Investor Meeting - Key Opinion Leader *(Corrected version)*

Event Details

Date: 2024-05-29
Company: Eupraxia Pharmaceuticals, Inc.
Ticker: EPRX-CA

Company Participants

James A. Helliwell - Eupraxia Pharmaceuticals, Inc., Co-Founder, Chief Executive Officer & Director
Evan S Dellon - University of North Carolina School of Medicine, Professor of Medicine & Adjunct Professor of Epidemiology

Other Participants

George Farmer - Analyst
André Uddin - Analyst
Gary Nachman - Analyst
Rahul Sarugaser - Analyst

MANAGEMENT DISCUSSION SECTION

Operator

Good morning and welcome to the Eupraxia Virtual KOL Event. At this time, all attendees are in a listen-only mode. A question-and-answer session will follow the formal presentations. And if you'd like to submit a question, you may do so by using the Q&A text box at the bottom of the webcast player. As a reminder, this call is being recorded and a replay will be made available on the Eupraxia website following the conclusion of the event.

I now like to turn the call over to James Helliwell, Co-Founder and CEO of Eupraxia Pharmaceuticals. Please go ahead, James.

James A. Helliwell

Kiana, thank you very much and thank you to all of you for attending today. We have a lot of appreciation for your time and look forward to giving you an informational session this morning.

Just a brief note, as our lawyers like us to say, we are going to be making some forward-looking statements and making some projections about the program and the products here today. So, familiarizing yourself with this would be particularly helpful.

With me from the company and beside me today is Dr. Amanda Malone, our Chief Scientific Officer; and Dr. Mark Kowalski, who is our Chief Medical Officer is also on the call. I'll be introducing Dr. Evan Dellon in just a few minutes.

So, a little bit about Eupraxia Pharmaceuticals to set the stage for really what we want to hear today, which is hearing from Dr. Evan Dellon about our eosinophilic esophagitis product. So, Eupraxia Pharmaceuticals really is aimed at trying to take drugs that we understand, but to improve their pharmacokinetics. In other words, to actually make them deliver better, to try and avoid large peaks where we see a lot of side effects and avoid troughs, where what we end up seeing is lack of efficacy. So, this is all about being able to get the right dose

of drug to the right place for the right amount of time in indications with high unmet need, exactly what we're talking about today with eosinophilic esophagitis.

So, let's talk a little bit of the technology here. So, when you think about a lot of whether they be oral or injectable, what are traditionally called extended release products, what they tend to do is still look like a mountain top with a high peak and a drop off with a logarithmic decline. That's because they tend to use degradation as the method by which they're delivering drugs. So, it's a whole bunch of drug jammed together that then breaks apart to release the drug that's trapped inside.

We flip that upside down, and under Dr. Malone's leadership, have really created here the DiffuSphere. It's called that because it uses diffusion that allows us then to be able to put the drug where we want it, in this case, as you can see here within the esophagus, delivered by expert gastroenterologists and then being able to deliver the drug at a steady state over a long period of time, exactly where we've put that drug.

So, what does that actually look like? So, this is looking at pharmacokinetics from our first pivotal trial in osteoarthritis, the SPRINGBOARD trial, which was 300 patients. But this is how we look when we see ourselves in a variety of places in the body, including the esophagus. And what you see here is that there is not a large peak in the beginning, so we avoid the traditional side effects that one often sees with first dosing.

And as you can see here, in this particular indication, we are delivering six months of very flat and stable pharmacokinetics. We believe that when we apply this in eosinophilic esophagitis and in other indications, that is this that enables us to be able to get optimal efficacy, optimal safety for a duration of time that fits the pattern of practice that's really important for the expert physicians in this area.

So, speaking of expert physicians, we are incredibly pleased today to be able to have Dr. Dellon join us to be able to tell you a little bit about eosinophilic esophagitis and we'll just be scratching the surface of his expertise here.

Dr. Dellon is a Professor of Medicine and an Adjunct Professor of Epidemiology at the University of North Carolina in Chapel Hill. Dr. Dellon did his undergraduate degree at Brown University, his medical degree at Johns Hopkins School of Medicine. And he did his internship and residency in internal medicine at Harvard's Massachusetts General Hospital. He performed both a clinical and a research fellowship in adult gastroenterology at the University of North Carolina, during which time he also continued to overachieve and received his Masters of Public Health degree in epidemiology at UNC School of Public Health.

Dr. Dellon is currently the Director at the UNC Center for Esophageal Diseases and Swallowing or CEDAS and has served as an Associate Editor for Clinical Gastroenterology and Hepatology. Dr. Dellon's main research interest is the epidemiology, pathogenesis, diagnosis, treatment and outcomes of eosinophilic esophagitis or EoE and eosinophilic GI diseases. The goal of his research is to improve the lives of patients with EoE and eosinophilic GI diseases by learning how to better diagnose, treat and monitor these conditions.

So as you can see, we're just thrilled to be aligned with Dr. Dellon here and Dr. Dellon, with that, I will hand over to you and thank you.

Evan S Dellon

Thanks so much for having me. It's great to be here and be involved in this program. What I'd like to do over the next bit of time is to sort of provide a broad overview about the field of EoE, a little bit about diagnosis, epidemiology and treatments, what the landscape is looking like, and then we'll delve into a little bit more about how the medication delivery system can be applied to EoE.

So, we're just going to start with a very high level conceptual definition about what actually is EoE. And so it's eosinophilic esophagitis or EoE is how we abbreviate it or will otherwise be here all day. But it represents a chronic immune antigen-mediated esophageal disease, and it's characterized clinically by symptoms that are related to esophageal dysfunction and histologically by eosinophil predominant inflammation. And that's a mouthful and what I'll try to do is expand on each of those points as we go forward. So next slide.

So, this is the diagnostic algorithm for EoE. And in order to diagnose it, you have to have a clinical presentation suggestive of EoE. We will talk about those symptoms. This leads to an endoscopy with biopsy. Right now, this is the only way to diagnose EoE and there are typical endoscopic features that raise the suspicion. And when you do the biopsy, one of the things we're looking for under the microscope are elevated levels of eosinophils, and we have a threshold of about 15 eos per high-power field. If you're doing density, it's about 60 eos per millimeter squared. That's markedly abnormal and that lets you consider the diagnosis.

The next step is to evaluate for other conditions that might cause eosinophils to be in the esophagus. EoE isn't the only condition that may do that, although it is the most common one in general. And once you make sure there's nothing else at play, you can go ahead and definitively diagnose the condition.

And if we go to the next slide, you'll see that in general, when we're talking about adolescents and adults, the main symptom is dysphagia and this is trouble swallowing and that can range from a sense of food actually sticking in the esophagus and not going up and down to going down slowly and to causing patients to really modify the way they eat. But this dysphagia or trouble swallowing is the hallmark and if you get a food impaction, which is where food gets stuck so badly that you can't get it up or down, you have to go to the emergency room to get a emergency endoscopy to pull the food out, EoE is now the most common cause of that. If that's happening in the ER, it's at least 50% chance, if not higher, that you're going to find EoE.

But if you talk to patients and you ask them, do you have trouble swallowing, a lot of people may say no to that question. The reason is, is the symptoms are chronic and last a long time before patients get diagnosed. So patients modify how they eat. And this acronym of impact kind of gives you the sense of what people do. So, when I'm talking to people, I ask them, do they imbibe fluids. So patients have to drink fluids to help get food down. And so people may never eat unless they've got a huge glass of water or other drink. They modify their food by cutting it into tiny pieces or pureeing it. They have prolonged meal times where they're eating really slowly. They avoid the foods that get stuck, different meats or breads often. They chew excessively to get the food to a mush to get it down and a subtle symptom is they actually have trouble swallowing pills, so they turn away tablets or pills. And when you start asking about these, you really see a profound impact of the symptoms on many patients with EoE.

Next. So, when we move to the endoscopy, there's a range of typical features that are seen in EoE and a range of these are displayed here. And so if, for example, in panel A, this is the classic kind of appearance of a ringed esophagus. It's actually an esophagus and not a trachea. It should be a smooth tube with basically nothing to see. You can also see fine rings like in panel B. In panel C, you have these deep furrows. These are these train tracks going up and down the esophagus. Panel D shows white exudates in the esophagus and then the other panels E, F, H, and I also show a mix of these findings, so you can see rings and furrows and exudates, you also see a lot of edema or swelling. You don't see the normal vascular pattern.

Sometimes the mucosa is very delicate, and so passing a scope can lead to a tear in the lining, like in panel G and then, you can see scar tissue. So, not only the rings in panel A, but you can see narrowing in panel E. That's an esophagus that may only be, say, 12 or 13 millimeters in diameter, so smaller than the size of a dime, obviously hard to swallow. And F is a focal stricture, so a narrowing or a constriction in one place of the esophagus, and that one's probably 9 or 10 millimeters in diameter. So, very difficult to get food down past those areas.

So, next slide. Once you see those findings, this is what biopsies look like. In panel A, you can see the little biopsy forcep that's just pushed out in the front of the scope, and in B and C, it shows you grabbing a piece of the tissue right over one of those furrows for a high yield. And then you remove it, you get a small piece of tissue and that's what the biopsy is.

And panel A and B shows you what a biopsy looks like under the microscope. And A is normal, this is the normal esophageal lining. It's called a stratified squamous epithelium. It's similar to the skin, but it doesn't have the thick protective keratin layer. And in panel A, there's not a lot of inflammation. That purple layer in the middle of that section is the bottom of the esophageal epithelium and that's very narrow, just a few layers of cells. But in panel B, you see what happens with EoE and it's very thickened. That bar in the middle of the figure that shows proliferation or expansion of the basal zone, you can see lots of eosinophils there. And in the bottom half of that, you actually see a lot of fibrosis and scar tissue under the epithelium of the biopsy. So, lots of things going on there in addition to just the inflammation with the eosinophils.

So, now, we're going to switch over to the epidemiology. And years ago, EoE was considered a rare disease. It was case reportable, but over the last two to three decades, there's just been a marked increase in the incidence and prevalence. The incidence is on the left, the prevalence is on the right, and pretty much everywhere – and this is from a pooled meta-analysis of studies globally, but everywhere you look in the world, the incidence is increasing and it's not just recognition. The incidence is actually outpacing the number of endoscopies and biopsies that are done to diagnose it, indicating the changes in the environment are causing this rapid increase. And it's the same kind of increase that we're seeing with other allergic diseases as well.

In terms of the prevalence, sorry, if you go back one more, on the right, you can see the prevalence, which is getting up above 80 to 100 per 100,000.

And so, it's actually no longer really a rare disease in practice. I mean, people see this as new diagnoses multiple times a week. Every time I'm on call, I'm in the emergency room, I'm in the middle of the night doing a food impaction case. And so it's becoming a real common cause of morbidity in the upper GI tract.

So, if you go to the next slide and it's likely that these estimates are underestimates. So, this is a recent study done. The goal of it was to look at sort of the burden of emergency visits, so people with EoE who are known to have it coming into the ER with food impactions. And that was estimated to be about 5,000 people over the past decade, and that's projected to double over the next decade.

But to me, the most interesting thing in this study was, they looked at patients who were not known to have EoE, but who came to the emergency room with either trouble swallowing, a food impaction or an esophageal stricture. And they focused it on men less than 40. And the number of those cases was actually 700,000. And most likely the majority of those patients have EoE. There's not much else that causes someone to go to the emergency room at that age with dysphagia, food impaction or stricture. And so that estimate alone might double or triple the number of cases that we think there are in the US. And that's, of course, only for young men. It doesn't include women or older people. So I think as we're becoming more knowledgeable about EoE, we're really going to hit a big wave of new diagnoses and new cases in the US.

So, that raises the natural question of why is EoE increasing so much? And this is an area that I do a fair amount of research in, but you don't see changes that quickly due to genetic factors. There may be some intrinsic factors like in the middle of this figure that may predispose to EoE so, for example, having a tendency to have, say, a less tight or a leaky or barrier in the esophagus or being more of an allergic predisposition, but likely changing things in the environment, whether it's more aeroallergens, whether it's differences in pollution or population density or food packaging. There's a theory about detergents, and

there's a lot of work on early life exposures on the right side of that figure. All of these are implicated in the increasing rates of EoE.

Go to the next slide. When we think about the natural history of EoE, it is a disease that evolves and generally we think the model is, it involves from an inflammatory predominant condition which is seen in children or in people without a lot of time with symptoms to a condition where if you don't treat it, it progresses to fibrosis and you see narrowing of the esophagus rings and strictures. And this is pretty much closely linked to time. So, the longer a patient may have symptoms, even if they're subtle prior to diagnosis, the higher the likelihood that they will get diagnosed with an esophageal stricture or these fibrotic complications. And so early diagnosis is key to try to prevent this, but also consistent treatment over time.

Next. So, when we think about treating, what are we trying to do? Well, we're trying to, of course, help improve patient symptoms and quality of life, but there's biologic factors that we want to improve as well, including the endoscopic appearance. All those pictures I showed you when I'm doing a procedure, I like to see them normalize when patients are treated. I like to see the biopsies normalize, if possible. We like to improve esophageal distensibility. In EoE, the esophagus can get really stiff. And so if that compliance improves, that's a good target. And then, of course, like I mentioned that progression of disease, we would like to prevent that and prevent complications like strictures, food impaction and then, in children, poor nutrition. We want to prevent problems with growth and problems with feeding. There are ways you can monitor for improvement of biomarkers and other molecular features of the disease as well.

So, go to the next slide. So how does this look these days? Well, when we – this is a treatment algorithm that was presented in the American Gastroenterological Association guidelines a few years ago. And after you have a diagnosis of EoE, the first real step is to talk to the patient and decide what kind of therapy would they like? Do they prefer a medical or pharmacologic therapy there on the left, or do they prefer a diet elimination therapy where we're trying to figure out if there are foods that trigger EoE? And in general, we think for most people, EoE is a food allergic disease.

If they choose diet elimination, then there are choices. The main choice these days is what we call empiric elimination. We know, on average, the most common food triggers for EoE and patients may eliminate those, so they may do a dairy elimination alone, or a dairy and wheat, or some people may go to what we call the six food elimination, which is getting rid of dairy, wheat, eggs, soy, nuts and seafood. Kind of a tough diet. You're not going to be able to eat much that you had for breakfast this morning on that kind of a diet, but it can be effective. And then, on the other side, patients often offer medical therapy. So these can include proton pump inhibitors. Now, although these are approved for GERD, they're off label for EoE, but have some EoE specific mechanisms.

It's thought that the PPIs in a way that's acid independent actually decrease some of the inflammatory factors related to EoE, in particular, one, chemokine that draws eosinophils to the esophagus is blocked by the PPIs. They also help improve esophageal barrier function. So there's some real mechanism there as to how those work.

Another class of medical therapies or the topical corticosteroids. So the idea here is to swallow an anti-inflammatory steroid to coat the esophagus. It has a broad anti-inflammatory action. The key, of course, is formulation. It's hard to get something to stick into the esophagus for a long period of time. And so those have a role as well and then recently, biologics have been studied and dupilumab has been used for EoE now generally for the more severe patients.

Now, in parallel to all of this, if you have an esophageal stricture that has to often be open and that's a mechanical thing with esophageal dilation, which is done during an endoscopy, and there's a couple of techniques, but you're basically mechanically opening those narrowed areas that I showed you to improve symptoms. And then, after that, because EoE is chronic and we know that if you stop the medications, EoE essentially recurs in everybody. Patients who are responding go on to maintenance therapy, which is

continued long term, and they're monitored with endoscopies and clinic visits. If they're not responding, they'll switch between different treatment options and then go back for another endoscopy to see if it works. So, when you finally get to a therapy that works, they would be maintained on that treatment, too.

So, how do we know whether patients are better? Well, generally, we want to assess response in a number of domains, and this is two different ways of looking at it. There's a more technical way on the left where you're looking at these domains of histology, what's going on, on the biopsies, symptoms, how the patient's feeling and endoscopy findings, how it looks when you put the scope in, and people can range from non-response to some partial or incomplete response to being completely normal. And then, you could kind of do the more friendlier consumer reports way of sliding around from like the happy face with the symptoms, the histology and the endoscopy. But the point of this is that you can't really just look at one domain here. You can't just ask a patient, how are you feeling?

You got to also look at the endoscopy and the biopsies to assess both the clinical response and the biologic response because they don't always act in concordant fashion and you want to get a good sense of the overall patient.

Okay. Well, with that, I'd like to talk about the RESOLVE Phase 1b/2a trial and how EP-104GI is working in this trial. And this is a proof of concept study to look at safety and some potential efficacy parameters of using the injectable fluticasone in the esophagus. And the way this is structured is you can see sort of this dose escalation scheme and it's in a cohort format where starting with lower doses and just a few small number of injections, assessing patients and then moving up in a stepwise fashion to more injections, higher doses, looking for safety, and also starting to see where the efficacy threshold is compared to what we know.

And so, as you could see here, it's – the protocol has a minimum of the 4 milligram total injection, up to more than 80 to 120 milligrams for maximum injections. There are structured follow-up periods of time. This is an unblinded open label study. We talked about the dose escalation and I'll show you what that looks like in a schematic version in a minute. And there are sites in the Netherlands, Canada and Australia. And the idea here is, is this may have a very favorable safety profile, efficacy and pharmacokinetics that having somebody swallow a topical steroid twice a day to try to coat the esophagus. And that's just a few seconds of contact time in the esophagus as to potentially a very prolonged mechanism here.

So, in terms of the endpoints, the primary endpoints are really the safety, tolerability and pharmacokinetic profile of EP-104GI. Secondary endpoints are looking at disease activity with the understanding that these cohorts are very small numbers of patients. And so it's just getting a sense of proof of concept across histology and symptoms like dysphasia, difficulty swallowing and odynophagia, which is pain when swallowing. Also, we are looking at the endoscopic appearance and – which is a score called the EoE endoscopic reference score or EREFS and the histology score which is called EoEHSS. Now, we think a lot about eosinophils in EoE, of course, in the biopsy, but there – as I showed you on that one image of the biopsy slides, there's many more features than just eosinophils at play here. And so the HSS allows us to look across a broad range of histologic severity.

So if we go to the next slide here, this is the injection and dose escalation scheme and the way to think about these grids, as you know, the esophagus is a tube. So, if you think about splitting that tube open longitudinally and sort of displaying it out, so you have a flattened esophagus tube there, then what you're looking at here is the bottom of the esophagus at the bottom of the slide, the GE junction all the way moving up the top of the slide. And what you can see is the injection sites which are in red and the biopsy sites which are in blue. And so, essentially, it's like quadrants of a clock face. And so that's what that 3:00, 6:00, 9:00 and 12:00 means on the top of the screen.

So, in the early cohorts, say, there's four injection sites. The first cohort had four 1 milligram injection sites, as you can see in those four quadrant areas towards the bottom of the esophagus with multiple biopsies to look at histologic activity. And as we escalate to 8 injection sites, 12, 16 and 20, you can see that more and more of

the esophagus is covered with these injections, while we're still checking the same number of biopsies. So, we have very high resolution to see what the local response to these injections are when we look under the microscope at this. So, this is a really, I think, a comprehensive and actually very unique and innovative way to deliver drug and also as a study design.

So, let's go to the next slide here. So, these are some of the preliminary results from the RESOLVE study. And the first couple of slides are going to show you some symptom information. Now, the way this is organized on this slide, this is something called the Straumann Dysphagia Index, which asks over the previous seven days, how frequently are patients having trouble swallowing and how severe is it? And that goes on a score from 0, which is nothing, to 9, which is basically I had to go to the hospital. And so the different cohorts are in different lines. So the dotted – the fine dotted line is cohort 1. That's the 4 milligram total dose, four 1 milligram injections, three people. Cohort 2 is in the solid line, 8 milligrams total dose, eight 1 milligram injections, again three patients. And then, cohort 3 is in the longer dashed line in the circle dots, so that's a higher dose, now 20 milligrams, which is eight 2.5 milligram injections, also three patients. Cohort 1 and 2 are through 24 weeks of observation. Cohort 3 is still at 12 weeks. And what you can see is for all of the cohorts, we are seeing a decrease in the symptoms after the injection, as measured by the Straumann Dysphagia Index.

If we go to the next slide, it's a similar set of data on the left for a Dysphasia Likert scale. That means patients are ranking their severity of symptoms from 0 to 10, 0 being none, 10 being the worst, and it's all the same kind of formatting for the cohorts over time. So, again, you're seeing a decrease in the symptoms in general. Obviously, cohort 3 is only partially through the follow up, so we don't have quite the length of time on those data. Now, on the right side, this is the pain with swallowing Likert scale, the odynophagia. Some people with EoE do experience pain when they swallow and so here you can see in general for the longer follow up, some decreases in the severity of the swallowing pain as well.

Now, this next slide shows the peak eosinophil count data and the EoE histology score data for these different cohorts. And endoscopies here were performed at 4 weeks and 12 weeks with biopsies, so you could see what's going on with the eosinophil count. So, on the left, the peak eosinophil count means the highest count from any of the sites. And you can see for cohort 1, which was the 4 milligram dose, really no decrease in the counts. But for cohort 2 and 3, particularly at 12 weeks, you're seeing a decrease in the eosinophil counts now, indicating biologic activity in a very short period of time and also at very low doses of these medications.

On the right side, you're looking at the EoEHSS, so this is the severity score. The top part of the table is the grade, which is the overall severity in the biopsy. And the bottom part of the table is the stage, which is the extent of involvement of a finding throughout the biopsy. And similarly not too much, maybe a mild decrease to no change with that low dose in cohort 1 and then in cohorts 2 and 3, you're seeing a decrease in the overall histologic severity, again. at these low doses and early at week 12. And this is again important because we're realizing more and more. It's not just what's going on with the eosinophil count, but are you reversing other findings like thickening and proliferation in the biopsies, barrier function changes, and even scar tissue and fibrosis?

So, go to the next slide. Now, what about the safety and pharmacokinetics? The graphs that you can see here on the bottom left is showing that the – is the plasma fluticasone levels and we do see a dose dependent increase with the dose. But that scale, I want to note, is on a picogram level. This is a tiny, tiny amount of fluticasone in the blood, not really clinically significant.

Glucose and cortisol remain stable. So these are the graphs on the right. We worry about glucose, of course, because systemic steroids can increase glucose if you're predisposed to diabetes, and long-term steroids may suppress cortisol levels, leading to something called adrenal insufficiency. And we don't see any suppression here in that bottom right panel. The safety so far has been very good. There have been no serious adverse

events, and there's only been one event, chest pain, which was possibly related to the medication injection. So, overall, very reassuring safety and pharmacokinetic profile so far.

Can we go to the next slide?

James A. Helliwell

Absolutely. I mean Dr. Dellon, thank you very, very much for that exceptional overview and we'll be back with questions fairly shortly.

I just wanted to highlight a few more quick things here. Obviously, you've seen Dr. Dellon here who is the Chair of our Clinical Advisory Board and as you can see, as you look through the resumes that are here on our Clinical Advisory Board, I would argue that really we are being advised by Dr. Dellon and this exceptional group of key opinion leaders who understand the disease and are motivated as we are in improving patients' lives and conditions with EoE.

So why is it that we believe that EP-104 is really going to help patients with EoE? So, from the discussion that you've just heard, there's a variety of things that need to happen in order for patients to be able to feel better. One of the lines that Dr. Dellon just used was that the key is in the formulation.

So, when we look at the steroids that have been used in the past and their efficacy, that limited time that's actually within the esophagus, our belief was an issue in order to be able to get maximum efficacy at the same time taking something orally in a steroid in the oropharynx and the complications such as oral candidiasis that are often associated with that are problems for patients and for physicians in compliance.

So, when we look at this, we believe that giving steroid in the manner that was described by Dr. Dellon in this study is going to hopefully be able to improve efficacy for patients and efficacy not just in terms of symptoms, but also in terms of what we're actually seeing in eosinophils, in the EREFS, so those reference scores and the histology scores. So really improving a patient for a long period of time and ideally seeing this as being an annual therapy delivered by the physician once a year.

In addition to that, one of the other challenges that certainly has faced payers and providers and patients is the high cost of goods, in other words, the actual high cost of therapy that exists today and we believe that EP-104GI is, because of its low cost of goods, is really likely to be able to be a higher choice treatment we hope based on efficacy, safety and duration, but also in terms of costing. And as Dr. Dellon has already commented on the safety we're seeing to-date, avoiding the unwanted side effects from corticosteroids.

Without going into great detail here, we do believe that this represents a very significant commercial opportunity in being able to provide that better efficacy and that better safety to patients. We believe that this provides a very large market opportunity, something we haven't talked about today, but Dr. Dellon is a great expert in, is actually looking at the opportunity as well within the benign stricture category. And so that may be something that we have an opportunity to touch on in the Q&A.

When we look at the development path forward, as you can see, we're in the middle of a Phase 1b/2a. We just announced sort of an extension and expansion of that trial. And so really what that means is based on the feedback from Dr. Dellon and from others, from what we are seeing that we have the safety as well as we are seeing effect. And so we want to go up in dose. So as commented, the first three cohorts we just showed you are of very low dose. So, we now have the opportunity to provide more injections covering more of the esophagus, going to a higher dose and ideally giving us a longer time period as we're now following patients out to one year with that trial.

That trial is going to continue. When we get to a dose that we believe is the right dose, we are then going to expand that cohort and continue to recruit at the same time as going to the FDA towards the latter part of 2024 and really having a conversation about the next phase, which we believe we have the opportunity to do a single Phase 2/3 study design with roughly between 150 and 250 patients, really driven by the data that we're going to be seeing coming from this trial. And so that would be starting towards the latter half of 2025, but we would be continuing the current trial right up until we begin enrollment of that Phase 2/3 trial. Again, looking to a potential approval in mid-2028.

Lots of catalysts that continue to be coming up for this program, as you can see, with all the cohorts that are being dosed. We will be getting more voluminous data as we expand by three patients with each cohort as well as a longer period of coverage in higher doses. So, we're really going to be able to understand from this proof of concept study what that Phase 2/3 should look like with data being reported at least once a quarter throughout this, as well as that FDA interaction.

So with that, I think really the most interesting thing here is for all of you to have the opportunity to interact with Dr. Dellon and certainly, we at the company are happy to take questions. And so with that, there is an oral Q&A portion as well as a written one. We're going to begin with the oral Q&A. So I'll ask Kiana to take that over and give us those questions.

QUESTION AND ANSWER SECTION

Operator

Thank you, James. At this time, we will be conducting a question-and-answer session with our speakers. All right. So, our first question comes from George Farmer from Scotiabank. Please go ahead, George.

Analyst: George Farmer

Question – George Farmer: Hi. Good morning. Thanks for taking my question and thanks for that great presentation, Dr. Dellon. I was wondering if you could maybe comment on a few things. How would you be thinking about, as a kind of a key KOL here, guiding either physicians about actually where in the esophagus to inject? Does that really matter? And also thinking about how this drug would be used in retreatment settings and maybe it's still a little bit early based on the fact that you're just at low doses right now. And then, maybe I missed this, but is just kind of a naked formulation of corticosteroids often injected into the esophagus and what would you expect that, that would – what kind of effect would you expect that, that would elicit?

Answer – Evan S Dellon: Yeah. Hi. Great. Thank you for the questions. I think in terms of the injection protocol, we have to see how this escalation really turns out. I think, you know, EoE can – it can be variable in the esophagus. It can affect certain areas more than the other, so sometimes just the lower is affected, sometimes just the upper, sometimes the entire esophagus. So, I could imagine that it could be injected, targeted to areas that are actually visibly inflamed at some point or it may turn out that it's better to do an injection protocol over the entire esophagus, because sometimes the visual appearance doesn't always correlate with what's going on below the surface. So, I think we would have to wait to see how that's looking.

I think one of the other benefits of this kind of injection protocol that I didn't mention is, those biopsy pictures that I showed are just from the first 0.5 millimeter of the esophageal wall, because that's what we can easily and safely obtain during routine procedures. But, actually, EoE involves the entire esophageal wall. It's 3 or 4 millimeters in thickness and in EoE, the whole esophageal wall is actually thickened. And I think with these injections, there may be the benefit of improving inflammation throughout the entire wall. And so

that may be another reason to do a standardized injection protocol. But again, I think, as we go forward, we'll learn that from these studies.

In terms of retreatment, I think that won't really be an issue. I would imagine that once you do the treatment, when you bring the patient back, if it's at a year, ideally, you would sort of repeat the same injection therapy. And that obviously will be able to be examined as studies go forward that allow multiple treatments for patients.

The last question now is in terms of the other kind of steroid formulations, and these are not used for EoE. The only formulation that's really available for esophageal work is a formulation of immediate release triamcinolone, and that is sometimes injected into patients with refractory strictures. And trials of that have basically been a wash and I think the reason is, is the dwell time of that kind of solution and immediate release solution in the esophagus is very, very short. Actually, too short to impact the healing and fibrosis that may take weeks – a week or more to develop after a dilation therapy. And because of this and the really the short acting length, it's not a routine thing. It's sort of used as a salvage therapy in strictures and hasn't been used at all in EoE. So, this would really be a very novel approach and the critical thing is, is the long-acting nature of this particular medication formulation.

Question – George Farmer: Great. Thank you.

Operator

Thank you for the questions, George. Our next question comes from Andre Uddin at Research Capital. Please go ahead, Andre.

Analyst: André Uddin

Question – André Uddin: Thanks for that. Good morning, everyone. Dr. Dellon, realize that this is a little bit initial data. We have initial data so far, but if you're sort of looking into the future, where do you see EP-104 fitting into the competitive landscape? Do you think it has any potential to be first-line therapy? Thank you.

Answer – Evan S Dellon: Yes, I think it could. And endoscopy is such an important part of EoE diagnosis and evaluation. You could certainly envision a time where you might combine diagnosis and treatment in a single procedure or come back from diagnosis into a therapeutic procedure that would be potentially very appealing to patients to have a one-time treatment and not have to take something on a daily basis or weekly basis for a long time. And so I think it could be have a very high uptake.

Question – André Uddin: Okay. And just looking at budesonide, I have a question there. In terms of utilization, it can only be used for 12 weeks. And I was just wondering why that is, like, is there any sort of explanation as to why you could only be used for 12 weeks? Thank you.

Answer – Evan S Dellon: Yeah. So, for the budesonide oral suspension product that was recently approved in February, it was based on strong data from a 12-week trial. The extension trial there did not meet its primary endpoint. And so that's why at least at this time, the approval was for the 12 weeks of use.

Question – André Uddin: Okay. And so if I look at the chemical structures and I know it's different administration and I know it's also a different formulation, but they're both steroids. And so do you think, based on what you're seeing so far, that there are some differentiation with the different steroids for utilization for beyond 12 weeks? And do you think there could also be longer dosing with your proxy as a compound?

Answer – Evan S Dellon: Yeah. So, outside of the budesonide suspension, there were some things with that particular study design that led to the primary outcome not being statistically significant. It was a very small study. And if you look at the per protocol analysis and if you look at the overall wealth of topical steroid data in EoE, it's very clear that for a lot of people, maintaining steroid therapy, whether it's budesonide or fluticasone, is effective. And for example, the European product had a much larger long-term trial that was a randomized withdrawal trial, and they showed clear benefit of continuing a long-term steroid.

So, I think there are quite good data to suggest that a steroid would continue to be effective long term. And the difference, again, is for those topical steroids that we're looking at, it's twice a day therapy every day. And if you could and again, I mean, you know, I think everybody on the call, right, if you drink a sip of water or if you drink a sip of a milkshake, which is thick, right, you can tell it goes down if it's cold, but it's not in your esophagus for all that long. And so it's got to be this sort of spike dose that goes up and down. I think if this actually – if this works, where you have this long-term slow release to give you constant medication dosing, I think you may see very good long-term efficacy with it.

Question – André Uddin: Okay. That's great. Thank you.

Answer – Evan S Dellon: Yeah.

Operator

Thank you, Andre, for your questions. That's all the verbal questions we have for now. So I'll now turn it back over to James to read the written questions that came in from the remainder of the audience. Please go ahead, James.

Answer – James A. Helliwell: Perfect, Kiana. Thank you. Thank you very much. So, here is a question from Serge Belanger at Needham. Dr. Dellon, can you talk about your use of Dupixent? How commonly is it used in EoE? And what is the level of payer access for this indication? There's a secondary question, which is how different is your treatment paradigm for EOE versus GI strictures? And would EP-104 play a different role across these two indications?

Answer – Evan S Dellon: Okay. Great. Yeah. So the first question, as all of you know, the Dupixent is approved for EoE and different from its other indications where there's a severity kind of caveat for asthma and eczema, there isn't one for EoE. But in practice, most insurances are gatekeeping this medication and mostly allowing its use for more treatment refractory patients. And in general, I think that's appropriate. If you look at the Phase 3 trials for that med, the patients were all PPI non-responders, most of them had topical steroids and of those half were non-responders. In patients on average who've had EoE for five years and about 40% of them had had prior dilation. So, it's a really fairly severe – moderate to severe population that was studied. We don't have any data for Dupixent use in brand new diagnoses of EoE or in people who are PPI naïve.

So, I think it's appropriate to use it and consider it more as a step up therapy right now. I can say in my own practice, it's been about 10% of the patients meet the thresholds that I can get for insurance approval right now. So it has been actually reasonably difficult for me to get access. I think in talking to my colleagues around the country, there's variability by state by state in terms of the insurances, but it's certainly not a medication that's used for everybody with EoE. I think that's – is that enough of the first part of the question or did I miss any part of that first one?

Answer – James A. Helliwell: I think that got the first part there.

Answer – Evan S Dellon: Okay. So, the second part is, yes, there are a lot of differences in the treatment paradigms for esophageal strictures that are not due to EoE and that are due to EoE. And so the EoE strictures, often they can improve when you are using an effective anti-inflammatory therapy.

But in terms of the question earlier about how might you use EP-104, you may specifically inject it into an EoE stricture in addition to the other areas of the esophagus in EoE. The treatment paradigm for other strictures really depends on the underlying cause, and the stricture is really a sign and if you – of course, cancer can be a big cause of strictures. We'll leave esophageal cancers aside. But other causes of benign esophageal strictures can include reflux. Those are called peptic strictures when acid damage comes up and irritates the esophagus, causes ulcerations and erosions, and the esophagus heals with strictures. Other causes can be surgeries, radiation therapy. The esophagus is very radio sensitive and causes strictures. You can have causes related to ingestions of caustic materials, people with critical illnesses or certain substances can have relatively low blood flow to the esophagus and get ischemic strictures. So, there's a whole host – and there could be congenital issues as well. So there's a whole host of different things that can cause strictures. And the treatment paradigm generally is removing the underlying insult and then dealing with the strictures.

Unfortunately, the esophagus, once a stricture has developed, they can sometimes be very tough to treat. If you, say, have an injury on your arm, whether you burn yourself or cut yourself, you get a stricture, you get a scar there, right? And that scar doesn't really go away. And that's the same in the esophagus. You get a scar and that's what a stricture is but because it's a tube, it heals and it constricts. And that's where the problem is.

And so this is, I think, a very fertile area for using EP-104 for in the future. And in particular, I was just able to work with some colleagues and we studied the prevalence of esophageal strictures in the US. And it turns out that the prevalence was anywhere – it ranged from 1 in 100 to 1 in 1,000 based on age. So, as you get older, strictures get way more common. I think that prevalence being 1 in 100 in older patients was far more common than I had suspected. And it suggests a very large burden of disease and a proportion of those patients are going to have difficulty with treating the stricture and they would be a perfect target population for this medication actually.

Answer – Evan S Dellon: So, Dr. Dellon, thank you very much you very much. And I believe we actually have two more oral questions here. Gary Nachman from Raymond James, I believe, has a question.

Analyst: Gary Nachman

Question – Gary Nachman: Hi. Great. Thanks and good morning. So it's early data, but just talk about the dose response you've been seeing so far with EP-104 and why is cohort 3 not looking better than cohort 2 so far? Did I actually see that correctly in your charts?

Answer – Evan S Dellon: Yeah. I think it's really hard to extrapolate on these low doses. And cohort 3 hasn't reached the final follow-up period yet. And so usually we expect ongoing improvements over time with this. So, I just think it's a little early. And to give you a sense, right, so cohort 1 and 2, the one I'm just looking at so I don't misspeak on the dose, right, so cohort 1 is four 1 milligram doses at a one-time and when we're doing – treating EoE clinically, we're talking about a total of about 2 milligrams of steroids a day for weeks and weeks. And so this is really a substantial under-dose purposefully, right, because we're building up to safety and experience with the injection protocol.

So, I think my takeaway is, we're seeing some biologic effect that's very encouraging despite these really low doses and only localized in a very small area of the esophagus so far. So, I think that's why you're seeing those patterns so far. My suspicion is, as we move into the additional cohorts, where we're getting much more coverage of the esophagus at a higher dose, I expect you're going to see a much more clear dose response then.

Question – Gary Nachman: Okay. And just on that point, how high of a dose do you think you can go? So, are there any safety concerns that you're worried about as you move into the higher doses? And what do you think is the efficacy zone that you'd like to get into? And is Dupi sort of the standard there in terms of the different endpoints? Thanks.

Answer – Evan S Dellon: Yeah. So I think this is – for your first question, this is really why we're doing the study. There's not an empiric limit, I don't think, on the dose that we can inject. And it really depends on what the pharmacokinetics tell us and how much is getting into the blood. If it remains at these low picogram levels and we're getting increasing yield on the local effects, then that's the whole purpose is to increase that dose and see what the symptoms and what the overall safety and efficacy is. So, I don't think that I would say that there is empirically a dose yet. If you're going to say that your dose is, say, 4 milligrams for a year as opposed to doing 2 milligrams a day for a year, right? You have a lot of room to go in terms of what people cumulatively use for a dose.

So even when we're talking about 30, 48, even up to 80 milligrams or higher, it's the local delivery that's going to be so effective with that drug being delivered. So I think we'll see as – we will see if we get to some kind of plateau with efficacy or safety with this.

I think in terms of the efficacy plateau, it's been fantastic to have dupilumab for these more difficult to treat EoE patients. But it's not a cure and it certainly doesn't work in everybody and it still requires a shot once a week. And so, yes, their 60% histologic response rate and the improvement in symptoms is great. And there's patients who do really, really well with that. But if again, you'd have to individualize it for patients. But if you could tell patients you're going to have similar efficacy or something in that range with a treatment you only have to do once a year, that may be a huge benefit.

So, again, it'll depend a little bit but remember, again, most of the dupilumab – a lot of the dupilumab data are in these more difficult to treat patients who already are steroid refractory. So, I think this would be aimed earlier in the algorithm.

Question – Gary Nachman: All right. Great. Thank you.

Answer – James A. Helliwell: Great. Wonderful. Thank you very much. And one more oral question here. Rahul Sarugaser also from Raymond James.

Analyst: Rahul Sarugaser

Question – Rahul Sarugaser: Thanks. Thanks, James. Dr. Dellon, thanks so much for your insight here. So, Gary – yeah, Gary asked some of my key questions, but I also wanted to talk about the extension of the protocol from 6 months to 12 months? Given that, I mean, just like you said, based on Dupi being once a week, even once every six months would probably be a significant benefit to patients. And given that the data we've seen so far, cohort 3 notwithstanding is demonstrating so far that there is this benefit up to six months, how would you compare and contrast a six-month versus a one-year delivery of the therapy?

And then second – as a second question, I'll throw in is that another KOL we spoke to was surprised to see the response at these really low doses. And so what's your view on this response that you're seeing at the low doses?

Answer – Evan S Dellon: Right. So, to your first question, I mean, I think as long – the longer you can do between therapies, the better, because obviously it is an endoscopically delivered therapy. But I think I agree with you, even six months would be fantastic. If you could get to nine months or a year, I think that would be even more patient friendly in terms of the approach. Yeah. I mean, I think, to see these responses at these lower doses is, I think very, very encouraging. It is a little bit surprising, but there's a couple of ways to think about it.

One, to me, as I mentioned, this transmural or full thickness inflammation for EoE, that may be a reason that we're seeing these symptoms improve with trouble swallowing. If the esophagus is stiff, patients really perceive a lot of pressure and fullness of food, even if it's going down slowly. And if the medication starts to soften up the esophagus and make it more compliant and floppy, that could be a reason and a transmural injection has that potential basically.

Question – Rahul Sarugaser: Perfect. Thank you. And just a follow-up question. I know Gary did ask about that cohort 3, but I just want to press a little bit further there, given that there are two patients already read out there and we do see quite a significant difference. Yes, the data is early, but particularly with the Dysphagia Likert or the Odynophagia Likert scores, there's a pretty big delta between the response on cohort 3 versus cohort 1 and 2. Not sure if we can specifically ascribe that to the early stages. Is there anything else that you would potentially ascribe this to?

Answer – Evan S Dellon: No. I mean, I think, the symptom data (00:56:16) I just said, this is an open label study. People know exactly what's going on. It's just really – it can be really hard and again, it's three people, right? So, if one doesn't feel well and the other two do, it's just – this is primarily the safety and dose finding exercise. And I think the signal that we're seeing in terms of efficacy is like a huge bonus. So it's just – it would be awesome if we saw like the step-by-step decrease in the symptoms as we bump up on the doses. But I think it's just not practical in this kind of a study so far.

Question – Rahul Sarugaser: Great. And then if you could indulge us one last question. In terms of the sort of the goal of an end of Phase 2 meeting near the end of this year and the readouts on these patients coming up every sort of 12-ish weeks and to Gary's point about the maximum tolerable dose and even to yours being potentially quite high, do you see the current dose escalation in the cohorts getting to a maximum tolerable dose or target dose in time for the end of this year?

Answer – Evan S Dellon: I would hope so. I think we just have to see how it plays out. It's a great question, but that's why it's built like this and it's built like this with safety primary in mind, right? And the protocol has a lot of endoscopy, a lot of monitoring to ensure the safety and to make sure we hit that – get that dosing correct. But, yeah, that's going to be a big thing that comes out of it and hopefully, we will get there as quickly as possible.

Question – Rahul Sarugaser: Perfect. Thanks. That's all for me today.

Answer – James A. Helliwell: Great. Wonderful. Thank you very much. And that really brings us to a close. Just to sort of answer a little bit of the question that Dr. Dellon was saying there about cohort 3 and the rest, we've dosed nine patients, eight of whom have responded very well. One of whom, exactly as Dr. Dellon suggests, really hasn't responded. So just that little additional piece there.

So, first, I just want to thank Dr. Dellon for taking the time, sharing your expertise today, very much appreciate it. To all of you who've taken the time out of your days to hear this, we really appreciate it. For the

fabulous questions, again, we really appreciate it. We look forward to continuing, as Dr. Dellon says, advancing through the doses and, hopefully, providing real alternatives to improve patients' lives living with EoE and, hopefully, we get to talk a lot more about strictures in the future as well.

So with that, thank you very much, everybody.