argenx BALLAD Bullous Pemphigoid Clinical Trial Information for the IPPF Community
Webinar Transcript- November 15, 2022

Becky Strong: Welcome, everyone to the argenx BALLAD Bullous Pemphigoid Clinical Trial Information for the IPPF Community Webinar. I'm Becky Strong and I will be your host for today's webinar. Thank you for joining us. Today, we are joined by Dr. Donna Culton, Associate Professor for Dermatology at the University of North Carolina, Chapel Hills and by Ravi Shah, Medical Science Liaison for argenx. I would like to thank you for being on the call with us and to our sponsor argenx, and for making today's call possible. "Information is a key factor in treating and living with any condition. However, every patient's situation is unique. The IPPF reminds you that any information found on the internet or during presentations should be discussed with your own doctor or healthcare team to determine if it applies to your specific situation." Before we begin I would like to go over a few housekeeping items… (Reviews Housekeeping Slides)

Becky Strong: Now, let me introduce you to Ravi Shah.Ravi is part of the argenx Medical Science Liaison team that supports a pipeline in skin blistering diseases. He covers the entire east coast while residing in Brooklyn and earned his doctorate at Touro College of Pharmacy in New York. With over 7 years of experience as an Medical Science Liaison, he was directly involved in launching multiple dermatology medications. Ravi has covered multiple dermatologic disorders including eczema, psoriasis, actinic keratosis, acne, and rosacea. Before transitioning to a medical science liaison, Ravi held positions in Medical Information and Drug Safety, which included responding to medical information requests regarding Cosentyx®. Ravi will now introduce Dr. Culton.

Ravi Shah: Hey guys, my name on the video shows as Shelly but I am not Shelly, I am Ravi and I have the pleasure of introducing Dr. Culton. Dr. Culton completed her medical degree at the University of North Carolina, UNC, at Chapel Hill. And while there she also earned her PHD in immunology studying autoreactive B cell development and regulation. She then continued retraining at UNC and following her dermatology residency, she began to apply our knowledge of autoreactive B cell pathophysiology in pemphigus and pemphigoid through basic science and translational research. In her current position, as an Associate Professor of Dermatology at UNC, she serves as a Director of the Clinical Immunofluorescence Lab, and Associate

Director of the Clinical Trials Unit at UNC. So she knows a thing or two about clinical trials. She sees pemphigus and pemphigoid patients from North Carolina and neighboring states in her specialty, which is the Autoimmune Blistering Disorder Clinic. She has served as an investigator in clinical trials in mucocutaneous autoimmune diseases, has contributed to the consensus statement publications, as part of the International Blistering Disease Consensus Group and supports outreach, education and advocacy through her involvement with the IPPF. Dr. Culton, I will hand it over to you and let you take the floor.

Dr. Culton: Thank you so much for that kind introduction and for having me as a speaker today. I am going to now show my screen and forgive all the messiness. So I'm really excited to be here to speak with you all about the Phase 2/3 study of Efgartigimod PH20 SC in adult participants with bullous pemphigoid, also known as the BALLAD Study. Here's the disclaimer slide. I am a consultant for argenx and other drug companies, such as Janssen. As mentioned I'm also a Principal investigator. I run clinical trials at UNC in autoimmune blistering disorders. These are some of the other companies that we are doing clinical trials for and argenx is compensating me to give this presentation.

Dr. Culton: We're gonna start with, this talk gets real, really fast. and we get into some really serious science, so I'm gonna just start at the beginning to try to make sure we're all on the same page. Hopefully you're here because you or someone that you know or love has bullous pemphigoid or you're just interested in learning more about Efgartigimod. We're going to start with bullous pemphigoid because that's really the topic and disease state that we're gonna be talking about. It's an autoimmune blistering disorder. It's a chronic disorder, and it's characterized by fluid filled blisters. A lot of itching and redness on the skin. You can see that over on the right-hand side of your slide in figure A, those blisters are really tense blisters and a lot itchy red spots on the skin. You can have involvement and some of the mucosal surfaces, so eyes, mouth, genitals as well but that's less common. There's a lot of different autoimmune blistering disorders and they're all pretty rare, but among them, bullous pemphigoid is the most common autoimmune blistering disorder. It affects anywhere between 2.5 to a little over 21 new cases per million individuals annually. And while it can affect a person of any age, it's more common as we get older. So it primarily affects people in their 70’s but certainly, there's a wide range that we see in the clinic from very young individuals, all the way up to people in their 90’s. Interestingly, and we're not 100% sure why, but the one-year mortality is 2 to 3 times higher in a patient with bullous pemphigoid than in patients of the same age and gender. So that's something that we're always trying to

understand a little bit more, whether that's the disease itself, whether that is the medications that we're using to treat it. But it does have a significant impact on people's quality of life, and also their psychological state. It's a tough disease to have, and especially being a rare disease, it can feel very isolating. In addition to the clinical features that we already talked about, the common way it looks on the skin with those tense blisters and the itching red plaques, it has a very classic appearance under the microscope. That's shown in figure B, with these the blisters you can see them on the skin in the top image and figure B you can see exactly where that blister forms. And it's right under the epidermis. The epidermis is that thicker purple looking layer. Then you can see right under there, there's all these little purple dots, those are all the inflammatory cells and then the big white space is the blister. That's just the classic histological appearance. As we start to talk about this disease a little bit more, it's helpful to know what it looks like, both clinically and under the microscope.

Dr. Culton: So now we know a little bit about bullous pemphigoid. This is the classic question people come in all the times in my clinic asking me, what causes bullous pemphigoid? Well, there's a lot we know and a lot we don't know, but what we know for sure is that it's caused by auto antibodies. Antibodies, we all kind of know a little bit more about these days, given the pandemic and vaccines. Everybody knows that when you get a vaccine, you make antibodies against it. So, antibodies are part of your immune system's repertoire to identify, typically or usually, identify things that are foreign to the body. Antibodies might recognize proteins on the bacterial surface, it might recognize proteins that are part of viruses, or fungus. Antibodies come in all different, I call them “flavors”, they come in all different types and they recognize all these different foreign things out there in the world. Autoantibodies are antibodies that have gotten confused and they're recognizing your own proteins. Antibodies come in a lot of different types. The antibodies which are the IgG type are critical in bullous pemphigoid. I'm going to now take you through this diagram and you can see my pointer, I’m circling the B cells down here so hopefully you can see that. The B cells are a particular type of cell as part of the immune system and the B cells make the antibodies. So you can see here the B cells are down here in red, they’re making the antibodies. In this diagram the antibodies look like little Y’s. The antibodies have binding ends up here, I am going to call them the claws. Then it has a tail end back here. And in this particular diagram they're showing B cells that are making autoantibodies. And those autoantibodies are binding right here to where the epidermis, which is the top layer of the skin, binds to the dermis, which is the bottom layer of the skin. This black line is where the epidermis and the dermis meet each other. So the antibodies are binding to proteins that hold the epidermis and the dermis together. The two main proteins that the antibodies are binding to are BP180 and BP230. The epidermis and the dermis are held together by lots of different proteins that

all come together but these are the two main proteins that are being targeted by these autoantibodies. When the auto antibodies bind to these proteins, what happens is the tail end of the autoantibodies starts to call in complement and we have that marked here with a C. So it's kind of a stepwise thing that happens. So, first thing is the B cells make the autoantibodies then the autoantibodies bind to BP180 and BP230 and then the tail end of the auto antibody calls in complement and all of these other cells come running. These are all other cells that are part of the immune system. Mast cells, macrophages, neutrophils, eosinophils. All these cells are called to the party and what eventually happens then is you get a blister formation. And in this diagram it is marked here in this kind of light gray with the hash marks, this is the blister that happens. Again, it happens right under the epidermis and it kind of pushes apart the epidermis and the dermis. There are a lot of proteins, proteases, which are special proteins that have destructive capabilities like they break down the other proteins. So it's a lot of chaos going on in here, but it's all triggered by these autoantibodies. So over on the right-hand side of your slide you can see again just a summary of what the autoantibodies do. They cause mechanical disruption between the adhesion of the epidermis and the dermis. They bring in complement, and then they recruit all of these other inflammatory cells, and again, enzymes that kind of destroy other proteins. It's a lot of chaos going on in here, but all triggered by the auto antibodies.

Dr. Culton: So how do we treat bullous pemphigoid? Now, we have several treatments. And I'll just start, when somebody has a confirmed diagnosis of bullous pemphigoid, we typically start with topical steroids. The topical steroids really are targeting all of that inflammation, all of those inflammatory cells that we saw downstream or after the fact. We often, if patients have more than just a few blisters, typically start systemic steroids, like prednisone or prednisolone and typically a steroids-sparing agent. There are several out there that we use. The whole point of the steroids-sparing agent or the other word that we sometimes use for those is immunosuppressive therapy. These would be Methotrexate, Azathioprine, and Mycophenolate, the point of the steroids-sparing agent is to allow us to spare you from prednisone or from the steroids. So we typically start that with the hopes that we're gonna need the steroids upfront to really control the disease but then we'll be able to bring down the dose of steroids as the steroids-sparing agent builds up in the body. Again, patients with more widespread disease, we typically prescribe systemic steroids and then the steroid-sparing agent is started about the same time. Now in patients that these things are not working well for, we may move to other treatments and those are down here in the darker green boxes. So Rituximab which depletes B cells; Omalizumab which targets IgE, which is a different kind of antibody; IVIg and plasmapheresis. The tricky part is that none of these are approved for use in bullous pemphigoid so sometimes it's hard to get insurance to

cover them. They can be very expensive and not all doctors feel comfortable using these medications.

Dr. Culton: Again, just a summary, bullous pemphigoid is a rare, chronic autoimmune disease. It has these fluid filled blisters, itchy, red skin. It is rare, but overall the most common of all of the autoimmune blistering disorders and more prevalent in older patients. And it has a really strong impact on quality of life. So, as we just talked about, we only have a handful of medications used to treat it, and we need more medications that are better and safer.

Dr. Culton: That was the introduction, really with regard to bullous pemphigoid and where we are currently with what we know about the disease and the treatment options we have available. Now we're going to tell the second part of this story, which is the role of FcRn. This is where you should just take a deep breath here, prepare yourself for some hardcore science. We're going to break it down. This is the story of the FcRn or the neonatal Fc receptor and IgG recycling. We talked about antibodies, the IgG antibodies. They're important in protecting you from viruses and bacteria from the outside world but they also are critical in causing autoimmune diseases such as bullous pemphigoid. A lot of people ask, I have these antibodies floating in my blood, how do they stay around or how do we get rid of them? We're going to tell the story from the FcRn point of view or the neonatal Fc receptor point of view. This is a receptor that's expressed in a lot of different cells including the cells that line the blood vessels. In this pretty picture here, this is a blood vessel and these little tiny squares, those are all the cells that are lining the blood vessel. Within the blood vessel is floating a red blood cell and you also have these antibodies that are floating in the blood there. What happens is that the cells that line the blood vessels, again one of these little tiny squared here is blown up very big for you over here on the right, the antibodies are taken in to the endothelial cell, again, that's the cell that lines the blood vessels. So the antibodies are brought into the endothelial cell and within that cell there's these little neonatal Fc receptors or FcRn. That's the yellow here and I'm just going to pause and tell you to think about this, like a game of musical chairs, which is my favorite analogy to use. So these antibodies, there's the red ones and there's the blue ones which are the the autoantibodies and the healthy antibodies, they're all brought into a game of musical chairs. And only the antibodies that get a seat on the FcRn are going to be recycled back into circulation. The ones that do not get a seat are degraded. They don't get to play anymore. So in this particular diagram, what you're seeing is that, as the antibodies come in, antibodies bind to FcRn, the ones that get a seat are recycled back into circulation. This is called IgG recycling, it's a natural part of what happens. It's how IgG these antibodies live. They have a lifespan of about 3 to 4 weeks, and it's all

because of this IgG recycling that happens and again it’s a natural part of what happens in the body. So that is FcRn and IgG recycling, hope everybody's got it because now we're going to talk about Efgartigimod.

Dr. Culton: Here we are looking at that same endothelial cell and again, the seats, the musical chairs. We have our little yellow seats that are here, and what just happened was the blue nubbins were going to call them, they floated in and they're blocking some of the chairs. So it's almost like taking some of the chairs out of the game of musical chairs. What happens next is when all these antibodies come in to the game, there's not enough seats for them so less antibodies in general get a seat in the game. So I am going to play this and a lot of interesting things are going to happen and I am going to have you watch it happen then I am going to talk you through it. So the antibodies that don't get a seat are degraded in the lysosome down here, they're destroyed. The ones that got a seat, not these guys because these seats are blocked by Efgartigimod but these ones that got a seat, they're recycled back into the circulation. So we started with this many antibodies, but because Efgartigimod was blocking some of the chairs, or neonatal Fc receptors, only a few antibodies are released back into circulation. Breaking that all down, essentially, what Efgartigimod does is, it binds FcRn, again the chair in the musical chair analogy, it black blocks at FcRn so then the IgG can't get a seat because there's less opportunity for the IgG to bind at FcRn, the unbound IgG including the autoantibodies are degraded and broken down. So there's fewer IgG floating around in the blood, fewer autoantibodies, less auto antibodies around to cause disease.

Dr. Culton: You did it, you made it through those difficult science slides. That's how we think that Efgartigimod may be helpful in treating bullous pemphigoid because of the role of IgG in the pathophysiology of the disease and how decreasing the amount of antibodies that are recycled essentially lowers the number of autoantibodies in circulation. This is the design of this Phase 2, Phase 3 BALLAD study. The plan is to recruit 160 patients with bullous pemphigoid. We're gonna go over the inclusion criteria in a second, but the highlights are that you have to have moderate to severe disease and that's based on this investigator global assessment. It can be a brand-new diagnosis or it can be somebody who's had control and then has a flare up, so relapsing disease. You have to be an adult, so over 18. And you go through a screening process to make sure there's no other issues with you being in the study. The total duration of the study is 36 weeks, and every person that's enrolled in the study will be randomized 1 to 1. That means half of the patients are gonna get Efgartigimod weekly, subcutaneously, that’s what the SC stands for, and half the patients are gonna get placebo weekly, subcutaneously or a little injection, you're

getting that doesn't have any Efgartigimod in it. But it's half and half. Different studies have different randomizations of how many patients get active drug and how many patients get placebo but in this study, it's 1 to 1. All patients are going to be started on oral corticosteroids, and that is going to be started at a fixed dose of 0.5 milligrams per kilogram per day. I realized that's not a way that most patients are used to thinking about their steroid dosing. But essentially, a 70 kilogram person is like, an average size person, would be getting somewhere around 30 milligrams a day. So just to kind of put it in the ballpark. Now, if you're a tiny person might have a smaller dose, still at 0.5 milligrams per kilograms a day. So a bigger person might have a higher dose, but it's all based on your current weight. And essentially, that gets started in everybody, every patient, with the ability to adjust the dose up, if needed. And then adjust the dose down, as you start to get control of your disease activity. So that fancy abbreviation, we use for control of disease activity is CDA. Control of disease activity means that you're not getting any new blisters and most of your old blisters are healing up and drying up. Once you reach that phase, we call that control of disease activity, no new blisters are forming and almost all the old blisters are healing up, you can start to taper down the steroids. And the hope is that as we taper down the steroids, the patients that are getting the Efgartigimod are not going to have new blisters form. It's weekly visits again, mandatory on-site visits, but they're also the option for some home visits so that you don't have to go into the study site every single week. There's going to be an interim analysis. They're gonna look at the first 40 patients, and see how they're doing. Then make a decision about the second phase of the study. You can see over on the right-hand side, the primary endpoints. This is how a company may decide how will we know if our drug is working, what are we going for here? So that the primary endpoint in this study is the proportion of participants that have complete remission, that means no blisters, no red, itchy spots while you are on the medication and you have been off of steroids for eight weeks, 2 months. You have been off of steroids for 2 months and you have no blisters and that's at week 36. This allows the medication to kind of start to take effect, allowing you to taper all the way down off the steroids. Again, you have to be on steroids for 2 whole months. And if that happens, that is meeting the primary endpoints. I think when we, as physicians and you all, as patients dream up, what would the best treatment be? It would be that you don't want to be on any steroids and you want to have no blisters on your body. So that's what we're going for here. They're also secondary endpoints, which are just other things that we might want to look at in this study that might be of interest that would still be very important, so even just being able to be on a lower dose of steroids, cumulative dose of steroids. You can see there's other ones here that really have to do with quality of life. Focusing on itch, focusing on safety, obviously, and quality of life. All of these things are going to also be analyzed, because they're also important in patients with pemphigoid and treating the whole person.

Dr. Culton: Now, this is always a big question, well, how do you know if I can be in a study like this? Each company conducting the study will have inclusion and exclusion criteria. Here we have listed the inclusion criteria for this study. You have to have a diagnosis of bullous pemphigoid. You have to have the clinical signs, which are blisters with or without these other things. So even if you just have blisters but you don't have spots of eczema or red plaques you can still be in the study. If you have them, you can be in it, if you don't you can be in it but you have to have blisters. You have to have the disease confirmed by both the regular biopsy. Remember, I showed you that picture of that blister and here's another picture of it here, the blister formation. You have to have that, and you have to have a positive, direct immunofluorescence, which is the second biopsy. Usually almost everybody who has a diagnosis of BP that's fully confirmed will have had this study done as well. This is what it looks like those antibodies. Remember, I told you the antibodies attack right where the epidermis and the dermis meets. That's just a test where we look for those antibodies all lined up right there in that bright green. Then the last bit is positive serology and that's blood work and we're looking for the antibodies circulating in the blood. So you have to have all of these things. Again, most patients with active bullous pemphigoid and have a confirmed diagnosis, they have all of these things already. If you don't, it will be done as part of the study. You also have to have moderate to severe disease. You can't just have, like one little blister. It has to be an investigator global assessment of 3 to 4 at screening and at baseline. If you remember, the screening visit is where you come in and you start to get all the studies done and see if you meet the criteria. Baseline is when you're starting to get the drug. So you have to be moderate to severe at 3 or 4. A lot of people will say, what does that mean? How will I know if I'm moderate to severe? These are assessments that the doctors at the clinical trial sites will do for you. But it's typically over 10 blisters. There's some other kind of permutations of what else that could look like but it's a good number of blisters. Again, you can be newly diagnosed or relapsing. This performance status is just to make sure that we have patients that can actually come into the study site, get the medication, administered, and participate in the study. For performance status, someone who is bed bound and can't leave the house would not qualify for this study. Women of childbearing potential can be part of the study, but have to be using effective or acceptable methods of contraception even past, when they're finished taking the active medication. Pregnancy tests are administered at screening and baseline to make sure that no one's getting pregnant during this study or starting the study pregnant. And the male participants have to use an acceptable form of contraception. Now, if you're postmenopausal obviously this does not apply and there as separate rules for postmenopausal women. So that's inclusion criteria.

Dr. Culton: Now we're looking at exclusion criteria. These are things that, if they were positive, would mean you probably cannot be in the study. So other forms of pemphigoid. There's a whole bunch listed here, but there's forms of pemphigoid that are due to drugs and as soon as you stop the drug, the pemphigoid goes away. That would not be a person that would be eligible for this study. Other forms that are mucosal predominant, so you don't really have any blisters on the skin only blisters or sores in the mouth, that is not what this study is recruiting for. So we're looking for patients with blisters on the skin. You can have things in the mouth as well, but you have blisters on the skin as well. And then other autoimmune diseases, autoimmune blistering disorder like pemphigus or EBA those patients are not eligible for the study. It has to be bullous pemphigoid in its kind of classic form. You can't have received unstable doses of medications that are known to exacerbate bullous pemphigoid. A lot of people when they get their diagnosis, the doctor will look at all their medications and see if there's any medications that are known to exacerbate bullous pemphigoid. You can be on those medications, you just have to be on a stable dose for 4 weeks before. If you have used other treatments for bullous pemphigoid other than kind of the classic treatments of steroids, either by mouth or topically or the other immunosuppressants we talked about such as Azathioprine, Methotrexate, Cyclophosphamide, Mycophenolate, Dapsone . If you use other treatments, a lot of them are listed down here, there's different times that you have to be off that medication before you can be part of the study. We won't go into that in detail. One that's worth taking note of would be, if you have had a B cell depleting agent like Rituximab, you can't have had that within 6 months before your baseline visit. That's just to make sure that some of these old medicines aren't hanging around and causing you to be better but then we accidentally attributed it to the study drug when it actually is one of those old medications. So that's the reason for this. Again, because the study design requires you to take steroids, exclusion criteria also include if you have a known contraindication to steroids, That means if you know like I have terrible diabetes and as soon as I get on steroids of any dose, my sugars are through the roof and bad things are happening. If you haven't known contraindications to taking corticosteroids that's an exclusion criteria. And, again, all of these inclusion and exclusion criteria are really meant for you to go through with the doctor at the study site. Some of them are pretty easy to say, that’s me or that’s not me but some of these, again just giving caution, we don't want you trying to figure out if you're eligible for the study based on these. A doctor can kind of talk through and your study coordinator can talk through some of these things with you. You can't have uncontrolled infection at the time of screening. You can't have a positive COVID test at the time of screening, any other autoimmune disease that might interfere with this study and then any malignancy. So that's pretty common for clinical trials is that if you have a history of malignancy, that you can't be in a study. And there are, of course, there are exceptions here. In

dermatology, we think a lot about skin cancer such as basal cell skin cancer or squamous cell carcinoma, cancers of the cervix and breast, Some of these you can still be part of the study. So, again, it's worth talking to the study sites and the study coordinator to see if any of these things actually would exclude you from the study. Then, here's the last few, any other serious diseases. Somebody who has recently had a surgery or is going to be having a surgery during the study period, it would not be a good idea for you to be in a clinical trial. Again, any other investigational product that means if you're an you've just been in another study and you're coming out of that, you can't just roll right into this study or if you have previously been in a study with Efgartigimod, which I can't imagine that applies to anybody but it's part of the exclusion criteria. With that, we'll just conclude.

Dr. Culton: Again, bullous pemphigoid is rare but the most common of the autoimmune blistering disorders with about 41,000 patients in the U.S.. It is caused by IgG autoantibodies against BP 180 and BP 230, those are the proteins holding the epidermis and the dermis together. And really, these autoantibodies are what's triggering that whole cascade of inflammation that causes the blisters and the disease. The pre-clinical and clinical evidence is what links, IgG, autoantibodies levels to disease activity, which makes us have the hypothesis that if we reduce the level of IgG autoantibodies, the disease activity will go down as well. So this is a registrational trial for BP, there's more information here. This is the patient inquiry study page that there'll be links to. Then the know.rare.com page as well, which is just a great resource for, for patients to link in too, to again, see if you might qualify for this study, to find out where the study sites might be. And, again, on every single slide, you probably notice it says the “The investigational study drug Efgartigimod has not been approved for the use in treatment of Bullous Pemphigoid by any regulatory agency as effectiveness and safety have not been established.” That's the whole point of the clinical trial, is to make sure and to assess, to study, whether the drug works and is safe in patients with this disease.

Dr. Culton: Just the last few important points, a lot of this stuff we covered, but it's placebo controlled, so 1 to 1. All patients are going get steroids. in addition to the injections. Again, you won't know, the investigator won't know, the doctor won't know whether you're getting the active drug or the placebo. And if the treatment is not effective, this is an important point, because not all studies have this, if the treatment is not effective, the patient can receive standard of care treatment so any of those other medications we talked about as a rescue therapy and stay in the study. You wouldn't be getting any of the injections. But you would then be eligible down the road for the Open

Label Extension, which is the part of the study where everybody knows that they're getting the active drug and nobody's getting placebo in the Open Label extension. So I believe that is the end, and maybe you can take me away from being the presenter so we can see everybody's face again.

Becky Strong: Thank you Dr. Culton. We really appreciate that. We definitely have learned a lot from you and from the presentation. We did get some questions coming in during your presentation, as well as pre-submitted. So if you don't mind, I'm gonna go ahead and ask you and Ravi some of the questions. So Robert is asking, can topical steroids be used along with the 0.5 milligrams per kilogram of corticosteroids?

Dr. Culton: So, I'm going to answer this and then just ask Ravi to make sure that I'm right. But topical steroids have to be stopped at the baseline visit along with all the classic immunosuppressive medications. So a lot of studies have what's called a washout which means you have to stop taking medication something like 3 or 6 weeks in advance whatever it may be. There is a defined period of time where you have to stop whatever medication you're on before you get that first treatment of the study drug. In this study, there's no wash out for those medicines, including topical steroids. But you do have to stop them on that baseline visit where you're getting your first injection.

Ravi Shah: I would just say it in addition to that, for topical steroids if you're going to receive treatment, whether it be the active treatment or the placebo it is definitely prohibited. Dr. Culton is right, that's something that we, we kind of have to control for that setting. So it would definitely be prohibited.

Becky Strong: Okay and you did say, you have to stop and go off of all of your current treatment to participate in this study?

Ravi Shah: That's correct. Let me just make a caveat, treatments related to BP. So again, if you have other health issues that are happening as well, people have to make that call such as your doctor about whether or not you'd be a good candidate. So if there are some other issues happening, that's a different story. But in particular for this trial, for bullous pemphigoid like everything that Dr. Culton said, we have to be able to kind of evaluate the effectiveness of this drug. And the only way to really kind of do that as deemed by the FDA is that we kind of have to stop your current BP treatments in order to evaluate the effect.

Dr. Culton: And I'll just chime in from a physician point of view. Again, having done studies, some clinical trials are designed that you have to be off all of your medications well before you get your first treatment which is really hard to do for a lot of patients. I think one of the benefits of this study design is that it allows you to stay on the treatment until that baseline visit. So there's no, what I think of is not really a gap in the therapy, because at baseline visit you're going to start getting your steroids and potentially study drug versus placebo.

Becky Strong: Great. Well, that leads right into our next question. The next question, this person says, I'm afraid I will get the placebo and get a flare. Is there a way to be able to get chosen for the study arm or the part that receives the medicine?

Dr. Culton: Wouldn't that be lovely.

Ravi Shah: That would be great.

Dr. Culton: I think that is the really difficult part about choosing to be in a clinical trial. Yes, you do have access to a brand-new medication that might be amazing, but there's also the possibility that you would get the placebo. The FDA is actually the entity that dictates a lot of how these trials are done and the FDA really pushes for placebo controlled trials, thinking of them is just the cleanest way to interpret whether medication works or not. So yeah, it's possible that you might get the placebo. Now in this particular study, as you taper the prednisone if the blisters come back, again, you would have to go back up on the prednisone and try again. But doing that twice, then you're a treatment failure and you would go into standard of care treatment and then you would still have access to the open label, like knowing that you're gonna get the drug down the road. But I definitely understand that that is a concern of patients going into a clinical trial that's placebo controlled, but I will say, most clinical trials are placebo controlled.

Ravi Shah: Great, I don't think I can add too much to that, because I think that's probably the perfect response that you can give. In an ideal world, we would love to give everyone the drug, but this is kind of how we have to do this in a clinical trial setting. Just real quick, I know we had a question about the wash out period. So, definitely for topical steroids, and Dapsone and things and Cyclophosphamide and some of more typical treatments there's not a wash out period but there are going to be some wash up here's your things like Tetracycline, like an antibiotic and that could be like 2 weeks. There can also be discontinuation for maybe 4 weeks, as well as IVIg,

Sulfasalazine and some other different drugs that might require a 2 month wash out. Again, I think Dr. Culton mentioned in the presentation itself, if you've been on some sort of investigational product as well, we'd want you to at least have, whichever is longer between the 3 months or 5 half lives, that's just a measurement to just make sure that drug gets out your system, So just, want to touch on that real quick.

Dr. Culton: I'll just chime in. I think a lot of this can be really overwhelming when you're sitting there thinking, like, gosh, I'm about to sign all my life away to be in a study, and then I won't have any control over anything. The whole point of clinical trials is to support the patient. At any time, you're consented, you're getting all the information, and at anytime you can decide with your investigator, with your doctor, that this is not right for you anymore. You want to make a good decision with all the information that you're given. But I think some people feel that once they decide to be in a clinical trial, they're locked in and bad things could be happening and there's no way out, and they signed up for this and they can't get out. And that's not how it is. It'simportant to remember, as a doctor who does clinical clinical studies all the time, always number one is patient safety and making sure that the patient is taken care of. You have the voice, at any point you can say, I cannot be in the study anymore, I need to pull out. Of course, we want people that are making an informed decision to be in the study in the first place but it's not like you're signing a contract that you can never back out of being in the study. So I just say that, because I think that's an anxiety, especially when you're talking about you have to stop this medicine and they might flare, and all this stuff's happening. The benefit of being in a study is that you're being seen every single week at no cost to you as a patient, and monitored so closely. So in some ways, you have such TLC around you, while you're in a clinical trial. So there are definitely perks, too, that I think, sometimes we get into the nitty gritty of inclusion and exclusion criteria it can feel we don't get time to cover those as well.

Becky Strong: Great. Robert is asking, have you done a safety study so we know the number of patients that have tolerated this drug well?

Ravi Shah: That's a great question. So there are definitely a safety pool of patients who have actually been already exposed to Efgartigimod. Efgartigimod is approved for a different neurological condition. We have had a trial done in that manner. We've also had a Phase 2 trial done in the pemphigus vulgaris arena as well. So there is definitely, safety data around Efgartigimod. From what I can say in terms of safety, just given the mortality of this disease and whatnot, there haven't been any deaths that have been reported due to Efgartigimod. There haven't been any serious adverse events as far as

we know about but that is something that we are continuing to monitor as well. That is the stuff that I can say on this webinar.

Becky Strong: Great, thank you. You had mentioned Dr. Culton, during the presentation, about having control of your disease. What does that mean? Can somebody have a blister, a small one, no blisters? What does that look like?

Dr. Culton: I'll just back up and say again, to be in the study you have to have active blisters at the time of the screening. So at the time that you kind of roll in and you're like, here I am, I might want to be in the study., you have to have some blisters, and not just like 1 or 2, you have blisters. You will get started on the steroids and then either the placebo or the Efgartigimod. Then what we're looking for is control of disease activity, which means no new lesions and most of the old lesions are starting to heal. So what that means is that even if you get one new blister during that period of time, you are not having control of disease activity by this definition. Which, again, a lot of the experts that treat these diseases came up with, all these terms so that as we started getting interest in doing clinical trials, we would all be using the same words, that we know what they meant and these are things that the FDA can kinda hang their hat on. For example they know, when we say controlled disease activity.

Becky Strong: Great. I think you answered this during the presentation, but if you could just answer again. Will argenx need a new skin biopsy if I've already had one to confirm a diagnosis?

Dr. Culton: Historical biopsies can be used. But we just again need to confirm that we have both types of biopsies. We talked about the biopsy for the regular histology and then the fancy biopsy that looks for those antibodies, the direct immunofluorescence. So both of those need to be done and then I'll just defer to Ravi to make sure that there's not a timeframe. Like, if it was done 10 years ago, was that still acceptable?

Ravi Shah: If there is history of it we'll definitely take that, as far as eligibility, but the thing is, there are also blood draws within the study as well. So, we can definitely confirm by the serum if there are antibodies as well. So that's another result that can give you a positive or negative, that we will take into consideration.

Dr. Culton: So yes, historical biopsies should be able to be used. Some people say, well, I had it like 15 years ago, and it was at mom and pop dermatology, in middle of

nowhere America. We have to be able to track down the biopsy report. So that's the only thing to consider. If you can't remember where you got it unfortunately, it can't be word of mouth. We need to have the actual biopsy report, which we're really good at tracking down.

Becky Strong: Great. And then this kind of plays into something that you said, Ravi. You said that bloodwork is necessary throughout the trial. Do I need to go to a special lab to have blood work done, or can I have it done at a lab near me as long as they're able to run the test?

Ravi Shah: So all the blood draws are actually going to happen at the site that you go to and the doctor's office you go to. They're the ones that are going to be sending it off to the lab. to look. So it's not something the patient has anything to worry about in that sense but it's more of the behind the scenes work so we know when it's done.

Becky Strong: Okay and you had mentioned during the presentation as well, that you need to have skin lesions. That it's okay to have oral lesions too, but you definitely need to have the skin lesions. There was a question that was asked, what if I have been diagnosed both with pemphigus and pemphigoid, can I participate in this trial?

Dr. Culton: Unfortunately, that makes you a very complex patient and this clinical trial is really meant for patients with bullous pemphigoid only. So if you also have a diagnosis of pemphigus or only a diagnosis of pemphigus this is not the study for you. Again, Ravi mentioned there's another study going on in pemphigus, so if you only have pemphigus you could be in that study. But if you have a weird overlap, I shouldn't say weird, rare, rare overlap of the diseases, this study would not be for you.

Becky Strong: So how do patients find a clinical site near them to see if they are eligible and how far they would have to travel?

Ravi Shah: Sure, I guess I could take this one. Earlier, Dr. Culton had mentioned that there is a patient website, which is www.balladstudy.bp.com. In there, there is a contact form for the organization we partner with called NoRare, which basically gives them permission, once you fill out that contact form, to have trained patient advocates reach out to you. Then basically what happens is these advocates will then call you, share more information about the study and then answer some questions. Then if it appears

that you're eligible, then they'll go ahead and review the locations that are nearest to you. Then in regards to, Dr. Culton had mentioned, these are weekly visits and we know that sometimes that can be burdensome, but any issues regarding travel, the same advocates at NoRare will research and share different options that are available. There might be transportation, including a car and obviously, this is at no cost to any trial participants. And if you need support from a care partner, please share that with the patient advocates. They'll make the arrangements for them to travel with you to the study site. Again, no cost for the participant to participate in the study. And anything in terms of meals and beverages while traveling to the site, that will also be covered.

Becky Strong: Great information. That was going to be one of the next question, was there travel assistance? So, thank you. You had also mentioned that this medication is injectable. Do people need to go to a special site to have this done or can they inject the medication at home?

Ravi Shah: Unfortunately, right now, it's not something that we're allowing for home use in terms of being able to inject. Right now, because we are in a clinical trial setting, for the visits that you do on-site, those injections are going to happen by sight staff, aka, somebody who's certified to give that injection. As Dr. Culton mentioned earlier, there are home visits that can happen, and that's going to be done by a nurse, at home.

Becky: Great. And also because this medication is injected, what sites can we use? I know a lot of patients in our community do have lesions in different places, and not everybody gets them in the same place. So what injection sites can be used?

Ravi Shah: Sure, Dr. Culton I'll let you give some experience about subcutaneous injections, just in your experience then I will go ahead and answer.

Dr. Culton: We do a lot of types of injections in dermatology. Sometimes when we're doing intralesional injections where we are injecting right into the skin where a spot is. This is different. This is a subcutaneous injection, which means it goes, when we looked at those picture, it goes through the epidermis, through the dermis, all the way down to the subcutaneous fat layer and even a little deeper in that. So it's going under the skin. Then the idea is that it circulates and goes all through the body. So you don't have to inject it into a particular lesion. So most subcutaneous injections are given in the abdomen or on the thighs, sometimes in the back of the arms. But those are the

most classic places. And I always think, because I have a lot of patients who have to do the subcutaneous injections for all different kinds of diseases, I always think would I be able to give my own self an injection? But a lot of what patients end up doing is either having someone else that lives with them help, again, this is down the road as Ravi said. During the study, it has to be done at the study site or by a nurse, but it can be given in the abdomen, it can be thighs. I don't know if this particular study has certain areas where it says it has to be in one of these areas. Obviously if you had a blister there, we would not be injecting it at the site of the blister.

Ravi Shah: Yeah, absolutely. What Dr. Culton said is correct. Abdomen, thighs and arms. The caveat on the arms is, and I'll just demonstrate here. It's really hard for someone to reach over and do this, but trying to get this in the back of your own arms for down the road use of when trying to administer yourself, we're taking into consideration. So this has to be done by a caregiver or somebody who's certified to give the injection. But typically the abdomen or thigh is the better site.

Becky Strong: Great. Thank you. You alluded to it, that you had to take a pregnancy test before starting the trial. But can I get pregnant while on this medication and what happens if I do get pregnant during a clinical study?

Dr. Culton: So, again, part of the inclusion/exclusion criteria is you can't be pregnant coming in, and you can't be planning a pregnancy like during the time frame of the study. And, again, that's just for safety reasons. We don't know the effect of this medication on patients yet so we certainly don't know the effect of this medication on fetuses or pregnant women. The goal would be for you, not to get pregnant. If you're already planning a pregnancy, this is not the study for you. And if you happen to become pregnant during this study, you would be removed from the study. The study medication will be stopped, you will be monitored. And then I'll let Ravi chime in if there's any other things. But most of the time, that's considered an adverse event and we would have to stop your participation in the study, again, mostly out of your own safety and the safety of the baby.

Ravi Shah: I don't have too much to add to that, except probably that privacy does occur during the trial, everything in addition to what Dr. Culton said, they'll probably be a pregnancy form that gets filled out as well and submitted within 24 hours. If you're planning to have a child or planning a pregnancy, this probably is not going to be the study for you because it is going to require a time commitment. Again, you want to take that into consideration in that sense. But, again, if there is something that happens

during the trial, where there's a pregnancy being reported, you'd be removed from the trial. We would actually still make sure that you're okay and safe in that sense. But again, there'll be a one that gets filled out and submitted within 24 hours.

Dr. Culton: That's all very common for clinical trials. So this is nothing unique to this study. Most studies have something saying that you can't get pregnant while you're in a study. And so again, it's just all around the safety of the patient and safety of the unborn baby.

Becky Strong: Our next question asks, can I participate in this clinical trial if I am transgender?

Ravi Shah: That's a great question. We are definitely in a new age so one thing I would like to touch upon is the protocol allows for all adults above the age of 18, and that's basically all the only specifics that I have in that sense. So I don't think that is an exclusion criteria by any means. So I'll leave it at that.

Becky Strong: Great. Thank you. And our next question is, how does COVID vaccination or infection affect participation in this clinical trial?

Ravi Shah: I know that this is always a hot topic right now Dr. Culton. I'm going to let you for, giving your perspective just uncovered back pain and infections then I'll definitely give specifics.

Dr. Culton: We encourage everybody to get their COVID vaccine and to try to stay healthy and safe. The pandemic has had a lot of twists and turns and we're just trying to follow along the best we can. But in general, as per the inclusion/exclusion criteria, you will be tested for COVID at the time of your screening visit and if it's positive, you not be able to be in the study. If you've already had COVID or if you're getting your vaccinations, most of that is not a deterrent to being in the study. If you were in the study, and you got COVID during the study, typically, that's something that's recorded, and, again we call an adverse event. Then different studies handle a different way. So, that's the part that I'll turn it over to Ravi to see if there's any particular guidelines around that for this study.

Ravi Shah: So, our goal here, if you become positive, your are going to have to do a lot of communication with the site, when I say site I mean doctor. Then basically, your doctor is going to make that determination as well when is it an appropriate time for you to come in to get evaluated again. We obviously encourage vaccinations prior to the start of the trial, so in that sense, you have some protection, but that is your choice. But if you are deemed positive, you shouldn't really go to the site itself for visits, nor should the home nurses be coming to you in that sense. And again, your doctor's going to make that determination when it's normal for you to return to study visit procedures based on any sort of local guidelines from regulations.

Dr. Culton: I'll just say, 36 weeks is a long time and things happen. Doing clinical trials, there's a protocol, and we do our best to follow it to a T. But the truth is, life happens, and sometimes somebody gets COVID and they can't come in and they miss a visit, or these things happen so we just keep a really close record of it. And you just stay in communication with your study team. Again the whole idea that we try to do our best to follow the protocol but we understand. Your safety, your health is most important but we understand that life happens in the background of a clinical trial.

Ravi Shah: Absolutely. I couldn't have said it any better. I don't know if we still consider if we're still in a pandemic or not but it is still very much that world. So I can't agree more with Dr. Culton.

Becky Strong: Mario asked a question, on the case of the transgender subject, what sex or gender will be allocated for the study, the biological sex or the new one?

Ravi Shah: That's a great question and I'm afraid I'm not going to have the answer on hand for that. That's probably going to be more of a case by case type of scenario. That's something we're happy to follow up on.

Dr. Culton: For safety purposes, a lot of it goes back to whether the person has the ability to become pregnant. So a lot of it is around that, even if you're not planning to become pregnant, if you physically could become pregnant, that may inform what you get assigned to.

Becky: Great, thank you. Our next question asks, if I have a history of fatty liver or gnash with any amount of scarring can I still participate in this trial?

Dr. Culton: Almost all studies have kind of a caveat that the investigator, the main doctor that's at that clinical site is gonna go through your medical history with you with a fine tooth comb and identify anything that they feel would put you at undue risk to be in the study and have a discussion with you. Then there's doctors that are part of the drug company too, medical monitors and everybody kind of weighs in on it and decides. Again, it's all around patient safety but it doesn't necessarily mean that you would be excluded. But a lot of it depends on a case by case basis and the doctor reviewing your medical record, and where you are with your diagnosis and treatment, or what other things might be going on with you. There are so many patients that have lots of different, serious medical conditions. So, it would be on a case by case basis, But that, again, happens for every patient, that's considering doing a study.

Becky: Great, Thank you. You had mentioned that this is a phase 2/3 study. How does this study differ from a purely Phase 2 or Phase 3? And does combining these phases together increase or decrease the length of time of the trial?

Ravi Shah: The only reason why it's reading like that is that we're just doing this study in two stages. I think Dr. Culton actually touched on this in her presentation. The first part is going to be a Phase 2, and the second part of it is going to be a Phase 3. The Phase 2, in particular for this trial, really has to deal with about 40 patients and that is really so that the analytical data is there to salvage the proper proof of concept. I think Dr. Culton was saying that we want to make sure that we're going in the right direction, and we're getting some outcomes that are benefiting these patients. Then in the second part for the Phase 3, further enrollment will continue to establish that proof of confirmation or concept I should say. But in terms of the timeline for the study, having a Phase 2/3 model, it doesn't really affect the length or duration for a patient in the trial. It still remains at 36 weeks.

Becky Strong: Great. The next question says, the end goal is stated as complete remission while receiving the Efgartigimod PH20 SC, or placebo or having been off corticosteroid therapy for eight or more weeks at 36 weeks. How is this endpoint determined? How was the timeframe determined?

Ravi Shah: That is another great question. We were just chatting about this right before the presentation. Part of it has to do with, when we develop a protocol for a study. Dr. Culton is obviously an expert in autoimmune blistering diseases and there are worldwide experts as well so we try to take everyone's opinions who's actively trained in this diseases, in terms of looking at what are the things that we should look

for, what are the things we should include, not include based on their expertise, So this is kind of an expert consensus in that sense of how we came to this for a certain timeline. Some of it is also FDA recommendations, based on some of the other similar trials that are there. This endpoint that we have, in terms of complete remission while receiving either the active drug or a placebo, then you're also off steroids for two months, we are setting the bar this high. I'm sitting right here but we're setting it this high. If you're really getting there, that's really going to give confidence back to not only the patient but also providers to see that we have another option for our patients out there. Dr. Culton I don't know if you had any comments?

Dr. Culton: I was just gonna mention the 8 weeks. So just last week in my clinic, I had a patient who had been on steroids and not on any other medications and had tapered steroids and been off steroids for maybe 4 weeks with no blisters, nothing. And they were asking me. are the blisters going to come back? And I was like, I'm not really sure I think you're still in the window where they could. But if they had been off for 8 weeks, I'd say probably if you're on nothing for 8 weeks and you don't have any blisters, that's a much more clear sign things are in remission. And so same with this drug, if you're on the medication, and it allows you to come off of the steroids for 8 weeks, it's probably working. The blisters probably aren't coming back. You would never set the endpoint of being off steroids for 2 weeks because blisters could come back, we know that, at two weeks. So, again, that kind of expert consensus of all of us who treat this disease, thinking, when do we feel really comfortable that the medication is working and the blisters aren't going to come back? And it's not like we are in that gray zone, where they still could. So 8 weeks is a good consensus around that.

Becky Strong: Great. Thank you. This next question is a big one in our community, many with bullous pemphigoid experience the dreaded itch. So the question is, is itchiness a symptom that Efgartigimid can control?

Ravi Shah: I will take the first stab at this. It's yet to be evaluated whether Efgartigimod is going to have an effect on itch. That's something that we can't say right now. What we are going to do from this trial is actively measure that. So we are going to implement a scale, which is a numerical rating system, or ERS scale, and then we're gonna ask all these patients to evaluate their itch. So that is something that we want to look for and hopefully our goal is to obviously decrease it. But right now at this point in time we can't definitively say that, but that's our end goal to hopefully get there.

Dr. Culton: As I was giving the disclosures and all that stuff, and I do this consulting for companies and a lot of it is to make sure that when companies are designing trials for these diseases, that they're taking into consideration the things that make a difference in the patient's life and itch is a huge one of those. If you never measure it as part of a clinical trial, you would never be able to say whether that medication helped with itch. So, I think, again, the idea is that we're measuring it in this study, and hopefully, we'll have information at the end of the study of whether it helps itch as well.

Becky Strong: Great. Well, thank you. That was a super quick hour, or a little bit longer, about 65 minutes, so I appreciate you hanging with the extra time. I didn't realize we were running late. Really appreciate you being on the call Dr. Culton and Ravi, and thank you for hanging with us. I would also like to thank argenx, our sponsor for today's webinar, to discuss their BALLAD study. Before I go, I do have a few announcements. Again, don't forget to check out the BALLAD Bullous Pemphigoid Study website. I took a screenshot of it here so you can see, the website is www.ballad studybp.com. And again, as Ravi said, you can go on there. You can find out more about the study and get in contact to find out if you're eligible to participate in the trial. Join us for our next Patient Education Webinar on Thursday December 1st where Marc Yale, IPPF Research and Advocacy Coordinator and Kelly Barta, President of the Coalition of Skin Diseases will discuss "How to Participate in the IPPF Externally Led-Patient Focused Drug Development Meeting" This is a huge opportunity for the IPPF to educate the FDA about pemphigus and pemphigoid disease burden and we are recruiting patients to share their experiences in living with these diseases. You can register online today to learn more.

Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance researcher to better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! You can find the Natural History Study by visiting www.pemphigus.iamrare.org

Do you want to become a hero in our community and continue to support the free services the IPPF provides to you, such as the IPPF's Peer Coaches and our find a doctor map? If so, become a Healing Hero today! Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small even a $10 or $15 monthly donation goes a long way and continues to allow us to provide for the greater good of our community.So, thank you again to Dr. Culton and to Ravi for joining us. And as a reminder, this call recording will be sent out with the survey afterwards. So, thank you all for joining.