investigation and neither the physician nor the participant in the study is usually aware of what they are getting in the treatment arms. This is called being blinded, so they are not aware and can't be biased whether or not they think they are improving if they think they are in the "better arm". Every patient in a phase 3 trial is watched very closely and the study will be stopped early if there are any side effects that emerge that are deemed to be too severe. If the signs show that the treatment group is responding much better than expected then the trial can be stopped because the drug appears to work so well that we want to fast track it and move forward. So phase 3 trials are what are required before we can obtain the FDA approval of a new drug before we can use it for the general public. And there actually is a phase 4, so phase 4 is when drugs have been approved by the FDA and they are in use but we are still collecting safety data from the public. So at this point depending upon the medication usually thousands of patients can receive the drug so we can get a better idea if there are really, really rare side effects that pop up that aren't present in a phase 3 trial which is a much smaller group as well as how it might interact with other medications and if it's optimally used in a setting of a cocktail of several drugs. So doctors can learn more about how the drug works and if it's helpful when used with other treatments. So those are the 4 phases of a clinical trial.

Becky: Wow, so it sounds like with clinical trials, it's not only is a drug safe but that is safe and effective and it works at least as well as the current standard treatment or treatments that are

out there and if there are any side effects or any interactions that doctors can find. So that really is a lot of information for clinical trials.

Dr. Czernik: Yes, so it takes a long time to get through to FDA approval and into the hands of the general public. Even then I think it is important to know that there is still surveillance of every single medication that's prescribed to you, even penicillin. There is still a degree of surveillance that is conducted in order to ensure that there aren't any safety signals that come up after decades of use for millions of people.

Becky: Wow, that is really good to know. So I know that you had mentioned that there are a lot of trials going on now for pemphigus and pemphigoid, do you know what stages most of them are at? Are they at the phase 3 or are they more in the phase 1 and 2 level?

Dr. Czernik: So in general you are going to have more trials in the phase 1 and 2 level just because they don't all make it to the phase 3 level. However, we are seeing that more studies are coming out, which is exciting, at the phase 3 juncture. Typically these trials recruit many more patients and so they go on for much longer period of time so the total time for which you are eligible for participation will usually be in the order of years versus in a phase 1 or phase 2 trial while there may be more of them they are only recruiting for a short period of time. So the availability of the trial depends on where we are at. For instance right now at Sinai we have one phase 3 clinical trial in pemphigus, pemphigus foliaceus and pemphigus vulgaris, which we are really excited about. So there isn't always a phase 3 trial enrolling patients in these conditions.

Becky: Well great, thank you. So when you start talking to a patient like me about joining a clinical trial, what are some things that you share with them or tips that you give them to help them determine if being in a trial is right for them?

Dr. Czernik: Because safety is the primary endpoint to all of these studies during all of the phases there's overall going to be a lot more surveillance of participants, meaning that there will be more office visits, more blood work, more counseling. For instance, in the prior study, the Pemphix study we were comparing Rituximab to Cellcept in pemphgius. Those were two available drugs and so I could give that to one of my patients in practice or I could enroll them in a trial and they could receive the same medications in the trial. If I were to give them that medication in my practice, I wouldn' need to see them nearly as often as if they were enrolled in the clinical trial because we are really trying to pick up as many safety signals as possible. So in order to do that, it requires much more surveillance of participants. Now, Rituximab is FDA approved for pemphigus because of studies like that but that is something to just be aware of, that there is going to be a greater degree of counseling and surveillance, which a lot of patients like because they are going to get overall more care but it's not for everyone. So that is one of the first things I'll bring up with people because that will quickly divide people into whether or not the trial is right for them.

Becky: Great, are there any other specific questions that you think patients should ask doctors or a pharmaceutical company to help them determine if a trial is right for them?

Dr. Czernik: Sure, often times they will want to know how far they need to travel, for often, what is the protocol? What obligations do they have to meet protocol? Are they someone that goes to Europe for half the year so basically they won't be able to come in for their visits. How long is the study overall? Because studies are usually divided into an active treatment phase where they are receiving medication and then there is the long-term follow-up which is looking at safety after they completed the portion of the study where they are on the study medication or on the standard of care therapy they continue to be followed. So there will still be expectations of them, so how long will that go on? And is there any reimbursement for travel or for participation in the study? Those are some of the questions to ask.

Becky: And that was going to be one of my questions, as you were talking, that you use the term surveillance but I think most of the patients that we were in our minds that would be doctors appointments or lab appointments. Is there generally a cost to participating in a clinical trial?

Dr. Czernik: Usually not, most trials will offer compensation if you are traveling from far away or if you need overnight accomodations, things like that. But if you have a work schedule that is not flexible, you'll have to take that into account and see what sort of arrangements make the most sense for you.

Becky: Great and why do you think patients should consider joining a clinical trial?

Dr. Czernik: I think it's very rewarding, patients have an opportunity to not only improve their own condition above and beyond what is available to them in general practice but also to advance medicine overall. So with each study we learn more about the disease and it's response and can better fine tune not only what medications work but what trial designs work, what therapeutic targets might be a better promise. Like we know that Rituximab is an effective therapy but what is it about CD20 and is there something similar to CD20 that is more specific to pemphigus that we can follow down the pathway and target more directly. So with each trial we learn a little bit more, we have another piece of the puzzle that we can put together, to make the disease overall more easily treated. And of course without participants in these studies, they can't be conducted. So the whole thing hinges upon people wanting to advance medicine and wanting to obviously treat their disease in a way that is better than what they are eligible to receive in practice.

Becky: Great, thank you. So when you are considering, as a physician, bringing up a clinical trial to a patient what are the things you take into consideration? Is it disease severity? Or what weighs in your decision if a patient would be good for a clinical trial?

Dr. Czernik: Sure, well number one, do they meet enrollment criteria? So like you were saying, usually each trail will have a specific enrollment criteria, they are looking for a certain condition. Is it pemphigus vulgaris and foliaceus or is it just vulgaris or is it just pemphigus foliaceus? Also, how severe is the disease? Do they want moderate to severe disease, are they okay with enrolling patients with less severe disease? And what criteria is used to determine that? What length of time has the patient had the disease? So we have seen protocols come across that were really very specific that they want newly diagnosed disease. It's going to be much harder to enroll for those studies, and how do you define that? Does that mean a month? Does that mean a year? Many patients aren't diagnosed for a very long time after they exhibit symptoms, so is it at the time of symptoms or at the time of diagnosis? So all of these things will be laid out in the protocol for the individual study. We sort of have to have that in the back of our minds when we are thinking about the possibility of bringing a patient into a discussion at least about the clinical trial. Also there are requirements of what medicines they have received, so a lot of the pemphigus studies they don't want patient's to have received Rituximab within at least 6 months because it still might have some activity which will impact the results of the study. Or they have specific doses of steroids that they require patients to be on as requirement and somebody that is off steroids is not going to want to go back on steroids in order to be eligible for a trial. Other trials require that patients don't have any preexisting conditions or infections. So they requirements are some of the greatest limiting factors in determining who's eligible for a study. But some other things that I take into consideration is kind of what we talked about already, how far away is the patient? Are they going to be able to make it to the office when they need to come in for their visits? Is the patient reliable? Have they missed everyone of their visits for the last 3 months because if they are signed up for the protocol we really need them to come in for their visits or else it's protocol deviation then the participation in the study overall is limited. So are they overall a good candidate for this sort of study? Will the patient benefit? We want this to be a better option for them than what their current options are. So fundamentally will they benefit? Are they poorly controlled on their current therapy or have they had an adverse reaction of some type to their current therapy or to the standard of care therapy? So I think introducing something different or new might be a reasonable option at this juncture. Or do they have a big deductible or lack of insurance where what I want them to get isn't really available to them right now and maybe trying something through the clinical trials route would take that burden off, at least temporarily where all of their care would be covered for free essentially. So a lot of things that go into selecting patients for clinical trials but we do our best to bring them up where it's appropriate.

Becky: Well thank you for that, that's a lot to consider when trying to decide if it's right to even bring up let alone to participate in. Our next question is one that we get fairly often and the question is, "What happens when a trial and therapy stage 2 or 3 shows up either ineffective or has substantial adverse reactions? Do you end the study and restore the patients to their standard therapy or does the pharmaceutical company continue until the scheduled end of the trial? Are you locked into that trial is the best way to say?

Dr Czernik: So no, you're never locked into a trial for any reason. So you can most certainly withdraw consent at any time. There's, most of the time, the way that the protocols are written is that if a patient doesn't appear to be responding to a treatment, then there's always another option for them. There's always sort of a way that they can get a different treatment or sort of move within the protocol, within the confines of the trial, so what's optimal and what's best for them. But if a patient decides that they, for whatever reason or for no reason at all, no longer wish to participate, then they certainly are free to leave at any time.

Becky: Great. Thank you. That's something that I think a lot of patients that are a little bit hesitant about. When you bring up a clinical trial how do most patients respond to the thought of participating in the clinical trial?

Dr. Czernik: I think most patients typically respond favorably. I think patients are eager to participate if they meet criteria and they can comply with the study protocol. I do think that in many cases they see it as an opportunity to have the potential for a better therapy and like I said, to sort of advance medicine. There are some patients that sort of right away know that trials are not for them. Usually these patients sort of associate studies with being a guinea pig. And I completely get that and because trials are always optional and I really want to know that patients are committed to this study, I really don't ever try to convince anyone that a trial is right for them if they are just not interested.

Becky: Great, thank you. Where can our listeners find more information about clinical trials that are happening in pemphigus and pemphigoid?

Dr. Czernik: There's two ways. One, you can ask your dermatologist or your specialists that you see for your condition if there are any trials that you might be a good candidate for, and nine and a 10 times your clinician will go to clinical trials.gov which has a comprehensive list of all current trials in pemphigus and pemphigoid and really any condition that you might be interested in looking up. Which you can go to yourself and you have the option of sort of selecting for trials that are actively recruiting in your condition or if you've heard about a specific type of trial you can look up that type of trial and so you can search through that. But that's really the main way that both your doctor and yourself can look up what's available.

Becky: Great. Thank you. So once you've had extensive conversations with your provider or even contact the pharmaceutical company then what happens? Like I've agreed, in your office and now I've agreed to participate in a clinical trial. What's the next steps?

Dr. Czernik: So once you demonstrate that you're interested in the clinical trial, generally there's some degree of what's called prescreening, where we kind of determined that you're eligible for the trial itself. And then informed consent, assuming that you are, an informed consent is signed. Usually I'd call in our research team, so we have a clinical trials research team and basically their role is to run these clinical trials. And so there are also physicians and they work with you, hand in hand throughout the course of this study. We'll be seeing you for all

your visits and they go into the nitty gritty, the details of the study and we have you sign the informed consent. And then once the informed consent, it's followed by actually a further screening period just to further ensure that you're eligible. And then what's called randomization occurs where you're put into your study group, assuming that this is a phase 3 trial. If there's only one arm, then all patients receive the treatment, and the study is initiated. And again, if you're not happy or you know, things aren't going well, you can always withdraw from the study at any time.

Becky: And can you talk a little bit about what if somebody decides to withdraw from the study, how does that affect the overall trial?

Dr. Czernik: So there's different ways and it depends on the study protocol, but most of the time these studies are written in what's called “the intention to treat analysis”, meaning that if you were to withdraw and you were put into either the treatment arm or the standard of care arm, either arm, we would still use the data that we've collected up until that point. But then you sort of make note that, for whatever reason there were more withdrawals from one side versus the other. And then still calculate the data as best we can with the information that we have. The purpose of course, meaning that if we were in practice and we were treating patients as we normally would and a number of those patients were lost to followup, for instance, they didn't come back, that's an important number to capture because there may be something with that particular treatment that led them not to follow up. Maybe there is a subtle side effect or something about it that led those patients to not feel comfortable with continuing on. And so we try to capture that data as best we can to make it accurately reflect sort of what would happen in natural practice.

Becky: Great. Thank you. I'm going to group the next questions. We have had quite a few questions about that, if somebody participates in a clinical trial, are they generally told the results at the conclusion of the trial?

Dr. Czernik: They are, but exactly how they're told the results depends upon the actual study itself. So when the trial ends and analysis is done of all of the data, and that could take a long time. And so after that analysis is complete, usually what happens is the sponsor tells the principal investigators of the study, what the results are. And there may be some preliminary results that come out, but generally they kind of give the full results to the principal investigator and the principal investigator then can go on and tell the participants in their trial what the results are before they're made widely available to the public. And then usually there is a press release and some scientific meetings that present the data and eventually publication. But yes, the trial participants are most definitely eligible to receive information about the results of the study at the time that it's available to the principal investigators who worked on enrolling them in the trial itself.

Becky: Great. Thank you. Our next question has to do with who has access to medical records. It sounds like there needs to be a lot of information sharing between physicians and hospitals and other doctors. How is this done and how did they communicate and what's the process?

Dr. Czernik: Sure. So your medical records are always what's called HIPAA protected. So they're protected by law by privacy laws to make sure that they're only exposed to people who really need that data. So your medical records are usually kind of contained with an a binder that is only accessible to what's called a study assessor who is one of the physicians working on the clinical trial team as well as the primary investigator, who is the investigator managing the trial. And the study assessor is usually the one, usually a research fellow who takes these meticulous notes each time you come in on the degree of the disease activity. So they'll count in each individual lesion, they order the lab work, they'll perform periodic disease assessments and determination of progress within the study. Your information from there is then sort of de-identified when it's analyzed. And so we take all of the numbers that are accumulated from all of the visits and any identifying information is stripped away before it's given to the sponsor where they can then sort of determine whether or not their treatments are effective. So, even though there's a lot of communication going on, the actual identifying information is still held very private.

Becky: Great. So going back to explaining, you had talked about explaining the information for clinical trials to the patient. Is there any one person who makes sure that the whole process is understood by the patient and you were talking about informed consent and information, is it written in a lay language so that patients understand what they're signing?

Dr. Czernik: It is, yeah. And so we have what's called an institutional review board which is a governing body that determines, to ensure the ethics of all clinical trials or all trials done with all human subjects across the board. And they will review the protocol as well as the informed consent to make sure that it's entirely written in terms that are very easy to understand. And they take it very seriously and scrutinize all of the words and phrases that are used to make sure that it's written in the best way, the easiest way to understand. And then it's really the clinical trials team's job to make sure that it's explained, word by word to the participants before we initiate the trial. Sorry, was there another part to that question that you asked? I think I missed it.

Becky: No, I think you incorporated it cause it was about like who makes the whole process is understood by them in a language. And it sounds like the institutional review board would make sure that all of that is understood by the patient and easily understandable and that they know what they're signing. Yeah. That's awesome. So when determining if a medicine works, is it necessary to check the wounds, measure blisters and collect blister samples? Is that how there is determination that a treatment is working is it done or is it another way?

Dr. Czernik: Typically we use a combination of, we're lucky I guess in dermatology where we can use outward visible signs to determine if our treatments are effective or not. And so in

psoriasis, we use the disease activity score. In pemphigus we use the disease activity score. So the pemphigus, PDAI, the Pemphigus Disease Activity Index is what we use as an assessment tool. So we have to be able to numerically assess how patients are improving in a standard way, so that “physician A” doesn't say, this patient has mild disease. Whereas “physician B” says, I think it's more moderate actually. So, that's sort of how we have the standard tool in order to best judge patients against each other, patients against themselves, what they were at baseline compared to later. And that's what we typically use. We're lucky in pemphigus where we also have the lab marker, right? So we have desmoglein antibodies and we can track those over time. So we have two numerical markers that are generally the standard and how we determine the degree of patient's disease activity and how they progress over time. And our goal of course is to show that overall they do much better than they did at baseline when they're on a particular treatment as compared to their standard of care therapy.

Becky: Well, great. So just kind of following up with that question, where does e-medicine come in? When you're talking about using like the disease index tool? It seems like that might be a place where e-medicine can be used, could it not?

Dr. Czernik: So by e-medicine, I think you like mean telemedicine, right? So this is still an area I think that is developing and it's expanding pretty quickly. I know in the Pemphix Trial, they tried to have sites that were that were more remote, that weren't close to a large research center or participants that weren't near a large research center participate. So they still had visits, they had a nurse come out to the house and do visits, but they really tried to get everybody mostly on telemedicine for throughout the course of the study. And I believe that in the end this was a more challenging task then they sort of had anticipated. I'm not sure if those patients who were initially wanted to be included or who initially enrolled were able to complete the trial or not. I think that their data wasn't fully included for whatever reason. And so I think there are still some kinks to work out with telemedicine, but I think that this is a rapidly growing field of course in clinical trials, but just in general that we're going to see some new advancements. And certainly I think in the future there's going to be a lot more opportunities for us to be able to make these sort of assessments through technology.

Becky: Great. Thank you for that. The next question is on how is the followup organized? Do patients have a phone number to call or an email to contact in case there's an emergency or anything that concerns them while they're participating in a trial?

Dr. Czernik: Yeah, absolutely. So the clinical trials team is always accessible to patients and an email and a telephone number will always be available. There's a structured sort of set of visits that are laid out to patients when they initiate the study. And so it will be quite clear from the beginning of the trial that, patients for instance will need to be seen every two weeks for two months and then every month for six months. And so you know, what's their contact with the research team will be pretty clear from the beginning, but if something happens and they need to be seen for additional visits, they absolutely can be seen for additional visits for any unexpected concerns. And then of course if any emergencies come up whether they're related

or unrelated to the study, participants should go to the local ER and inform their research team as soon as they can about what's happening and and then the research team will then follow up with what's appropriate depending upon what, you know, what exactly has happened.

Becky: Great. Thank you. Our next question is, is there a psychological follow offered during these trials and maybe even afterwards? It might be especially useful if trials don't work and in the case of some sign of side effects.

Dr. Czernik: Sure. That's a very good question. I know that one of the main endpoints, particularly in phase 3 trials is overall quality of life assessments. And so overall the wellbeing is inherently built into the study because part of the purpose of these trials is that the participants feel better overall. You know, for instance, if your lesions have completely cleared but there is a side effect that was intolerable to you, such as hair loss or hearing loss or something like that, your overall quality of life may not be improved at all. And so this measure is a major part of the trial itself and tries to capture some of the unexpected problems that might occur. There's actually an oral medicine that we use for patients with basal cell carcinomas, which is a type of skin cancer with very advanced basal cells that works really well to shrink the disease, but it causes hair loss. And so in older men who have no hair, they might think this is fine, but in a lot of women this is not going to be okay. And so if participants have any mood changes at all during the trial, so if depression or anxiety develops, it's addressed and it's treated appropriately. If it's thought to be potentially linked to the study itself, it's reported as an adverse event within the trial. And the overall wellbeing of the participant as assessed throughout this study and is a major component of how we judge the efficacy of the treatment.

Becky: Great. Thank you. Our next question says that if a patient is far from the investigation center, is there a communication link between the general practitioner and the specialist doctor in order to facilitate the patient's follow up and care?

Dr. Czernik: Well usually not. Once you're in the trial the local providers really no longer part of the decision making in terms of your treatment course. Of course you can continue to have a relationship with the local physicians and once the trial is over, your local providers will kind of move back into their original role. But during the trial itself, your medical care and changes in your medications can really only be decided at least the medicines of course that are part of the trial by the primary center conducting the trial. Otherwise there won't be uniformity on how the study was being conducted against all of the participants. Now of course if there's any side effects or issues that come up and you need to see for instance a endocrinologist or a cardiologist, then we communicate with those people in order to get a sense of what's happening. Some of these studies go on for years and things happen. People can slip and fall and hurt their ankle and that's recorded as a side effect or as an adverse event I should say within the trial. And we'll communicate with your orthopedic surgeon and things like that throughout the study to make sure that we're all on the same page about everything. But in terms of treating the actual disease itself, the primary care will be provided by the trial team that you're working with.

Becky: Great. And just to kind of reiterate this, I don't know if we've already implied it, but it seems like if you participate in a clinical trial, you are going to get the most focused attention. Like to me it almost seems like there is an overabundance of care and with more people watching you and how you're reacting and how your disease is progressing than if you weren't in a clinical trial. Does my perception seem fairly accurate?

Dr. Czernik: Yeah, absolutely. So every little thing is recorded and made note of because we don't want to miss anything. From having a toothache to things that are generally very common, they'll make note of and discuss and record it. If there was a huge difference in toothaches in one group versus the other group, then that goes on the labeling of the medication. That's sometimes why we see these labels of medicines that providers maybe have a greater feeling of the general safety of but there's 30 things that are listed as possible side effects because literally every single thing is made note of and recorded and scrutinized for if it related or is it not related? Because we don't want to miss anything of course. And so we're sort of, maybe a degree of overdoing it, but it's better than missing something.

Becky: Okay, great. Thank you. Our next question is, are patients involved in writing the consent forms and being part of the IRB team or patient organizations? Or is it just the medical team that is in charge of writing that?

Dr. Czernik: I'm not aware of patients participating in the actual informed consent. I could be wrong about that, but I'm not aware of any studies where that happened. I know in the IRB, the institutional review board will require that there's at least five members, usually there's many more than that and they must have a diverse background. Some of them in science, some of them not in science in order to really reflect the values of everyone. To really bring up everyone's sort of concerns and values as a society. And I do think that patients play a very critical role in determining what's going to suit them best. And their ideas and thoughts about what is important or not important in a study is very valuable. I don't know if they have a direct connection they may have more of an indirect connection through their physicians in the sense that the investigators play a big role. So people who work with pemphigus and pemphigoid patients on a daily basis play a very big role in representing them and representing their needs when the trial design is being discussed. You know, saying, this doesn't work for my patients or this does work. But I'm not aware of them actually sitting on those committees. But maybe the IPPF has a better connection to that because they obviously serve great advocates for patients across the board.

Becky: Yeah. And I guess maybe that's a good followup question. Like where do you see patient organizations acting as channels of information and support in the context of a clinical trial?

Dr. Czernik: Yeah, I mean this is more of a question for the IPPF. I would say that the IPPF has done an incredible job and really has been the best advocate across the board for patients and supporting them, for giving them information, for discussing the ins and outs of trials with

patients. And obviously doing forums like this where I can talk directly to a number of people about what my experience has been and what trials really involved in terms of being a patient and being an investigator.

Becky: Great. Our next question asks, is there any age requirements for clinical trials, any requirements or restrictions?

Dr. Czernik: Usually there are. Most trials in pemphigus and pemphigoid will have a minimum age requirement of 18. And because most of these conditions occur in adults, that's sort of a reasonable requirement. Of course, if we were studying a condition that occurred mostly in children like atopic dermatitis that would be a very harsh restriction on the study. There isn't always an age cutoff in terms of how old patients can be, but sometimes there are cutoffs in terms of functionality of patients. So what's called a Karnofsky score, we want to see that they kind of have the ability to have capacity to make their own decisions and they are living independently and things like that. So basically most adults are enrolled in and the majority of trials that are relevant to pemphigus and pemphigoid.

Becky: Great. Thank you. So it sounds like it takes up a lot of time to set up a clinical trial and then to collect the data afterward at the completion of the trial. Can you talk about that for a little bit?

Dr. Czernik: Sure. Most clinical trials, by the time they get to phase 3 are are sponsored by a pharmaceutical company who is looking to identify a new treatment that is effective for patients within a population. And so they do a lot of the leg work of setting up the protocol and working with teams of physicians to ensure that they're going about it in obviously an ethical way and in a way that's going to be a successful trial. And then once it sort of ready to go and they have identified sites where they think they're going to be able to enroll patients for this particular study. It takes about three to six months for the institutions, regulatory bodies to approve the space for the trial, the budget for the trial and the IRB approval to get started. And so then once we get started, it takes a few years to enroll patients to follow them through to see them towards the end of the study. And then once the trial is finished it takes another year or two for the results to be crunched, at least it did in the Pemphix study. And then it's done and then it's published. And we have the data as to whether or not our treatments were effective. On top of all that there's a lot that happens before we initiate a phase 3 trial. So the processing and the developing of the drug, what's going on in the lab the years beforehand. It really takes many, many years before there's even something that comes up that's even promising within this field. So it's a long journey really.

Becky: Great. Our next question asks, is anyone studying foods and foods that trigger flare ups or remission and what is the most current information on diet related to pemphigus?
Dr. Czernik: So, you know, I always advise patients with oral lesions to be very careful regarding eating foods that can possibly cause any trauma to the oral mucosa. And a lot of this is sort of more common sense than anything else. If it hurts, you know, don't eat it. So spicy,

salty, acidic, crunchy foods are things that we want to try to avoid as well as even just like aggressive dental cleanings and things like that. If patients don't have oral erosions though, I tell them that a really healthy diet is the best approach where they integrate whole grains, lean protein and just lots of veggies. This is especially true if they're going to be on any degree of systemic steroids, which is gonna make them retain water as well as be very hungry and often gain weight. And so being on a healthy diet is not only better for them overall. I do believe that it has anti-inflammatory effects and is going to help them maintain their baseline weight if they do need to be on any steroids. I know the IPPF has been a really good resource for patients in terms of advising them further about questions of food and it's a common question that I get in my practice, but I'm not aware of any very specific foods other than sort of what I already mentioned as being identified as causing or triggering flare ups or you know, leading to greater remission times.

Becky: Thank you. So Jennifer is asking, “What is the criteria for a clinical trial? I believe my pemphigus may be considered mild, but I don't know anyone else with the disease for comparison. And our clinical trials are available if you live in a small town?” In her case, she lives in rural Washington state.

Dr. Czernik: Sure. So most clinical trials at least right now are recruiting patients with more moderate to severe disease. Patients who generally aren't responding well to their current therapies or have added risks associated with those therapies. However, I believe that future trials will likely involve recruitment of patients with milder disease and how we define mild, moderate, severe really depends on the study itself and what their cutoff is. There isn't a clear boundary between those three things and it's not uniform for each study, it varies depending upon the study. Most studies will use the PDAI, the Pemphigus Disease Activity Index, with a certain threshold that they consider as the distinguishing feature between moderate to severe or between mild and moderate. In terms of living in a rural area, so using clinical trials.gov you can look and see what sites are the closest to you. Like, as I mentioned before, many study sponsors will allow compensation for travel if you qualify and you're interested in the study.

Becky: Great. So the next question, Eleanor is asking are any trials being conducted right now for patients with pemphigoid?

Dr. Czernik: Unfortunately, I'm not aware of any active trials being conducted in pemphigoid. We did have a phase 1 trial that no longer actually, there were several phase 1 trials that were in progress that are no longer actively recruiting. At least at our site we're not enrolling anybody in pemphigoid trials. Hopefully that changes soon. I know that there has been some interest and looking at a medication called Dupilumab or Dupixent® in bullous pemphigoid and I actually helped participate in our recent key series that will be published in the JAD, the Journal of American Academy of Dermatology, looking at 13 patients who had received Dupixent® or Dupilumab for really their itch associated with bullous pemphigoid. And 12 out 13 of those patients responded. And so this is a retrospective study that's not controlled, it's a very small,

limited number of patients. And so we can't really gather a lot of efficacy data from it just yet, but I know that the the company that makes Dupilumab and Dupilumab is an FDA approved drug for the treatment of atopic dermatitis of eczema. So we know it's a safe drug, the company has demonstrated some interest in running a trial. And so I have a feeling that this is something that will be on the horizon in bullous pemphigoid and it's very exciting because it's a very, very safe medication. And so we'll see.

Becky: Oh, great news. Thank you. Sue asks, “Could you share any information about the recently announced positive phase two data Efgartigimod in PV support advancement to registration trial.

Dr. Czernik: Sure. So that medication is an FcRn receptor inhibitor. So FcRn is a protein that's on the outside of your cells and what it does is it binds to immunoglobulins and it recycles them. So you have, it basically extends their lifespan. So your antibodies are around for a longer period of time. And what this drug does is it binds that receptor and basically blocks it. So those antibodies in your system are no longer going to be recycled. And so they're going to go down in numbers and so you're going to have less antibodies floating around overall. And so this drug is being investigated for use in conditions where antibodies are thought to at least cause the disease. So if you reduce your antibody levels, the disease gets better. And so it's being studied in conditions like my myasthenia gravis, immune thrombocytopenia, and of course in pemphigus where it's thought that the antibodies are actually linked to the disease itself. And if we reduce antibodies, we can reduce the disease activity. So this is one mechanism for which we think IVIG works. We think that when we use IVG, we essentially flood this receptor and it leads to increased degradation of all antibodies overall. And so in theory, this medication could potentially mimic the action of IVIG without the difficulties of use of IVIG. It's difficult to get approval and access and administration is difficult. And so if we have something that works just as well, if not better that we can administer a little bit more easily this is a good potential market for this drug. And so this was a study, I believe this is a company that was bought out Cint One, for which we actually participating in a phase 2 trial, but then they were bought out, they terminated the trial and it looks like now they, they've re-branded the medication and they're going going to move forward. Which is very exciting because they weren't sure for a while if they were going to move forward in pemphigus but they're now they're now publishing this early data and it looks like they're going to move forward to potentially start a phase 3 trial at some point, which will be very exciting.

Becky: Wow. Thank you. So our next next question comes from Deb and she wants to know if you have any information on the Coimbra Vitamin D3 therapy, which has been studied and reported to abate MS, but also help in other autoimmune disease conditions.

Dr. Czernik: So I'm not aware of any scientific studies looking at high dose vitamin D supplementation in pemphigus folicacus pemphigus vulgaris. There may be some anecdotal reports, but no full clinical trials on this or scientific studies on this. I did look into this a little bit and there is a study looking at high dose vitamin D in psoriasis as well as vitiligo. The study was

very, very small and only had a dozen or so participants and it did not have a control group. So interpretation of the results is very limited. As I mentioned before, we're really looking at studies that are randomized and placebo controlled and blinded. Those are the really the gold standard on what we consider to be the best evidence to what's an effective therapy. So small trials that don't have a control group really, it's hard to interpret those results. We use those studies more when looking at safety, not efficacy. But the patient's overall did seem to improve. I will say though that all of them had vitamin D deficiency at baseline. So they actually require the vitamin D supplementation to a certain degree. But I would be careful about this because very, very high levels of vitamin D can actually be toxic. So hypervitaminosis D is when your vitamin D levels are very, very high and it occurs when you take too much vitamin D. So the cause of it is taking very, very high dose supplements and too much vitamin D you can actually cause increased calcium in the blood and this could affect the bones, tissues and other organs. So I think if this is something that you're interested in, you should really coordinate with your physician to make sure that you're not doing any harm. We think of vitamin D as a vitamin that we all need, but you can have toxic levels of it and so we don't want to overdo it either.

Becky: Great. Thank you for that great information. Our last question, I'm going to group together. We've had a lot of questions come in that asks if you are taking new patients for both pemphigus and pemphigoid.

Dr. Czernik: Oh, of course. Yes. Come. Mount Sinai's doors are open. I'd be happy to see anyone and everyone. If there's any questions you can reach my team at this email czernik.nurses@mountsinai.org. So it's my last name dot nurses and we'll do our best to get back to you if you have any specific questions about scheduling or issues that come up.

Becky: Great. Thank you. I just want to say thank you for being on the call with us today. It was extremely educational having you here and I personally learned a lot on this call. I'd also like to say thank you to everyone who is listening in today and a huge thank you for Genentech and to Celgene for helping to make today's call possible. Before we go, I have a few last announcements. Our next Patient Education Webinar will be on February 18th with Dr. Fivenson to discuss information about treatments and side effects.

I would also like to remind you that the IPPF's Research and Advocacy fundraising campaign has kicked off with a goal of raising $15,000. Your tax-deductible donation enables the IPPF to advocate for patients and collaborate with stakeholders for the development of research of pemphigus and pemphigoid. We provide the most current information to clinicians treating these diseases, researchers investigating potential cures, and patients. With your support, we maintain relationships with congressional representatives and other rare disease support organizations who provide the IPPF with the opportunity to advocate for favorable state and federal legislation, research funding, and policies that benefit those affected by pemphigus and pemphigoid. Your tax-deductible donation will help the IPPF continue to provide the promise of new therapies, improved access to treatments, and a better understanding of these diseases

through our advocacy efforts, research grant program, clinical trial support, natural history study, and biobank.

I am very excited to announce that the 2020 IPPF Annual Patient Education Conference will be held at the Treasure Island Hotel in Fabulous Las Vegas from August 21st through the 23rd! Registration will be opening soon. We hope that you will join us this year for an educational and fun weekend!

If you have not heard, the IPPF has a natural history study! If you have not registered for the IPPF Natural History Study, we encourage you to do so. The IPPF Natural History study is a new patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). You can register today at www.pemphigus.iamrare.org. This online data system collects, stores, and retrieves patient data for analysis in research studies. The more data we can collect, the better the information we can give to researchers, the sooner they can find better treatments, earlier diagnosis, and one day – **A CURE**!

Lastly, If you have a question that didn't get answered on the call, or have additional questions please e-mail Becky Strong, at becky@pemphigus.org, or call (916) 922-1298 x:105, and we would be more than happy to help.This call recording will be sent out with the survey following this call.