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Transcript of Skin Porphyrias Q&A, Sunday 4 June 2023

Speakers

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Unidentified audience members 1, 2, 3, 4, 5 and 6

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Note:
The recording starts a few minutes into the first presentation of the meeting, so this transcript is missing the first few minutes of the meeting. As a summary of the opening of the meeting, Sue Burrell welcomed people to the afternoon session and introduced the panel, including starting with the presentation from Dr Will Savage from Disc Medicine.

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Transcript

Dr Will Savage: As a company, we're also interested in iron metabolism where we have small molecules and antibodies that address either low iron or high iron states that are not directly related to EPP, but just to give you a complete picture of what we're doing. So, I don't need to tell this audience what EPP is, but maybe perhaps to let everybody know that we are listening, and we've talked to many patients, and understand the disease I think very thoroughly. EPP is a genetic condition most commonly caused by a deficient enzyme, ferrochelatase. So as a genetic condition, it's present lifelong. This mutation in this enzyme causes toxic accumulation of protoporphyrin IX. There's also, in about 5% of cases, a defect in another enzyme, a gain-of-function in an earlier step of haem synthesis, and that's been classically called X-linked protoporphyria. But it has the same mechanism of disease, where protoporphyrin IX accumulates and causes the disease manifestations, which as you know are debilitating and potentially life-threatening. The hallmark of the disease is the skin phototoxicity, with disabling pain attacks that can last for up to a week or longer, and swelling. And then a concern is the liver disease, which in milder forms can result in lab abnormality changes or

gallstones. But it can also lead to liver fibrosis and even liver failure in about 2 to 5% of patients. And there's a fair number of liver transplants that have to occur due to liver dysfunction. And of course, being unable to live a normal life in sunlight is incredibly limiting. And it exacts a very large psychosocial toll, leads to a lot of completely understandable but detrimental manifestations like fear and anxiety, and particularly in children who are less equipped to be able to accommodate this sort of limitation on life. It exacts a large toll. There is no cure or disease-modifying treatment. The mainstay is to avoid sun, which is easier said than done. There is one approved agent, approved in the US and in Europe and the UK, afamelanotide. This is a surgically implanted, essentially a tanning agent and that tanning provides barrier protection of sunlight penetrating the skin. There are variable reports. I think it works very well. What I've heard from people is that it works very well for some, not so great for others. But the bottom line is we hear that there's an unmet need, even with this treatment available. So, protoporphyrin IX, or PPIX, is the driver of the disease. That's the molecule shown in the centre here. An accumulation of this molecule leads to all the manifestations that I mentioned, the skin problems, the liver problems, psychosocial. And then those follow on to other complications as well. So, bitopertin is an oral, selective glycine transporter 1 inhibitor. So, what does that mean? Well, GlyT1, or glycine transporter one, is a transporter that is present on early developing red blood cells. And the reason red blood cells have this transporter, they actually very specifically upregulate this transporter, making a lot more of it in early stages of development, during the time the cells generate a lot of haemoglobin. So, haemoglobin is an incredibly abundant protein inside of a red blood cell. Red cells make a lot of haemoglobin, and if you go backwards in the pathway, starting from a mature red blood cell, at the very beginning, the first step requires glycine and then an intracellular compound called succinyl-CoA. But basically this is a one carbon molecule and the cell sucks in a tremendous amount of these one carbon molecules to put all the little carbons on this ring structure, on protoporphyrin IX, and then ultimately into haem. So, the whole pathway is mapped out here with the eight enzymatic steps of haem synthesis. Each one of these is a different enzyme. And then in EPP XLP, the accumulation again of the protoporphyrin IX happens here, because ferrochelatase is defective. The role of ferrochelatase is, as an aside, it's just to drop in iron in the middle here. And when you drop an iron in the middle of PPIX, you actually make haem. And so our hypothesis is that, with bitopertin blocking the upregulation of glycine at the top of this pathway, we can slow down the accumulation of PPIX and modify the disease, make it less severe. And that's shown more closely here, where on the left we're showing the haem synthesis pathway, the same enzymes but in a different format, with glycine at the top of the pathway and the classic ferrochelatase block at the last step here. And then also the ALAS2 gene gain-of-function mutation that I talked about here basically pushes glycine through the pathway to make more protoporphyrin IX. And in either case, you end up with the vast accumulation of protoporphyrin IX. And with bitopertin, by decreasing the amount of glycine available at the top of this pathway, we're essentially starving, in in some sense, the pathway of the substrate needed to make protoporphyrin IX. And so we think that we're going to decrease the amount of protoporphyrin IX. So, an important question is, how much do we have to reduce protoporphyrin IX in order to impact photosensitivity. And there are two main data sets that bracket a greater than 30% - generally a 30 to 50% reduction - in PPIX that can have what we think will be life changing impacts in EPP. So, the first is a case series of people with EPP who become pregnant. There's a phenomenon of reduction of 30-50% of PPIX levels during the latter half of pregnancy, and that reduction is accompanied by marked improvement, essentially full remission of disease, in many people. There's also an experiment done in Denmark where patients' blood was exposed to light. Basically, the blood was taken out of the body - this is a very cumbersome procedure - blood was taken out of the body, that blood was then illuminated with the light to inactivate PPIX, and then the blood was returned back to the patient. So highly experimental, but very mechanistically interesting, because that procedure reduced PPIX levels by 30%, and then the daylight tolerance associated with that reduction of 30% was an increase of 14 fold. So, an average time of light tolerance for a person with EPP is about 30 minutes, and so 14-fold increases taking 30 minutes per day and increasing it to seven hours, which is, I think, life changing. So, we have run mouse models of both EPP and XLP with bitopertin, and these are data presented now a year and a half ago, showing that in an EPP model we reduced PPIX by 45% and in XLP by 73%. So clearly within the range that we think can be potentially efficacious. And we also ran a liver fibrosis experiment in the EPP model as well and showed that bitopertin prevented liver fibrosis, which makes sense because protoporphyrin IX crystallises, essentially, in the liver and causes backup of bile and leads to liver damage. So, by reducing the protoporphyrin IX you decrease the ability to block bile flow and cause damage in the liver. So, we feel encouraged by that, as well. And, of course, we have to follow this up with human trials to show how well this can work. And so, we have two ongoing phase two clinical trials. The first is BEACON, which includes EPP and XLP. It's open. It's been open for almost a year in Australia at two sites. This is an open-label study. And then there's AURORA, which is a double-blind placebo-controlled trial that's larger, 75 patients. It's EPP only. It's been in open in the US for about six months and this

is a 17-week study. What we're looking at are, first and foremost, changes in blood protoporphyrin IX levels, but we're also measuring a number of measures of light tolerance, time to prodromal symptom, safety, and a number of measures of quality of life, as well. So, the reason we were able to go very quickly from a mouse model into phase two trials with this drug is because this is a drug we in-licenced from Roche. They had used it for another indication that had nothing to do with EPP and they closed the programme for lack of efficacy. But in the process they did evaluate bitopertin in over 4000 people and over 30 clinical trials. So we have a vast database understanding of exactly how this drug works, its safety profile, and so we could kind of leapfrog from early studies straight into EPP. So, a closer look at the study designs. The BEACON trial, I want to highlight that actually in five days we are presenting the initial data from this trial at the European Haematology Association meeting, and we should have that data available on our website soon after or via Google, you'll probably find it as well. So we're looking forward to present that. Again, this study is open-label. We are evaluating two doses of bitopertin, we call them a mid and high dose. This is based on the Roche experience, as well. These are doses that have been well-studied by Roche. Participants, importantly, are not taking afamelanotide or not on a dersimelagon study as well. So, while we're presenting interim data in five days, we're going to have a more complete data set that we're going to present at the end of the year. And then AURORA, the phase two trial, has the addition now of a placebo group, and it's double-blind, so nobody knows if they're on placebo or active drug until the end of the study when we unblind it. We're also studying the 20 and 60 milligrams, and the study duration is 120 days or 16 weeks. We will have, we think, complete data by the end of this year, with the presentation of the data early next year. And thank you very much for your attention. I'm happy to participate in this panel. It's important for us to be here and I'm happy to take any questions or, Sue, whatever format you'd like, I'll remain here.

Sue Burrell: Fantastic. Thank you. So, Will, we've already got a question in the room. So, I'm going to pass you over to Pete.

Pete: Thank you very much, that was very informative and very useful. I'm just wondering if this mechanism that you've described, presumably you're also limiting or starving the amount of haemoglobin that's produced, and what are the consequences, positive or negative, of that?

Will: Thank you. Yeah, no, thank you for the question. That's a very important question, and I have two answers. One is that, on a practical level, in the animal models, we did not observe any meaningful changes in haemoglobin, and that's actually what we expected. So, we have some level of evidence that haemoglobin levels will not change. And then the second answer is the theoretical, which I think explains the animal model data, and that is that because protoporphyrin IX is in vast excess, people with EPP already make sufficient amounts of haem, and they have a vast excess of protoporphyrin IX. If we reduce this pool of protoporphyrin IX by 30 to 50%, that still represents a vast excess over what people with normal ferrochelatase have. So, in other words, there's a giant reservoir here that will always supply ample substrate for this last step, even if we reduce the amount in this pool. And I'll say that on June 9th, we'll be presenting data on haemoglobin as well.

Sue: That was a thank you there Will, for that question. Any other questions in the room? OK.

Antony Fearn: Well, sort of, I guess linked to Pete's question, are there any particular side effects that you're either seeing or we might anticipate, as well as the benefits from this, are there any side effects?

Will: Yes, it's a very important question, too. So, part of the vast Roche experience, there were three demonstrated side effects that are known to be caused by bitopertin, and those are headache, dizziness and somnolence. So, those tended to occur early in the initiation of treatment. So there's some sort of accommodation, it seems like, but very few people - and Roche studied bitopertin up to three years and more in long term extension studies - very few people, like, less than 1% in all of their trials, either dose-reduced or discontinued due to those. So, they're very--they're most often transient and mild.

Antony: I guess it's not uncommon to see those on most medicines you see when you look at the safety labels.

Will: Sure, that that is true. I mean, I take my antihistamine for my allergies and I get somnolent and sometimes dizzy as well, but I still take my antihistamine. So, that's true. But those are, at an increased rate versus placebo. So, they are kind of common that are seen everywhere, but it is those are ones that are known.

Antony: What age groups are you encompassing in the trials?

Will: So right now we have adults, 18 years and older, for both studies. We are interested in including adolescents, where, you know, we have to, that's a negotiation with regulators. And so, the reason we started with adults is because, in general in drug development, even though there's this well-established experience with bitopertin, given that we're using it in a different disease setting, generally people want us to start in adults, have some initial data, and then lower the age. So our plan is to use data from the BEACON trial to perhaps, you know, lower the age within this study. AURORA, that ship has sailed because the trial is already ongoing and it's double-blind, randomised, and going to be done enrolling relatively soon. So, we will start with the 12-17 years and then establish safety there, and then go to even younger. But we know from all the experience with Roche, all the non-clinical studies, that we can go down, you know, we have safety in animal models to go down to as young as one or two years old.

Sue: Antony, Liezel's got a question.

Antony: Well, final question from me then. So, you've got 24 weeks duration on the trial there. Is that long enough to be able to prove efficacy in an EPP treatment?

Will: Yeah, that's a great question. So the key is, we think that there's a very tight linkage between how much PPIX there is and how much light tolerance there is. And in the most conservative theoretically long limit, you would have to turn over your--your red cells live for about 100 days, your entire red cell mass. And so, if you waited 100 days, or like three months, your entire red cell mass would be turned over. And so, that would mean that every red cell, which is the source of protoporphyrin IX in your body, would be gone. So that's kind of the theoretical limit you would have. Basically, there's no potential for any more improvement after 100 days. That's on one extreme. On the other extreme, what is known in EPP is that the protoporphyrin IX leaks out of red blood cells and into the plasma. And then once it's in the plasma, which is the liquid part of the blood, it gets cleared in the liver. And so, there have been studies that show that that clearance, or that leakage, out of red cells occurs within about four weeks, and then it goes pretty quickly into the bile and excreted that way. So, on the other end, within four weeks we could expect to see pretty large responses, following that line of data. So that brackets a four-week to three-month window in which we should achieve maximal effect. And so, given that we're studying four months in AURORA and six months in BEACON, we should see the effects within that window.

Sue: I'm just going to introduce very quickly, we've had Dr Liezel Griffin, a consultant from Salford.

Dr Liezel Griffin: I have a very quick question, Will. I'm sorry if you've already addressed this. I had some traffic on my way here. Why was Australia chosen as the centre for the phase two trial?

Will: So Australia has, well, because BEACON is a relatively small study with only 20 patients. We knew we needed to only go to one country, and because AURORA was in the US and we had established relationships with a large number of investigators there, we didn't want to steal from the pool of potentially eligible people for that study. So we wanted to go to a different country. And then the reason why the other country was Australia and not somewhere else, is Australia, in drug development, has a pretty expeditious path that is, compared to other countries, light on red tape. They do a thorough-- they do a review of the safety and ethics of everything, but it's faster than other countries. So, it's actually common, not just Disc, but other drug companies, for early stage studies, when you want to get it going quickly, you often go to Australia. So that's part of it. The other part is that there are two, I mean, so this is Gayle Ross and Peter Stewart, who have a lot of experience in EPP in Australia and have participated in other trials as well.

Liezel: Thanks. That's a really interesting answer, actually, really interesting. Are you likely to be running phase three trials in Europe and would you include the UK if so?

Will: Yeah, so absolutely, that's our plan. If everything goes well with the phase two, we would like to initiate a phase three trial next year. I think we definitely want to include Europe. There are as many people in the UK, there's as many people with EPP in the US, or perhaps even more in UK and Europe. So, I think part of the reason we engage with BPA and in other conferences is not just to spread the word about what we're doing,

but it's also to understand what the interest and enthusiasm is for participating in trials. And one thing that's been very loud and clear from the UK group is the enthusiasm to participate. So that's actually a reason why we want to go to the UK.

Liezel: Right. I have a list of patients whenever you're ready [laughing].

Sue: Yeah. Well, that was the same question that someone else in the room was about to ask as well. So there's interest within the room as well.

Antony: Just building on that last question about location as well. I think one of the challenges that the Clinuvel and Mitsubishi trials have faced in the UK has been the nature of the UK climate. Does the nature of the way your drug works versus those other treatments make it more suitable to a UK-based trial than those other treatments?

Will: So that's an interesting question. And I think part of it, I'd like to turn the question around and ask you because I have not experienced EPP and so it's very, you know, people who have EPP or you, this group here, who knows more intimately people with EPP. You know, I mean, EPP is found in, you know, the north of Norway and in Miami, Florida and everybody seems to describe light intolerance, whether it's cloudy weather, sunny weather. And so, I haven't heard a narrative that says like, you know, light tolerance is exquisitely different in one location versus another. I mean, the disease is manifest kind of everywhere. And the Mitsubishi phase two trial of dersimelagon published an abstract last year saying that the season of enrolment did not affect the efficacy that they were seeing in terms of light tolerance. And that was obviously a global study. And so, you know, seasonality being a surrogate for location of kind of like wintery months versus summary months. So I haven't seen any evidence of that, but again I'd turn it around and say is there a reason that light tolerance would be different in the UK or northern Norway versus Miami?

Antony: I don't think there is a difference in my tolerance, I think the subtlety we have in the UK particularly is that the weather changes not just on a weekly basis but probably three times during the day. That the amount of exposure you're getting to that wavelength that triggers EPP can vary significantly even during a day and from day-to-day. So, for people who are probably slightly more tolerant to that wavelength of light, you know, you can have a relatively bright day followed by a very cloudy day where you probably don't have a huge amount of effect. But if there was two, you know, when you've got a very bright day or two very bright days, three very bright days, coming on top of each other, yeah, the effect happens, and you're just out of play. Now when it comes to patients being able to report the efficacy of a treatment and getting good data that is not highly weather-dependent, and taking out nuances like that, then
where you're relying on treatments that rely on you being able to get out into the light, which is not just weather-dependent, it's also lifestyle- and work- dependent, so you've got to trigger the melanin production in the first place for the other treatments to be effective, then that probably adds complexity to those trials that you might not be facing. Does that--?

Will: Yeah, no, thank you for that answer, that is helpful and it did bring up another response I'll just add quickly, that the important metrics or endpoints for approval are cumulative experiences. So, while the precedented endpoint for Scenesse was a total time in light over six months. So day-to-day experiences are less important than averaging it out over six months. And then when you compare that to a placebo group, you can then hopefully see the difference, and you don't have to explain necessarily one week versus another week, but just overall light exposure. So you should be able to get a signal, I think, regardless of the pattern that you're describing. If people are making an effort to get out in sunlight, it'll I think become apparent over the long run.

Antony: I guess what I'm sort of reading myself as a patient, I don't know the complexities here, is that because you're getting much closer to that, you're actually involved in the production of the haem process there, rather than suppressing the amount of light that's penetrating the skin to affect that production. Then in the UK, if you're taking that down to a certain level, it sounds really exciting in terms of, you could, you know, very quickly, UK EPP patients that probably have less exposure to regular light, it sounds really exciting as a treatment.

Will: Well, thank you. Yeah, I think it's independent of sunlight. I mean, that's why we're excited about it, too,

and why we chose to develop it first in EPPs. The amount of light should not matter whatsoever. And so this, I think, will work. You know, it doesn't require, to your point, any, you know, light for it to work. It works just through, on its own, as the blood cells are being formed in the marrow. So different types of experience with light hopefully should wash away and just say you can, you know, get a new experience with sunlight, regardless of what your prior one was.

Unidentified audience member 1: Hi Will, I was wondering if there are any plans to see if there are any additive effects of the bitopertin with any of the other melanin modulating drugs.

Will: Yeah. So I think at some point we may evaluate that. I think our first priority is for an approval pathway. It becomes a lot more complicated when you look at things in combination. So our first priority is to get bitopertin in isolation approved. It's not just complicated on a regulatory side, but scientifically you're adding in a confounder that makes it harder to understand what your drug is doing independently. So, that said, I will say there is, you know, I've kind of done the thought experiment, well, of people who are going out in sun more should get more tan, and there should be some compounding effects of the natural tan, to the extent that the drug allows people to go out in light. It's not a direct answer to your question because it's not taking another drug, but I think there's some of that activity going on in these trials, that as people go out, get a little bit of tan, and then they compound the efficacy, you know, perhaps as the study goes on. But I think it's something that we certainly will look at doing later on, once we're later on in development. And I'll just say, there's also no mechanistic reason that we're aware of now why it could not be combined with other therapies. I think we have to look more closely about the liver metabolism. Bitopertin is metabolised primarily in the liver by CYP3A4, and I think dersimelagon is a CYP3A4 metabolised drug. But it doesn't mean they can't be used together. It just means you have to be thoughtful about how they're used.

Sue: Will, I've got a question about, you mentioned about potentially that it could be available later for children and you said that dosage possibly from ages one or two. In terms of the formulation of the medication and the bitopertin already, is it in different formulations for youngsters, like for infants, or would you have to redevelop the formulation to be able to prescribe to children?

Will: Yeah, we would have to redevelop. So again, one of the reasons we were able to go quickly in EPP is Roche had done all of the manufacturing for tablets. And so, that gave us a blueprint to say, OK, we just need to do exactly that, and we know that regulators already endorsed that production. So we've only made tablets thus far, so adolescents should not have an issue with tablets. Going younger than that, we're still several years away. So we don't have final plans on what that could be, but we're certainly evaluating all the options. You could have a suspension formulation, that's a liquid format. You could have a smaller tablet, like very mini tablets, you know, this 20 milligram dose. We're not reporting which dose is necessarily efficacious but you have, you know, as you get younger and smaller in body size, you need smaller doses of drugs. So if this 20 becomes a 5 milligram, you can make very small tablets with that. So we're evaluating that too. But we won't know for a couple of years. And I think part of it is we want to see that, again, sequentially it works and is safe in adults, works and is safe in adolescents, and then we commit to the multi-million dollar process of making a different formulation for younger children.

Sue: Alright. Thank you. Any other questions? Any questions in the room from anybody? No. OK. So, I've just looked through my list of questions and all of them have already been asked and answered. So I think, Will you're very welcome to stay with us for the rest of the session. But if there's no other questions directed probably to you, if you wanted to disappear back to your day, you would be very welcome. I'll just check again that there aren't any other questions in the room before you disappear off the link.

Will: Well, I'll stay for a little bit. I do have to actually get to church in a little bit, but I will stay on for a bit. And I'll just thank everybody again for including Disc and me in this programme. And if there are questions that come up later, just let Sue know. We email about other things as well, so just let Sue know, I'll be happy to answer them. So thank you.

Sue: Wonderful. That's great. Thank you so much Will, very much appreciated. We'll leave you on the screen, but if you do want to turn your camera off, feel free to, we'll just leave you there. And we know that you're in the room and feel free to just butt in if you want to ask anything, I'll keep my eye open for your hand up if you put it, but if I don't see it, just ask it. Thank you very much though as well. We've also now got, as I said, Dr

Liezel Griffin in the room as well and we thought it would be nice, if you'd be happy to, to just give us a little bit of an overview of the cutaneous porphyrias. Just a little bit of a very brief overview. We've talked about them a lot already this morning at different levels, so a brief overview, but maybe a little bit about the different types.

Liezel: Sure, I mean, I have to apologise in advance, I haven't had any time to prepare for this at all. The reason being, I'm doing my MD at the moment with a focus on EPP and I have spent the best of parts of the last week reading about alpha MSH. So my head is full of alpha MSH, yeah, exactly, exactly. So, I'll start with EPP. So, my main clinical interest is in EPP and that's what the focus of my MD is as well. I work in the porphyria service at Salford Royal Hospital in Greater Manchester, alongside my colleague in chemical pathology, Denise Darby. So we split the clinic into the cutaneous porphyrias, who I look after, and the acute porphyrias, who Denise looks after. But there's obviously a bit of overlap. Also, twice a year Dr Schulenburg-Brand, who's based in Cardiff, comes up to run an outreach NAPS clinic with Denise. So I don't get involved with the NAPS service because that is solely for acute attacks of porphyria. I'm a dermatologist by trade, so I'm much more interested in anything to do with skin. And basically, we have about 55 or so EPP patients that I look after in Manchester, but not just from the Manchester area. Patients come from as far afield as Nottingham, Derbyshire, Birmingham, up to Cumbria, and I'm very happy to look after all of them, basically. I'm sure some of you in the room either have EPP or relatives with EPP and understand very well about the acute photosensitivity that's caused. So, how much detail do you want me to go into?

Sue: I think we've probably kind of covered the main elements there. I think Liz covered the basic bits this morning. And then I think if anyone's got questions, I think it's the main thing.

Liezel: I'm quite happy to go into stuff, but it might just be very boring for you. So we could do an interactive kind of thing.

Sue: Yeah, I think that would work nicely. Interactive, yeah. So and in the room, we've only got EPP in the room. Kirsten's here as well, her family have VP, but Danja's in the other room going through the cutaneous, as well as the acutes in there, so anyone with VP and HCP is in the other room. So everybody in here, we haven't got anybody with PCT. So everyone is EPP in the room. So we don't even need to go through a PCT.

Liezel: OK, I could have done, but it's probably not very interesting for you. So does anybody want to ask me anything about our service or what we can do to help or what you can do and what's available out there?

Sue: So I've got various different questions that we've collated and some people sent some in advance. It's for the whole panel, so the mics can move around. So, we've got presentation in a little bit that we'll put on from Clinuvel that is a short presentation about Scenesse, but the question was that they've read about Scenesse as a treatment for EPP and that it's in Scotland. At the minute, it's still not available in England and we have no idea, really, anything around that. The question specifically was, why is it only available in Scotland and not elsewhere in the UK?

Liezel: I can answer a bit of it then I'll pass over to Robert and Vicky who will be able to explain why the Scottish regulatory authority's so sensible. So, the approval for Scenesse has been through a six-year process in England and Wales, through NICE, which is the National Institute for Health and Care Excellence, and they have a panel who decide whether medications can be approved for use in England and Wales. And they go through very set criteria, which unfortunately don't always take into account the intricacies of rare diseases. And if there are small numbers of patients, which there are in EPP, they don't see it as being beneficial, in terms of cost benefit, for them to approve it because it's an expensive drug. However, we in this room would obviously all disagree with that. So it went to appeal, and then went to appeal again. And most recently, I'm sure this information's already been shared, I know it was in the newsletter, so I can say that in the last couple of weeks NICE have decided not to approve Scenesse in England and Wales. However, I don't think the story is over, and I hope that that situation will change, but obviously we'll keep you posted. I can tell you that's the reason it's not approved in England and Wales, because NICE didn't accept that it was of enough financial benefit, basically. So, I'll move on to Robert who can explain why Scotland is so sensible. Just before I do, just to mention that unfortunately I have had patients say, well can't I just go visit Dundee and get some afamelanotide, and I said no, unfortunately not. It's not possible for you to be treated as a non-Scottish resident, and I have a patient who actually is considering moving to Scotland in the hope that they may get afamelanotide. I'll pass on to Robert.

Dr Robert Dawe: I'm not sure exactly why we're allowed it the moment in Scotland. I mean, the background is, as I think you all know, that afamelanotide increases your melanin in the skin. We don't know exactly how it works, but we think it's not by physically darkening the skin, it's more by getting an antioxidant to your melanin where you want it in the skin, and there are other treatments that do that. So, part of the reason why it has eventually been conditionally approved through the ultra-orphan drugs route in Scotland--so this is just a conditional approval, they're only allowed to use it *at the moment*--I think part of that reason is that there is a national Scottish Cutaneous Porphyria Service and that does mean that we've been able to set criteria, including having tried other treatments like UVB phototherapy without sufficient success before moving on to this. I think that maybe has made it a wee bit easier that we have that system. But part of it is also political, this still fairly new ultra-orphan drugs route, that's the Scottish Medicines Consortium, which is the equivalent of the English NICE, National Institute for Health and Care Excellence, and recently they've had this ultra-orphan drugs route, where medications that are for less than 1 in 50,000 of the population can go through that route, and it's been conditionally approved through that route. Sometime early next year it's going to be considered again by the Scottish Medicines Consortium and we don't know what they're going to decide. I mean, to my mind it still seems a bit silly, but I think the idea is to see if it works on Scottish people as opposed to other people.

Sue: And are you having to gather a lot more data to be able to feed back to them so that they can then evaluate it based on your data? Or, how will they then review that process?

Robert: We do need to collect data. It's the same data that's been collected in the registry in Rotterdam, that most people who are getting this drug with EEP want to participate in, and so far all the people in Scotland who've had it have participated, and are participating, in that. I'm also collecting other bits of information, I don't know whether it will be looked at or not, trying to deal with some of the difficulties. So, like, one patient who really benefited, she fills in her diaries and everything, and she didn't have much trouble in the winter months because she wasn't going out, because it was too cold, and so it looks as though the treatment's maybe had a neutral effect, but it's really been massively effective, and so I don't know how much that extra information is going to be looked at, but we've been trying to collect it.

Sue: Great, thank you. That's really helpful.

Antony: Sue, you probably know, well, everyone, pull me up if I'm incorrect on this, but I think to try and explain one of the reasons why this process seems to be taking so long, is that NICE want the treatment, the efficacy data, to be presented in a certain format, and the way that it's been presented by Clinuvel originally wasn't in that format. So, we've got a scenario where we've got apples that are being, sort of, you know, an orange, you're trying to compare it in apple or, probably more subtle than that, you might have a lime that's been, you know, presented as a lemon, you know, trying to compare lime and lemon. And the difficulty has been trying to get Clinuvel and NICE in that common dialogue, where they're agreeing on the way the data is presented, the way the data is measured, so that the health economics can be really nailed down and we know what the true cost per benefit is that treatment gives us. And I think that's where we're at and that's the reasons we just need to, you know, everyone needs to find a way of getting that dialogue together.

Sue: Yeah, and I think the BPA are working as well with the doctors, so with the British Association of Dermatologists, with other partners, charities or patient organisations, the International Porphyria Patient Network, that have done a massive amount of research on pulling together data. They've spent a lot--they're EPP patients but they are also scientists and Dr Jasmin Barman has done so much work in trying to present it in a different way so that they'll really look at the fine figures. So much work has gone in on so many levels that it's really frustrating, but I think the dialogue with NICE is still open and new medicines now coming forward, it's just been a very frustrating state when there is a treatment that is helping some patients in places that it just isn't available at the minute in the UK.

Liezel: But it's not over yet.

Sue: It's never over [laughing].

Liezel: Maybe the data from Scotland will help, potentially. And how many patients are on afamelanotide in Scotland?

Robert: I've given it to seven patients, though only two have had three implants. I'm going to be doing another few next week. One in the west of Scotland, in Glasgow, has also had it from doctor care there, so 8 in total, so not large numbers at all.

Pete: Why so few, given you've got 40-50 patients?

Robert: For a variety of reasons. So quite a lot of the patients don't need it and don't want it because they have UVB phototherapy, they do extremely well with it, so they prefer to continue with an established treatment that's been around for a long time. And another reason is a practical one. The manufacturer doesn't supply any device to implant it, so I won't go into the graphical details of how we end up getting the implant in, now. The patient who talked earlier mentioned that the first *[inaudible]* was a bit fiddly, and that's true. So one of the difficulties is just practically delivering it. I mean, ideally there should be an implantation device. And another part of it is that we have had to set quite rigid criteria as to who is eligible for it. I think if we hadn't done that, the Scottish Medicines Consortium wouldn't have conditionally approved it.

Pete: OK, so what rules do you have around who can have it and who can't?

Robert: We've tried to keep it as simple as possible, so people have to score severity more than six on quality of life over the last two months on just a simple 1-10 visual analogue score, and similarly a number of problems with skin phototoxicity. And they also have to have tried other treatments, including UVB phototherapy. Fortunately, we didn't have to be too specific about what means a success or failure of the other treatment. It just has to be deemed by the Scottish Cutaneous Porphyria Service, so essentially I have to say I think they haven't done well enough with UVB, and then that's another eligibility criterion.

Pete: OK. So have you actually had many patients coming to you asking for it where you said, sorry, you've not quite met the criteria?

Robert: No, no, I mean, usually the people who've asked are severely affected, some more than others, but they've all been eligible.

Pete: OK, thank you.

Robert: I had one patient who was thinking about it, but she agreed to try phototherapy first and she had benefit, but not enough of it. So there are some people who've tried something beforehand.

Sue: So, is it OK if we move to just talk a little bit about symptoms and general complications? I've got a huge list of questions that I'll just start running through. These, again, are ones that have come in via the helpline or from some people in the room. So, one was just general discussion about how people manage the pain of their actual photo reactions. So, what would you guys recommend as doctors when you're treating patients? What would you be recommending for people to use when they're in that reaction state?

Robert: As I'm holding the microphone, I'll start. Usually, actually, people, by the time I see them, even when they're children, they and their family have discovered things that work. So I'm usually not advising specifically things to help with the pain when they've got it. Sometimes they haven't tried some things. So, if they've not tried things like menthol containing preparations like tiger balm and things like that, that quite a lot of people seem to find helpful, I might suggest that. If they're having really severe trouble with the pain, I have occasionally recommended nerve pain medications like gabapentin, which for some people does seem to help. But usually I go by what people have found helps, because they've already tried lots of things by the time they see me.

Liezel: In my experience, I've found that conventional painkillers, which I'm sure you know already, don't really work. I haven't actually tried gabapentin and other medications in that class. Maybe I'll suggest it to certain patients just to see if it helps. A lot of patients have their own ways, as Robert was saying, like using a cool fan just for some relief or distraction. I have one patient who says a hot shower actually helps and others who say that cold showers help, and others who say that they can't stand, actually, having any water on their skin because the pain is so severe. I try and focus on prevention rather than treatment because we haven't had effective treatment. You know, there certainly isn't effective treatment once the episode has started and

you've gone past the prodrome into that severe pain. So I'm sorry, that's probably not an extremely helpful answer, but that's just the experience I've had in clinic.

Sue: I'll bring this remote to Victoria.

Victoria Harrold: I was just thinking prior to my diagnosis. I was admitted to hospital on quite a number of occasions and all I can remember is that somehow they managed to stop the pain and I seem to be able to heal afterwards, despite having to go back out in the sun again. I was given steroids and I believe I was given sleeping tablets. If somebody was in a reaction, a painful reaction, would that be something that could help?

Liezel: I wouldn't recommend oral steroids, only because there isn't any proven benefit and there's shedloads of side effects with oral steroids. I think that'd probably be—

Victoria: I was kind of looking at the sleeping tablet side, because I think what helps us to feel better is being able to sleep. And if we don't get the sleep, then the reaction tends to continue.

Liezel: That's a very tricky one because sleeping tablets are not recommended, other than for just a few nights, just to, if you were having repeated, you know, severe episodes of EPP and having repeated courses, even though they're short courses, of sleeping tablets, some other kinds of hypnotics, even benzodiazepines, that could cause other problems. So I appreciate they might help in the very short term, but I wouldn't recommend them for other reasons. I'll just see if Robert's got anything to add to that.

Robert: I would agree, general systemic steroids, there's probably not enough good evidence that they would help, I haven't prescribed them. If somebody has redness from the *[inaudible]* as well as swelling from the vascular permeability, often I think the redness comes after swelling, but if you have that, then a very potent topical corticosteroid can constrict blood vessels, so I might, as a short term measure, buy that for somebody. In terms of sleeping tablets, I haven't used sleeping tablets as such, but sometimes a very sensitive antihistamine like hydroxyzine or something, to try and tide somebody over a bad spell.

Sue: I think also we do hear, and it's not what I'm recommending from the BPA, but I do know from patients that they drink alcohol after an episode. And also, we had a discussion on one of our last meetings about people trying CBD oil to see whether that might help. So it was a general discussion that we'd had. So those are things that we hear about patients doing.

Liezel: Have people reported benefit with the CBD oil?

Sue: It was a discussion. So a couple of people had recently tried it and they said it helped maybe relax them when they were in that state at that point, but definitely they'd said that alcohol helped them to finally get some sleep because they just couldn't get to sleep. Which I know is not a healthy—

Liezel: Very difficult and I totally understand why somebody would do that. Maybe I would if I was in the same situation, but I have one patient who actually developed alcohol dependency pre-diagnosis because they used alcohol as a coping mechanism and it led to other health problems unfortunately and liver problems unrelated to the EPP. But I can completely understand why somebody would do that.

Sue: Is there any patient in the room that has any other recommendations for anyone else, of what they do, that we haven't kind of talked about already this morning or this afternoon?

Unidentified audience member 2: It's probably not the right thing to do, but it makes me do it when I have a flare up, is to immerse my skin in cold water, as cold as I can get it, icy water. But I don't know if that's a good or a bad thing long term, or if it's regular.

Liezel: I have heard of people doing that and I don't see that, you know, that would particularly cause you a problem. It might cause some vasoconstriction even, you know. So perhaps it would help, but not for everybody. Some patients can't stand cold water coming into contact with their skin either, so I don't think there's a problem with that.

Unidentified audience member 2: Warm water, to me, feels as if it's boiling water.

Liezel: Yeah. So some people say the opposite. Yeah.

Unidentified audience member 3: I use an ice towel. That kind of helps me cool down. It's meant for like after sports and stuff, but it's really cold. You just have to soak it under some cold water and then it goes, like, ice cold. But they're very expensive.

Liezel: I might mention that to some of my junior, oh and senior, EPP patients in clinic, if you feel it helps.

Antony: Something, I don't know if anyone's tried it or even seen it, but there was an Israeli EPP patient who's discovered what's known as a cooling mattress. So it's a mattress that has almost like a cool environment. So I don't know if anyone's tried that, but if you're particularly struggling with that, I'm wondering whether that--to me, it sort of suddenly chimed a little bit, you know, because towels, they're they're only effective for so long, You have to replace them, you're constantly moving around, and this notion of not being able to get sleep, if you've got something that's more consistent, possibly, they may help in those really difficult circumstances. I don't know.

Liezel: Just going on from that, I've just remembered, one of the children that I look after with EPP, they have a gel cool pad, I think it comes out the freezer and then you can basically sit on it or, sort of, semi lie on it, and some people do find that helpful. It might be slightly cheaper than an ice towel, I don't know, but that could help.

Antony: I don't know if anyone's tried to sleep on a glacier or anything [laughs], you've then got two things you're dealing with, the temperature, the extreme cold, as well as the EPP pain, and what you're actually trying to do is get some rest and some sleep. So maybe, that's why I think the mattress is interesting. I don't know if there's any benefit but it's something we probably need to keep an ear out for.

Sue: We need to try and find out what brand it was. Was it someone we can connect to? Was someone from Sofia?

Antony: Yeah, you know the guys.

Sue: OK, I'll find out because maybe we can ask them to do a little review on it or something that might be a little article we can put in the newsletter. Because if it is something that people might want to think about, especially you're thinking of a new mattress, maybe not to go out and buy it at that point, but when you next need a mattress, if they're a similar kind of price, it might be worth a consideration to try.

Antony: Just follow up on the question of water. Could I just ask the room, when you apply water and you've had towels or you've had your hands under water or in water for time, does anyone notice that that has an effect on the swelling, either worse or not as bad?

Unidentified audience member 2: Yeah, it is worse after. Yeah, for the time you're doing it, it's OK, it helps. But then after, it flares up again, and yes, it does start to swell very often and redden.

Antony: Anyone else find that at all?

Unidentified audience member 4: I'm just going back to pre-diagnosis cause I haven't actually allowed myself to have a severe reaction since I was diagnosed. But pre-diagnosis, I can remember one particular holiday where we went camping and it was the worst reaction I'd ever had, and we'd got, like, bottles of cordial that were made up with water, and my sister was asleep at the time, and I was pouring cordial on myself, you know, and whatever else I could find. And actually, that was actually the worst time for swelling. Like, my whole face swelled. My hands were like golf balls. My feet were like golf balls. I was in a wheelchair. Blood blistering, scabbing, everything you name, that's what I had at that time. And they did try to say that the reason why I'd swelled was because I was putting the cordial on myself and I was having an anaphylactic shock.

That's in my notes. It's written in my notes. You can have a look [laughing]. So I don't know. I have wondered if it does. I'm not sure.

Antony: Would there be any medical reason why regular immersion in water might promote swelling?

Liezel: Aside from the EPP? No, no.

Unidentified audience member 4: [laughing] I'm just special.

Sue: It may just be that it was the worst reaction that you'd had and the swelling would have come up anyway. So is that a possibility? Yeah, it may just be that it was the worst one that you had.

Liezel: I think it was a severe episode of undiagnosed EPP that was misdiagnosed as anaphylaxis, which does seem to happen fairly often when somebody presents to the emergency department.

Sue: Any more questions in the room? OK. So I'm going to keep going down the list. So we had discussions about variations in the time it takes for a phototoxic reaction. So, obviously we hear about, people say the first tingles, etc., etc. But also, I've got some questions around, is there any reason for the differences in exposure and reactions, to do with the amount of time in the sun? Could it be a cumulative effect? Could it be seasonal? Or could it be all of the above, as to why they might be having worse reactions? I know we'd had some questions about, that certain seasons were definitely worse, and and whether that's because of all the reflective light or whether it is just that there is more light naturally at that time of year. So maybe just some idea as to why is there such a variation, even in the same person, as to how they react?

Liezel: I was going to ask, whether it's within individual or inter-individual reactions.

Sue: Even within the individual, at different times of the year, and even like the cumulative effect.

Liezel: We don't know, is the answer. From what I have gathered, there doesn't seem to be a great correlation between the protoporphyrin levels in the plasma or the erythrocytes, in comparison to the severity of symptoms. I don't think we're aware of why. Some patients are worse on windy days and overcast days. Some patients don't have any symptoms whatsoever in winter, whereas others do. I mean, there might be something to do with, obviously, reflective light there, if it's snowing, that that makes an awful lot of sense. But why people react in certain ways, I don't know.

Robert: I don't know either. I think probably part of it is the mixture of different wavelengths on a particular day and we know that protoporphyrin is absorbed at different peaks within the visible spectrums, and there's a big peak in blue light, but then there's wee peaks further on, there's a wee peek at red light, there's a wee peek even for infrared heat rays. And so, depending on the day it might look rather similar but there's a different mixture of wavelengths reaching you. And I think that's probably part of it.

Sue: And would that change depending on the time of year? Because one of the things we've heard from one patient in particular was that in the autumn/winter, they're affected more by direct sunlight, whereas more in the spring/summer months, it's just any light, or I think she said any daylight, seems to cause a reaction. It doesn't even have to be the direct sunlight, as such.

Robert: I don't know what the answer is for that patient. It might be the overall amount that in the summer, even though proportionately you're getting more ultraviolet B, which isn't harmful for EPP compared to longer visible wavelengths. Although proportionally there's more ultraviolet, you've got more of everything. Whereas in the winter you maybe do need more direct sunlight to get enough of a dose.

Sue: Yes, OK. So I'll keep going. If anybody wants--Oh, we've got question over there. Let me take this to you.

Unidentified audience member 5: Can I just ask, from your experience with the patients that you've seen, what your, I don't know, top prevention and would be? What you believe works the most, I guess.

Robert: Avoidance, I think, is the only definite prevention. And emphasising, as probably everyone here knows,

but for a newly diagnosed patient, sometimes they're not so aware that it's so important that it's visible light, not ultraviolet rays. So that's why, for example, normal sunscreens don't work as part of the protection. Whereas new things, like the La Roche-Posay Mineral One sunscreen, which is special for visible light, or the Dundee sunscreens, which were designed for visible light, can be part of prevention.

[inaudible follow-up question from audience]

Robert: That is common, and including for people in Dundee. And Tayside Pharmaceuticals is not directly attached, well, they are physically attached, but they're separate from Ninewells Hospital in Dundee. They are having great difficulty in getting the pigments that they use for some of them. So I'm more and more recommending things like, La Roche-Posay Mineral One, which has good visible, well, equally good to Dundee sunscreen, visible protection, as well as being a normal sunscreen. I think sunscreen manufacturers have realised that, well, EPP's never going to be a market for them really, but they've realised that this big market, particularly in Southeast Asia, for sunscreens that will reduce the melasma, the pregnancy masks that you can get out of pregnancy. And presently, places like Japan, there's a big push to get sunscreens that reduce that. And sunscreens that reduce increased pigmentation problems tend to be sunscreens that block visible light well, as well. And so, there's at least one, there are probably more and more, sunscreens that are actually quite good for visible light, as part of the package of photoprotection, behavioural, environmental, clothing and sunscreen.

Liezel: We've had supply problems with the beige formulation at my hospital and I have many patients who swear by the beige formulation and I was told by our hospital pharmacy it would be back in stock mid-May, but I don't think it is yet. So the Anthelios Mineral One may be a good alternative. The problem with these new marketed sunscreens is that they're quite expensive. So I'm giving the information out but with the caveat that I'm afraid we can't prescribe it at the moment, so you have to buy it over the counter and it is quite a lot of money. Just going on from what Robert said, I absolutely agree with the addition of skin hardening in spring, early spring, and it has to start in early spring otherwise it won't be as effective. Just to build up tolerance, basically thickening the top layer of your skin, the epidermis, a bit. It can be with UVB phototherapy, or natural hardening you can just do yourself by going outside just for small fractions of time, without provoking EPP symptoms, and gradually building that up in early spring. But it does have to be early spring. So, March time, I would say, at the very latest.

Sue: Something that the BPA are planning on doing literally imminently, we're in the process of contacting all of the suppliers of these new creams, to see whether we can get four or five donated and get some patients to trial them and write a review for us, to find out how good they find them, what they like, what they didn't like. Because it isn't just whether it works, it's what it feels like on the skin. Antony and I had conversations about general sunscreens, and that it doesn't always work for you in terms of how it feels and you're saying you can't always bear it. And there is a new one, I should probably bring up the presentation from Clinuvel now. There is a new one that they have developed as well called Cyacelle and they talk about it in their video, which is very, very new. It's only recently launched and at the minute we don't know how effective, or anything really about it. But would now be a good time to put that video on? OK, let me try and do that and if there's any questions whilst I'm doing that, Antony--

Antony: While you do that, I think, if the light avoidance is the only sure thing, that aside, probably the next most effective thing for me is clothing. And that's become easier over the last couple of decades with new materials, you know, with sun protection just being more generally acceptable, and the way people dress, and the clothing that can protect you from the sun, has become far more accessible, looks a whole load more stylish, and you don't feel as abnormal by wearing it, do you? I guess, yeah.

Pete: So in terms of clothing, a company called Coolibar based in the US have got a new range and it's very new, so it's quite a small range at the moment, but they do have both long sleeved tops and trousers that are very light, comfortable material. It is UPF50. But in addition to that, it's got zinc oxide woven into the fabric. I'm at the more extreme end of EPP, at this time of year, I have, sort of, 2 to 5 minutes in direct sunlight, and I've been walking around wearing these tops in Tamworth for the last few days and not got ill wearing them. So they seem to have quite good efficacy.

Sue: OK, I think we're ready to play this presentation now. I will put it on now, let's just hope the sound comes out OK.

[Pre-recorded presentation played to the room]:

Genevieve Tay: Good morning everyone. First of all, thank you to everyone who is here today. I'm Genevieve Tay, Communications Associate at Clinuvel Pharmaceuticals. I'm based out of the Singapore office, which is why I am not able to join you in person today. But I would like to acknowledge Dr McGuire and others in the BIPNET team who helped facilitate this presentation. Clinuvel is a specialty pharmaceutical group developing and delivering treatments for patients with genetic, metabolic, systemic and life threatening acute disorders, as well as healthcare solutions for specialised populations. Our headquarters are in Australia and we have operations in the UK, USA, Singapore, Switzerland and Ireland. We have developed the only approved treatment for Erythropoietic Protoporphyria, or EPP, and it is on this programme that I will mostly focus on today. I would like to pause here to make a disclaimer. The medical information discussing my presentation is not medical advice. I will mention the brand name of a treatment that is approved for use in the United Kingdom. This treatment is subject to additional monitoring as a black triangle product. For any patients receiving this treatment, we ask that you report any side effects to your healthcare professional. The prescribing information for the product is available on our website clinuvel.com. Clinuvel's drug is the afamelanotide 16 milligram implant also known as Scenesse. It was developed by Clinuvel since 2005 for the prevention of phototoxicity in EPP patients, and has been approved for use in Europe, the USA and Australia. It is also available for patients in Switzerland, Israel and Canada through special access schemes. Here in the UK, the product is available under a Patient access scheme in Scotland. Clinuvel has engaged with England's National Institute of Health and Care Excellence, or NICE, since 2015, to make afamelanotide available for EPP patients in England. NICE is responsible for making decisions about resource use in the National Health Service in England, Wales and Northern Ireland, including decisions on the use of medications within the NHS. It has been a long and challenging process to date, but we are very thankful for the support we have received thus far from the British Porphyria Association, the British Association of Dermatologists, the International Porphyria Patient Network, and some individual patients. In the "Final evaluation determination" document published by NICE's highly specialised technologies committee on the 13th March 2023, afamelanotide was not recommended for use in the English NHS. We do not agree with the committee's decision or the process by which it came to its conclusions, and have asked to pursue an appeal through NICE's internal appeal process. An appeal hearing was held in mid-May of which the outcome will determine the next steps. But the company is prepared to pursue all avenues available to it. We recognise the impact of the disease on young EPP patients who are forced to avoid light exposure from a young age, which is why we have sought to extend the use of afamelanotide 16 milligram to adolescent patients aged 12-17 years within the European Union. Discussions with the European Medicines Agency are ongoing, but we have announced that we will conduct a pharmacokinetic study in EPP patients as part of our ongoing dialogue. Details of this study will be made available in due course and pending an EU approval we would seek to mirror the label extension submission in the UK. Apart from seeking to extend the use afamelanotide to adolescent EPP patients, we also see a good reason for extending the use of afamelanotide to Variegate Porphyria patients, given the clinical similarities between VP and EPP, in particular the phototoxicity manifestations. Just to quickly give a brief overview of Variegate Porphyria, it is classified as both a cutaneous and acute porphyria. Just like with EPP, VP patients can suffer from phototoxicity, particularly in the spring and summer, where the atmospheric intensity of light increases. But while the phototoxic symptoms that EPP patients experienced are largely invisible, phototoxicity in VP patients generally manifests as blisters on the skin. Earlier in May, we commenced a new phase two clinical study to evaluate the safety of afamelanotide and its efficacy in the prevention of phototoxicity in VP patients. Six patients have already been enrolled to receive treatment across two study sites and we can expect the first results in 2024. Earlier this year, we launched our first healthcare product line, Cyacelle. As the first of 4 product lines, the polychromatic screen is formulated to protect skin against both UVA and UVB, as well as high energy visible light. For EPP and XP patients, Cyacelle can serve as an adjuvant, not substitute, photoprotective product to the systemic treatment from afamelanotide. This product will be distributed through hospitals to EPP and XP patients, and we will be in contact with UK centres shortly to discuss this in further detail. Cyacelle also benefits 3 distinct populations at highest risk of photodamage and skin cancers. These are individuals who are longer term immune suppressed, people who are affected by skin cancers, either personally or with a family history, and those who spend extended time outdoors. For more information, you can visit clinuveldna.com. Thank you to the BPA team for having us. If you have any specific questions, you can reach out to us at mail@clinuvel.com.

Sue: OK, so that gives a bit of an insight to the new cream which is available with them. And they have already agreed, we just need to contact them again about it, but they've agreed to donate five samples for us to try, and it's quite expensive so we're hoping that we can get those to some patients to try and see whether it helps. So when we do that, we'll be putting things out, probably across social media or email, so just get in touch if there's any volunteers who might like to have a go at trying one of those creams when we get them. So if I could get the panel back up, we've got a few more other questions, if that's OK. I've just gone through the list while that was on and I've earmarked all of the questions. So there was a few questions around iron, and people that have low iron levels, and what kind of supplements they should be taking, should they be taking any, etcetera. So, I think something around maybe why they're deficient in iron, or what might be the cause, and also, what would you recommend, if it's that simple?

Robert: Is it OK if I use that to draw a wee pathway?

Sue: No, go for it.

Robert: It helps to explain it, I think. Does anyone who's got a protoporphyria in the audience have X-linked protoporphyria rather than EPP?

Sue: I think we may have one, I'm not sure.

Robert: Because the answer is quite different for the two types.

Sue: Ah OK, is there anybody with XLP in the room? I had a feeling there was, but maybe there isn't. Liz isn't in here, she did all the sign-in sheets. We'll go with that we haven't.

Robert: I'll draw the wee diagram that I'm sure you're all used to, because I think that does help to explain it. My writing is not very neat but, so you've got, *[a few seconds of inaudible speech as speaker moves away from microphone and explains a diagram to the room. The diagram is not visible on the recording]*. So, as you know, in EPP you've got a shortage of the enzyme that puts iron in protoporphyrin IX to make haem. In X-linked protoporphyria, you've got an increase in activity of the ALA synthase 2 found in the red cell line, and so the problems are increased action *[inaudible speech as speaker moves away from microphone]*, and then you've got too much protoporphyrin IX you can't use it all with iron to make haem, so you get a build-up of protoporphyrin IX. So you get the same things in the skin because of the build-up of protoporphyrin IX that absorbs visible light in the skin. And because protoporphyrin IX is very fat soluble, it stays around the fatty lining of the blood vessels and nerves that run along blood vessels, rather than diffusing out, which is why it absorbs visible light there, so you get pain. If you get enough damage to the blood vessels you get leaking of fluids out and you get swelling, but, unlike in some of the other porphyrias, you tend not to get blistering early on because protoporphyrin IX doesn't diffuse out to the junction between the top layer of the skin and the deeper layer of the skin, causing inflammation there, so you get blistering as the top layer of skin lifts up off the bottom layer of skin. But to answer the questions about iron, well, in EPP, almost everyone has a lower haemoglobin, which is the compound that carries oxygen around the blood, and to make haemoglobin you use haem, which you can think of as a cage to carry iron around the body, because free iron is very toxic, but you get a slightly reduced haemoglobin, the red blood cells are slightly small, and unless you know somebody's got EPP, that looks like iron deficiency. So the patient will often be given iron, if they've not been diagnosed as having EPP. If you give iron to somebody who's got EPP, you can give iron, but the ferrochelatase enzyme here isn't any more active, so they can't use the iron. The iron increases activity of the enzyme up here, so you end up with more protoporphyrin IX, so you can make the problem worse, if the iron isn't being used. The exception is if you happen to have really severe shortage of iron as well as EPP, if nobody's got it here I won't go into detail about X-linked protoporphyria, but there the answer is different, iron might actually help, but, with EPP, unless you're severely iron deficient, basically iron doesn't help.

Liezel: So I recommend iron supplementation very, very rarely. Only if somebody has very low iron and is very symptomatic. So if somebody's mildly anaemic, I wouldn't recommend it at all. I had one patient, I won't go into details, recently, who was extremely symptomatic and was having a huge impact in quality of life, and giving her exogenous iron was actually detrimental to her. So I'd be extremely, extremely careful with iron supplements and wouldn't recommend them in general.

Sue: Lovely, thank you. Can I ask one further question that's kind of linked with that? So I'm going to try and pronounce this right. So, can normocytic anaemia be caused by EPP, or would that be a separate condition completely?

Robert: So, normocytic anaemia is a reduced haemoglobin, which is the red pigment in your red blood cells. Normocytic just means normal size red blood cells, microcytic means small size red blood cells, and you can also get conditions where you have macrocytosis, which is big red blood cells. If it's normocytic, that won't usually be EPP on its own. Usually EPP on its own causes, it's very like iron deficiency, so you get a microcytosis, but you can occasionally, and in fact not so uncommonly, it can be a bit complicated, you can have something like vitamin B12 shortage, which is fairly common, which causes macrocytosis, big red blood cells, and you can have EPP causing small red blood cells, and it's sort of averaged out. So on the machine that reads a normal full blood count, they come out as normocytic. So basically, normocytic anaemia is not going to be EPP on its own. But if somebody has a mild iron deficiency and the normocytic anaemia, it could partly be EPP that is causing it.

Sue: And if they had normocytic anaemia, how could it be treated if iron infusions can't be used? So this was obviously a specific question from a specific patient.

Robert: I would again, in general, be very wary about iron infusions. Unless you thought they were really severely iron deficient, and in that situation usually I would give oral iron and usually a much smaller dose than in a normal situation. By a normal situation, I mean if you've not got EPP. If somebody's not got EPP, it's common to give 200 milligrams of ferrous sulfate or 210 milligrams of ferrous fumarate orally, 3 times a day. In EPP, I would recommend something like ferrous sulfate, 200 milligrams every 3rd or 4th day, and repeat measurement of the red cell protoporphyrin after two weeks to make sure it's not going up. And in rare situations where there were problems with absorption and you were giving iron by other means such as injection, then I would be very cautious. I've never had to do it. I would be extremely cautious about the dose and checking red cell porphyrins to make sure you're not making the EPP worse.

Sue: Right, thank you. I think we'll go back to that patient and suggest that they take it up with their porphyria specialist, and if they haven't got one, we'll help them find somebody. Is there any more answers to that? If not, I've got another question which we discussed at length last night, a few of us who were chatting after the meeting yesterday. So, across social media, there's lots of information out there on TikTok, etc., around melanotan 1 and melanotan 2. And some of the information, there are people appearing to be marketing it, and there are various articles that appear that it can be quite dangerous. So, we wanted to ask if anybody has used it to treat EPP, so we did a bit of Googling last night, and then what your thoughts were on it were for patients? Because it's come to us from patients, but the more that I've heard from other patients, it is out there within the community.

Liezel: This is very worrying to me. So, melanotan 1 and 2 were produced, kind of, as cosmetic products to enhance tanning and they are available commercially for that purpose. But they're not medications that have been regulated and they're administered by, I think is it subcutaneous injection?

Sue: I think melanotan 1 is an injection and 2 is a spray, I think.

Liezel: So, they would help in terms of increasing pigmentation, I've got no doubt about that. But I would strongly warn against obtaining them and using them because there are potential severe side effects and they are unregulated, basically. I wouldn't recommend it at all. Well, for anyone, whether they've got EPP or not.

Robert: I've not really got anything to add as I've not come across anyone who's said that they've tried any of these.

Liezel: I haven't in my porphyria clinic, but in my Two-Week Wait clinic I have come across patients who have used these products, along with the sun beds, which obviously is another story entirely, so I hope that answers the question.

Sue: Yeah, no, that's really good. And it might be that afterwards we try and generate some content and get it

checked by you to put some information out there, because if it's readily available on social media, we need to put something out there to make sure that there's some information.

Liezel: Very worrying.

Sue: So I think on the back of that, it doesn't quite link with it, but maybe if the microphone could go to Vicky, I think it would be quite good for Vicky to mention that there's some cosmetic products around at the minute, body lotions that can trigger phototoxic reactions in the general public. So if somebody with EPP accidentally used one of these they could have quite a severe effect. So I'll let you explain what it what it is.

Dr Vicky McGuire: So there is a brand of skin care products called Ameliorate that are being pushed quite heavily at the moment. I've been hearing them about them on podcasts and all sorts of other social media platforms. There is a product called Transforming Body Lotion, which you're advised to use every day for a period of time and then drop it to weekly. And there is a warning on the bottle which says that it might increase your sensitivity to sunburn. I did not read the bottle very carefully when I used it and I ended up with a very severe reaction. So I would strongly advise anybody, especially patients who are already sensitive, to not be using these products. And I won't show [laughing] any of the pictures of what happened, but it's been a very unpleasant experience and, you know, just be very, very mindful of the product. I can give pictures of what the bottles look like if anybody wants to know what they look like, to avoid them.

Sue: This is something else we'll put out across social media as well.

Liezel: That's very interesting and a salutary tale, Vicky. Do you know what the photosensitizing ingredient is in these products? Alpha-hydroxy acid? So we need to--

Robert: Alpha-hydroxy acids are not directly photosensitising, but they strip off the top layer of the epidermis and make you more prone to, essentially, not a normal, or it can be a severe, sunburn reaction. And at high concentrations and used or kept on for long enough, they and other fruit acids can be used for chemical peels. I don't know if there's much cosmetic dermatology in Scotland, but in countries where it is cosmetic dermatology, I think they use that type of thing.

Vicky: The other thing to be mindful of as well is that it doesn't--you have to wait for the skin to grow back before the sensitivity goes away. So they say it can last up to four weeks, that you can be sensitive to sunlight, and you shouldn't go out.

Liezel: One to avoid then.

Vicky: Hard lesson learned.

Unidentified audience member 6: What was the name?

Vicky: Ameliorate.

Sue: So, we will be sharing that. We'll start on social media and then we'll make sure we're get it out to people via an email as well. So, there's a few things which have come up at this meeting that we'll definitely share then with patients. I think the only other question, within the others that I've got left here, is the BPA are trying to really help support patients psychologically and with their mental health. And I think as we come into the spring/summer months, the general population is woohoo, it's summer, it's lovely, we're out, all of the social media, everything on the television, everything is a visual about summer family time, etc. Mental health has a huge impact as we move into those months. Anything that you can recommend to help support patients through that? As a charity, we're trying to connect people together and support people emotionally. Is there anything else that you would recommend as doctors to the patients that you see in clinic?

Liezel: Well, we have a clinical psychology service at Salford Royal, but it's not enough, there's never enough out there because the waiting list is massive and you wait up to 12 months for an appointment. It's just an entirely unsatisfactory situation at the moment. I hope it changes. My ideal porphyria clinic would be to have a psychologist in clinic with us. That's the dream, but hopefully going to work towards it in the future if I can, and

having a specialist nurse as well to provide extra emotional support. Unfortunately, we don't have that at the moment. I have put patients in touch with the BPA to look for peer support and I think that can be a huge help. Sadly, psychological and psychiatric services are really below par, certainly in the area where I work, and I think it is a nationwide problem. Same in Scotland.

Sue: So I think the big thing that we can say is, with the BPA we try to offer as much support to patients as possible. Obviously, coming and meeting another patients really helps you to really not feel like you are alone. We can help connect you with other patients. We are here to listen to you as well. And I think the other thing is we also are doing a mental health project at the minute, and we have some funding for psychological support and counselling sessions. So, if there is anybody in the room who might feel that that would help them, please get in touch with us. We have a helpline, email and telephone number, and we're always happy to help. And we also reach out to the doctors via email with things if there's something that we see that we're concerned about, we reach out and can connect you to them directly. So just reach out. You're not alone in what you're going through.

Liezel: There is support out there, but we just have to think creatively and it might not be a clinical psychologist, it might be another patient with EPP. I try and link up with children with EPP, with their schools as well, to try and educate them, which is something I want to develop in the future as well. So that if at least the teachers understand a bit about it, they can look after them and look what their different needs might be. Especially in the summer terms.

Sue: OK, I think that takes us probably to the end of this session. So before we close, has anybody got any other questions they would like to ask? No? OK. I feel like we've got a few people missing from the room. Did people stay in the other room or did people come back? There's some that stayed there? OK, so I'll wait for everybody to come back up. They might just come up in a couple of minutes at the end of session, but I'd like to say thank you very much to all of our speakers. Honestly, we're very grateful--Antony?

Antony: I don't, well, tell me if we can't go there on this question. I recently saw some early data that suggests there's a cream that's coming along that might be as good as Dundee cream. Is that--?

Liezel: Isn't that the Anthelios Mineral One? It was you and Eadie's paper from Dundee. So that was the cream that Robert mentioned. Yes, the same one. It's exciting though.

Sue: Fab. So we're all here to close this first session, but I'd like to thank the panel of speakers. I hope you've all got lots of it in the room, you know, found a real benefit of being here and listening to the specialists and also the talks from pharma. I think the only thing we haven't really touched on, we touched on it a little bit this morning, was the Mitsubishi trial. So there's not really any findings to report as yet on it. So it's still ongoing and we talked a little bit about how it was taken and how it works, a very little bit. So there's nothing really else to report on that at the minute, is there?

Liezel: Not yet. Watch this space. We'll keep everything crossed.

Sue: And as soon as we get news, we put everything into the newsletter, as we get information, we pass that out. And I know that Will has left now, but we will also be keeping an eye on--they're releasing some data in June at a conference on the 9th, so it's only a few days away, and we'll be monitoring what has been released and sharing accordingly, because we will be keeping up to date and sharing all that information when it comes available. So thank you very much, lovely panel speakers.

Liezel: Thank you. I'm sorry I was late!

Sue: OK, so that brings us to the end of our day. So I'd just like to say thank you again to our sponsors that have helped make this possible. Thank you to all the speakers that have come, and there's lots of other doctors and scientists in the room who have come from far afield, that are here for another meeting tomorrow but thank you for coming and being part of our day as well. And thank you to the patients who gave their experience talks. I think we all found that really emotional and nice to connect and feel that you're not alone, that there are other patients going through what you've been through or are going through as well. And thank you all for coming, really, it's been a great two days. We hope you've got lots from it and we hope to see you

at other events in the future. We've got the event in September that if you are interested in attending with your families, we really would like to make it a really good activity day, and we also hope to be able to offer some psychological support there as well. So it's still in the process. We haven't got that far, but we're hoping to hopefully have a counsellor on site with us for the day that may be able to offer support to parents and to family members and patients affected. So we're still developing it, but if you would like to be there, you're very welcome. So just let us know. So thank you all very much. I believe that refreshments will be served shortly at the back of the room. We've got the room for another hour, so feel free to stay, talk to other people, and thank you very much for coming. I should also mention, if you want any merchandise, just let one of us know from the BPA and you can take some bits as you're leaving. OK. So thank you very much for coming.