

WEBINAR TRASSCRIPT: Small Fiber Neuropathy and ARA-290 Results

May 17, 2017 - Dr. Daniel Culver of the Cleveland Clinic

I would like to thank the Foundation for Sarcoidosis Research for organizing this event. I know that small fiber neuropathy is something that affects quite a few patients with sarcoidosis and we'll be talking about the disease itself a little bit today.

I also know that people have been waiting quite a long time to hear about this clinical trial and that several of you had participated in the trial. And, so we're going to go through a little bit of the results of the trial. Again, thank you for any of you who did participate, and thank you for your involvement with it. The first thing is that this is a collaborative effort it's a group effort and really this is an industry sponsored trial from a company called Araim and there's a whole team in Araim who are committed to the space and who are really very compassionate and care quite a bit about the patients and with whom we've worked and that the other investigators in other countries have worked closely to try to move the space forward.

One thing that I want to say is that this medication now has a generic name it's called Cibinetide. So, what we knew before is ARA-290 now has an official name called Cibinetide and when you look online or do Google searches and work throughout the rest of this talk I'll be referring to this drug as Cibinetide and not ARA-290. I put just a little snapshot of this paper that came out which describes the trial will be going through today and there's a link at the bottom which would allow you to go into this open access journal. And see all the details of the trial, but that just came out this earlier this month so this is all really hot off the press that's a disclaimer about what we'll talk about at the end.

But, let's talk about small fiber neuropathy a little bit in general first. As you know, sarcoidosis causes a lot of symptoms and not all those are easily measurable with pulmonary function tests, breathing tests, bloodwork x-ray. But, pace with sarcoidosis quite often comes in talking about fatigue, talking about pain, talking about dyspnea, which is shortness of breath, and this is a cartoon that Kate Lazar made a couple of years ago; which just goes through some of the things we think about when we think about symptoms.

And you can see small fiber neuropathy is listed there is one of the potential causes, but I would also say that although pain is what we think of with small fiber neuropathy, most of the time there are very strong correlations with fatigue and I suspect to some degree also with other symptoms like shortness of breath.

And so addressing really the symptoms and the quality of life in the sarcoidosis population really requires us to think about all of these kinds of parameters or at least to have them in our mind while we're going through things. I think a small fiber neuropathy really as two separate symptom sets and I'll talk a little bit about what small fiber neuropathy is in a minute, but here are the sorts of symptoms that we really think about there are ones that are affecting sensation and ones that are affecting the autonomic nervous system.

Sensation symptoms tend to be neuropathic pain, burning type of pain, sometimes aching pain, painful to light and touch sometimes changes in temperature perception. Limbs sometimes, sensations of needing to move the legs at night, and what we call restless leg syndrome. So those are sensory symptoms and I think those are, you know, at least as common or important as the autonomic symptoms are.

Some patients have almost entirely sensory symptoms and some patients have almost entirely autonomic symptoms but in reality most patients exist somewhere on the spectrum with both of

these sets of symptoms. The autonomic nervous system is a part of the nervous system that is kind of like the gas pedal and the brake of your body. So you remember from biology class the rest and digest functions versus the fight-or-flight functions and so the autonomic system is really intimately involved in controlling those sorts of things.

So sweating, bowel function, symptoms of dry eyes and dry mouth those are sicca of symptoms heart flutteriness or palpitations. I would distinguish that from the kind of palpitations that occur with cardiac sarcoidosis which are usually malignant, serious, and life-threatening. The kind of applications occur with small fiber neuropathy tend to be premature contractions. A lot of times these are coming from the upper chambers of the heart and you really can only sort this out by some additional testing like a halter monitor.

Flushing or the stasis which means lightheadedness when you stand up or when you raise up sexual dysfunction and cognitive deterioration; those are all part of autonomic. Although, I think cognitive kind of spans all of these things. So, these are questions that sometimes we ask and that really would suggest the diagnosis of small fiber neuropathy as possible. I think it's important to remember that these are all very nonspecific symptoms and you can certainly have some of these symptoms and not have small nerve fiber disease.

When we make a diagnosis of small fiber neuropathy we have to think about can other diseases be the cause of it. The most common one is diabetes. Even people who have relatively good control of blood sugar can have neuropathy from diabetes- from the effects on small nerve fibers. Here are some other ones that we kind of look at thyroid disease. Maybe not tremendously common B-12 deficiency, I think is pretty important autoimmune diseases I think are fairly important.

And then the familial history of polyneuropathy there's also a couple of other ones that aren't listed here. Some chemotherapy agents for example can cause small nerve fiber disease and so we have to kind of go through a mental checklist of thinking what else could be causing this before we say okay this is probably from sarcoidosis how do we diagnose it?

We really have a battery of tests what I would say is that the standard tests that neurologists like to use to diagnose large fiber disease. Diseases where maybe you have a weak limb, or where you have a numb foot, don't do very well for diagnosing small nerve fiber disease. Because they're really looking at the large fibers, which are the big nerve, running from the spine into a limb for example.

So, we kind of combine some of these tests together in most cases to make the diagnosis of small nerve fiber disease. The first one there is the inter epidermal nerve fiber density- that's doing a skin biopsy and looking at the number of nerve fibers unmyelinated small nerve fibers in the skin biopsy.

It's very labor-intensive and it really is only done in specialized centers, although most places now you can do the biopsy and send it off to some referral labs and they will do the analysis so for sensation symptoms in the U.S. That's the most common way of making the diagnosis and deemed to be probably the most accurate.

The QST or quantitative sensory testing is really probably the best example of that is the thermal threshold testing where you're blindfolded. Then the examiners ask you whether or not you can discriminate a change in temperature, and as the nerve fiber function gets worse your ability to tell differences between subtle temperature changes goes down. That's much more widely used in Europe than it is in the US.

The quantitative sudomotor ex-owner reflex test is looking at sweat production after a little stimulation, many of you have had that. That gets a little bit more to those autonomic parts of this

rather than to the symptom part other than pain parts of this. Cardiac autonomic testing are things like table testing and looking at how the EKG looks over time.

There are some other ones that are done with that. And a couple of these other ones here are kind of a little bit more experimental now. The one test that's not on here that I'll talk a little bit about in the context of this trial, that's really becoming very important in this field, is the corneal confocal microscopy; and we'll talk a little bit about that as we get into this trial.

So, small fiber neuropathy as many of you know is a really important problem in the sarcoidosis population. We wanted to look at it just in our population, the Cleveland Clinic patients to see what does it look like, how does it, you know, how does it present, are there any particular predilections and so this slide which, I'm sorry is a little bit busy and complicated and is also not appearing here, there it is, looks at 115 sarcoidosis patients with small fiber neuropathy.

And what we did, is we compared those to the same time period when we saw around 1600 patients in the sarcoidosis clinic in general. So, on the left side of this we're looking at differences in gender and on the right side of it we're looking at differences in race, and the y-axis is just showing percentages. So, the red and pink over here is showing small fiber neuropathy in the patient or it's showing the gender disposition, the percentage of females in small fiber disease, sorry males.

Females and in all patients, both males and females and you can see that there's a female predominance in sarcoidosis that's very similar for small fiber disease. So it just means that if you're a female you probably have sarcoidosis and similar percentages that people have small fiber disease whether they're males or females.

Race is a little bit different of an issue. So, here again is small fiber disease, here are all the patients and if we're looking at the number of patients in our Center that are Caucasian or European American which is this bar, versus African-American, which is this bar; we have a referral bias which is probably not exactly accurate in the total sarcoidosis world, but we do tend to have about 75% percent of our patients here in Cleveland, at the clinic that are Caucasian. \

However, the percentage with small fiber disease is even higher. That's even more influence towards Caucasian whereas it's relatively uncommon in our population just compare this pink part of this aqua bar in the African American population. So, that's a little bit about the demographics. Now how do we treat small fiber disease?

Most of you who have this have gone through some of these things for the sensory symptoms, the pain symptoms we use things like GABA analogs those are things like Neurontin. Or, Neurontin is probably the most commonly used one, lyrica is another one. Sometimes we use antidepressants like duloxetine which is celexa, tricyclic antidepressants like amitriptyline which is elavil Topamax, is topiramate and some of these other ones that are listed here.

For the autonomic symptoms, those are much more difficult to deal with if there's a problem with ortho stasis. Compression stocking can be helpful fludrocortisone which is actually a steroid that promotes salt retention can be helpful. If there's a problem with palpation sometimes beta blockers, like metoprolol agents that are used for high blood pressure and fast heart rates can be helpful. But suffice it to say for those of you who have gone through this that there's not a tremendously effective benefit for a lot of patients from these sorts of agents.

We've tried over the years of course to treat things with steroids and with methotrexate and other conventional medications for sarcoidosis. And I can tell you that those by and large aren't very

successful. There are some groups that seem to feel like the TNF antagonists can be successful. And, I think maybe there's a little bit of a story to that, but I don't think that they're a homerun at all.

So, a few years ago we actually started looking at using immune globulin for small fiber disease and here's the protocol that we typically use, although many patients have had variations on this. We like to use a lot, we use two grams of immunoglobulins per kilogram of ideal body weight. So, for a kilogram person that will be a hundred and forty grams of IVIG. That is a heck of a lot of IVIG. For that reason, we have to load it in relatively slowly so we can avoid side effects like, headaches, problems with the kidneys, and problems with infusion reactions.

So, some of you have come in and had five days in a row of this, for eight hours a day. Sometimes we do it forty-eight hours continuously and because of the reactions. We give patients a little bit of steroids, a little bit of that's benadryl and a little bit of that's Tylenol to help with those reactions. And then we give it again in three to four weeks at a half dose and usually, I think after the first infusion, or certainly after the first several infusions we can tell what we're going to get from it.

And I'll show you some data about what we think patients get from IVIG and one of the problems with this is that there's really no great way of measuring response. We don't have a forced vital capacity to measure response we're really looking at things like pain scales or patient reported symptoms, and those haven't been studied enough in this area to really be certain about what they mean.

Here's a paper that came out recently that looks at idiopathic small fiber neuropathy and I think that those are similar sorts of symptoms to what we see in the sarcoidosis. And I don't expect you to look at all these symptoms that are listed here on the x-axis, but when you look at the dark black bar, the small fiber polyneuropathy patients, you can see that for many of these symptoms for example, tingling or pins and needles, this is much higher in a small fiber group.

Skin that has less sensation or numbness is much higher in the small fiber group, so these are some of the symptoms that we asked about when we're going through things and the sort of things that maybe could make a scale for measuring the effectiveness of some of our agents. So, what about IVIG?

Here are the data, and again this does not use any rating scale at all to measure it, but these are the data that look at the benefits. Which green means we thought that it was beneficial to treatment with IVIG in the Cleveland Clinic population. Yellow was maybe a little bit of benefit but not a ton and red was no particular benefit and the gray means that we didn't really have any follow-up data on the patient.

So, you can see that all the ones who have green bars that IVIG has a much higher bar than either the TNF antagonists or no treatment at all. And you know maybe combining them has a little bit of benefit, although I'm not sold on that, personally. Patients who experience no benefit were much more likely to be in this group who were not treated. And so, I think that the bottom line is that, although we don't really know the magnitude of the benefit and it is a cumbersome, toxic, and expensive treatment, that IVIG has been the thing that we've used for some patients who have very severe disease. How does it work? We don't really know, but I think that maybe as we understand the disease a little bit better we'll be able to come up with some treatments that are more targeted.

Here's what we think of with small fiber disease, and I'll walk you through this because it's a little bit complicated. Here is a spinal cord, and the spinal cord has neurons in it and the neurons connect. And they come out of the spinal cord and they go into something called the dorsal root ganglion. Where the nerve body is, and then that sends the next neuron out and that goes all the way down

the sciatic nerve, or down any nerves in your upper limbs until it finally ends up in the very furthest reaches of the body.

In these very small unmyelinated nerve fibers that are going here into the skin. And so, you can see these nerve fibers reaching up here and they have lots of branches. And they're integrating things like sweat glands, they're integrating sensation on the skin. And so these control the autonomic and the sensory portions of the small fiber functions we don't understand why these nerves, in particular are lost in small fiber neuropathy.

But if I do an MRI over here in the spinal cord, I don't necessarily see any changes. Is there something happening in a dorsal root ganglion? Maybe. Is there something happening here at the local level? Maybe. Is this an inflammatory thing? I think it's possible, but we don't completely understand why this happens.

I will say that if you compare patients who are controls to those with length dependent, like diabetic small fiber neuropathy, and those with non-length dependent small fiber neuropathy, like sarcoidosis patients. And you look at some of these proteins here, which are probably important for inflammation, that there is definitely inflammation in the length dependent, small fiber neuropathy. And, about 50% percent of sarcoidosis patients will actually fall into this category.

And maybe some inflammation, but not nearly as robust in those with non-length dependent small fiber neuropathy. So, I think this does lend some credence to the idea that inflammation at some level might be part of a process that's causing small fiber neuropathy.

This leads us into a story about C1q and the story starts off with this issue. If something happens to you, if you get a cut, if a bacteria goes into your right lung, if you get some sort of an injury where there could be infection, the body is very good at triggering cascades of inflammation that rev up and try to control the disease.

And it needs that, so the bacteria doesn't overwhelm you and so you can actually overcome it. But, if you think about a drop falling in the water... what happens there are ripples, and those ripples, they can peter out as they get further away from the inflammation. That certainly could happen, but also, sometimes those ripples can get stronger and you can end up with this.

You can end up with a bigger and bigger problem or a tidal wave even and when that inflammation becomes overwhelming. It actually might be more harmful to the host than the initial assault was, and so what is the body used to control these ripples. So, that they don't spread out across the whole pond or at least the ripples quiet down instead of becoming the tidal wave.

And that's part of the work that goes into this C1q story. And so, the work was really to look at the innate repair system, which is a system that gets activated when there's some inflammatory stimulus. So, if you just imagine that this area here is the surface of a cell and you have part of a receptor sticking out of the cell and part of the receptor in the cell, and this is the common receptor here.

When there's damage or stress a different subunit of the receptor comes out of the inside of the cell and comes up and joins its partner, joins the beta common receptor here on the surface the cell and it makes this dimer, this two-headed receptor, now it's sticking out there and if something comes in, like this little u-shaped thing this little Wiegand.

When that gets to a high enough concentration, that sends a signal through this receptor that switches it on and what does that do? That prevents cells from dying, that prevents cells from doing

inflammation, and it turns on repair mechanisms so the idea is that this mechanism gets expressed away from the damaged area and prevents the spread of those ripples. How does that apply to neuropathy?

Well, this innate repair receptor has lots of ways that it can affect neuropathy so it is expressed and helps modulate inflammation and activated microglia those cells in the spinal cord, in dorsal root neurons that I showed you. And it does this through several different mechanisms.

Both decreasing pain and decreasing nerve injury and so all of these things are potential ways that Cibinetide, which is a way of triggering that receptor. And turning it on, can have benefits here, on the inflammatory cascade. That sounds like a very good theory, but does it actually work in practice?

Well, here are two clinical trials that were done, the one on the left is in sarcoidosis patients who have painful neuropathy, the one on the right is in diabetes patients with neuropathy and these y-axes are just looking at how much pain the patients have using a score.

And so, the more the score drops the less the pain so starting off here at zero, patients treated with Cibinetide, who had sarcoidosis, this was an earlier trial using Cibinetide, decrease their pain score by about 1.7. Whereas those treated with placebo, it only decreased by about one.

You could say well, why did the placebo group drop at all? You know they probably should have just stayed right here at zero but I think that gets back to when patients are in a study, they wanted to believe that they're better. They want to feel better. They're being seen a lot and so this placebo effect, we'll see this in the Dussehra trial, is common to all of patients' trials where we're looking at pain scores.

The main thing is to say there is definitely a difference between this group and that group and it's about .7, that should be down here, suggesting benefits for Cibinetide that aren't seen in the placebo group and this is actually the same kind of magnitude of a benefit that you would expect with any of the medicines we use to control neuropathic pain.

Same story here in the diabetes trial, maybe even a little bit bigger effect size. Those are small numbers of patients, but those do suggest benefits from use of Cibinetide. If you go into a little bit more basic mechanism and you look at animal model you can look at a model of spinal cord injury in rats and this is looking at placebo. This is PBS or Cibinetide treated and we're looking at micro wheel injury by standing with this particular protein and you can see that there's a lot more heavily concentrated green. Suggesting more injury in the group that was treated with placebo than the group that was treated with Cibinetide after injury happened.

What does that mean to the patients or the animals in this model? It means that if you look at how well those animals are after two weeks, after the injury tolerate any stimulation to their paw that the placebo group has very sensitive paws they can only take this many grams of stimulus to their paw before they withdraw. It is the group treated with Cibinetide and looks almost the same as when they started, so that suggests that nerve injury in the spinal cord can be modulated using this particular agent.

So now let's get to the Dussehra trial for the last few minutes of this and we'll just go through that trial for a minute. For those of you who participated in this, this may look familiar, and those of you who didn't it may be an introduction. So, this was a phase 2-B trial, which means that it's really a trial designed to both prove that there's benefit, but also to look at what the right doses for a potential later trial.

This was done in Cleveland and in Leiden in the Netherlands it included 64 patients and it involved treating with one of these four regimens placebo subcutaneously one milligram four milligrams or eight milligrams for 28 days and then the patients were followed thereafter for a period of time, another 12 weeks at least.

So, that was the trial and this was randomized, meaning that the patients were put into it, they didn't know what they were getting, I didn't know what they were getting, the coordinators didn't know what they were getting, only an investigational pharmacist could break the code and say AHA is this particular bottle- goes to this particular number, so now we always had a fail-safe mechanism to know what the patient was getting.

If you look at how the trial actually was conducted, this is called a consort diagram, you'll find this in most clinical trials, patients were screened and some of them didn't meet the eligibility criteria and a lot of patients would say, well I want the drug why didn't I get to be in this trial? Why don't I get to meet the eligibility criteria?

But, you have to remember that trial is primarily designed to answer a scientific question. And if we're not reasonably strict about, including patients that are fairly homogeneous and that really truly have clear-cut small fiber disease and in whom we really feel that we can measure things will just get noise and it will be a waste of everybody's time and we'll never go forward.

So, we have inclusion and exclusion criteria and unfortunately only a minority of patients did not meet inclusion criteria. So, 64 patients were randomized and you can see that it was 16 in each group, most of the patients 16,15,15 and 16 completed the trial and most, of those in fact had analyzable data.

And so, this trial actually compared to many trials had a very high rate of patient retention. Now who were these patients and what did they look like? I thought there were a couple of interesting things to look at. Number one, look at how many medications these people were using for neuropathy before they came in and this just underscores the seriousness of this issue so more than 80%.

We're using analgesics about two-thirds of them are using antipsychotic medications, but also for control of neuropathy, some of them are using anti-seizure medicines and some of them using anesthetic medicines. So you can see these patients in general were taking about two medications, each multiple pills a day just for their neuropathy and usually not achieving very good benefits.

There's another thing that I want to point out about this, and that is that a small fiber neuropathy that influences physical function. You wouldn't think that sensation has a very big influence on physical function, but it really does appear to so here is a measure of neuropathy. It's the neuropathic pain symptom inventory score and as you get higher here. It's worse these people here have worse neuropathic symptoms than these people here.

And if we measure physical function just by something we call the six-minute walk test- how many meters can walk in six minutes- and you adjust that for age, weight and height; which are important covariates you can see that the higher the score on the neuropathic pain symptom inventory the lower on average people walked. So this influences physical capacity.

And I realized that when people were talking to me about how they felt when they were taking the medications in the trial what we really wanted to look at was what happens to small nerve fibers. Now, many people would not want to go through multiple skin biopsies and in fact, I told you that that's a tough test to do.

So, we used corneal confocal microscopy, this is basically a microscope with a camera on it that looks at the back of the cornea and looks at these nerve fiber networks. It looks like a spider web I think, sort of in the back of the cornea and here's a healthy person. Here's a sarcoidosis person before treatment you can see there's much less of this in branching is much less.

I mean look at this you know the long road before there's any intersections after treatment there are improvements. And, we can measure that and quantitate that using several different metrics it didn't in days get back to this.

But, this is some substantial improvement and I'll show you the numbers. The other thing that we can look at is we can actually look at skin and look for regrowth of nerve fibers. So here's the before treatment, here is a stain that looks at nerve fiber growth and you can see there's a few of these black lines. And then after treatment, you can see that there's a lot more of that, so that suggests that what you're seeing here in the eye is similar to what's seen in the skin.

A problem with this is, someone may say well look you're measuring these nerve fibers that's very nice, good job. Does that really mean that you're treating the pain? Does that really mean that you're improving the symptoms? And that's something that the FDA will ask you all day long and you have to have good evidence for how that works.

Here's a cartoon that I think captures some of that and this is talking about endpoints in sarcoidosis trials this one's actually about IPF, a different disease. But I think it highlights the point that we would like, when you have a disease and you have something that's important to patients like symptoms.

We would like a surrogate endpoint, meaning an endpoint that's not your symptoms, but it's something that we're measuring to lay directly in the pathway between the disease and what you experience.

So, for example if we intervene here we should be able to see benefits on the surrogate endpoint even if we don't always have the ability to measure the clinically meaningful endpoint. And, you can see that there are different ways here how that an intervention might not exactly fall into the causal pathway. Or might not be the only mechanism of influencing the clinically meaningful endpoint. And heaven forbid that you're measuring something that affects a surrogate endpoint.

But it doesn't have anything to do with the clinically meaningful endpoint, because then you might end up with a medication that is beneficial to something we measure but not beneficial to how you feel, function or survive. So, that's something that I think is important that we are wrestling with in this particular area.

And I do think corneal confocal microscopy is more and more appearing to be a very good surrogate endpoint. So, let's talk about the results. Here's the primary endpoint we looked at corneal nerve fiber area from those microscope images I showed you. And what we did is we looked at patients starting here at the baseline of zero, that's whatever their number was that we gave that zero.

And we looked at the change from baseline by day 28 and you can see that in the two highest groups, the highest those groups that there are important changes, increases in the density at day 28, but not in placebo. And, actually not with the low dose which was on a sort of predictable.

By day 56 some of that goes back to the baseline. Now I think that that may be having several explanations. One is that this is a very short period of treatment and if you're going to have sustained durability of the effect it may be that you need a longer period of treatment.

I don't think that necessarily means that patients have to be treated forever with Cibinetide to get a durable benefit, but it looks like 28 days is probably not going to be enough to maintain a durable benefit. What about other sorts of things? What about looking at the skin?

Here is the inter epidermal nerve fiber density and here are the four groups in different colors. And you can see at day 28, actually all the groups improve by just a little bit. But there are no differences between them, those are all the same. If we look at this gap 43 standing, however, which tells us who's growing new nerves in the skin.

In the four milligram group, there are big benefits on gap 43 area versus the placebo group which did not show such a benefit. And so, it suggests that although we didn't really measure very well using our conventional technique if we're looking at the rate of new fiber growth in the skin in the sarcoidosis patients that Cibinetide had a substantially better effect than placebo.

So, that fits along with our idea of the eye being a good way to measure what's going to happen in the skin. What about functional capacity? Here's the six-minute walk test the Cibinetide group showed improvements, the placebo group showed no change. And I realized this was going to be a big deal when one of the patients who was one of the first people in the trial told me, "Hey I just went to the mall all afternoon and I haven't done that for many, many years. I'm able to do much more than I was ever able to do."

And I think this is one way of trying to reflect that and in fact, if you compare the improvement in the corneal nerve fiber area in the eye compared to how much people can walk, there is a correlation where the more your eye nerve fiber density improves. The more you're able to walk further, compared to your baseline.

So again, this suggests that you're not just seeing improvements in things that we measure, but also in functional capacity and that that relates very directly to nerve fiber density. What about how patients feel? This is a little trickier and again it's because of that big possible effect that occurs in these kinds of trials every single group had improvements including the placebo, just like those other trials that I showed you before.

However, for patients who had more severe numbers on pain scores at the beginning, if we take that group alone which are the group that probably have the most gain, right? They don't have a ceiling on how much their pain can improve and you look at Cibinetide four milligrams versus placebo, you're seeing very similar effects sizes as to what you saw before with those other two trials I showed you.

So, significant improvements in the mean pain severity score. So, I think this is something that is very important because this is a patient reported outcome and it's what you guys wrestle with every day. One other thing that we always measure in these sorts of trials, and it's very important is the issue of safety.

So here's a comparison of safety across all the four groups you can see them in these four columns. One for eight milligrams and placebo. And you can see that if you count up everything that happened you tripped on the sidewalk and got a sprained ankle that most patients have something happened to them if you're watching them closely.

But if you start to talk about serious adverse effects, those numbers get much smaller and in fact only one patient had a serious adverse effect that led to drug withdrawal and that was relatively clearly related to, sorry I shouldn't say it was clearly related, that was possibly related at all, no deaths.

My impression of this is that this is probably consistent with no important serious effect although we should say that you know we're analyzing small numbers of patients here so we'll need a larger trial to really answer the question. But, I think the Gestalt on this is that there's no clear-cut serious or even not very serious adverse effects that occur very frequently with the medication.

So, just to wrap up here on small fiber disease, as many of you know, this is under-recognized, the first step for the physician just is to recognize it and to address it. We talk about maximizing nonspecific therapy I like to use medications like neurontin and if those work that's great that's inexpensive and it's accessible.

I also think that complementary and alternative medicines, things like yoga tai chi can be very, very important. IVIG we talked about a little bit, that it's expensive, toxic, cumbersome, we use it when we have to but it certainly is not a panacea for this. And, I hope we'll have better ways to treat this in the future and I don't know if a phase three Cibinetide trial will happen, but just so all of you understand how the FDA works, a phase to be trial does not equal approval of a medication you must have a phase three trial and sometimes two phase three trials in order for the FDA to approve a medication for commercial distribution. So those are the sorts of things that have to happen and the similar sort of process would have to happen in Europe with the European Medicines Agency in order for Cibinetide to be commercially available when something that all of you could use if you wanted to.

I'm going to stop there with whatever comments I have, and I think there were a few questions and we can take some time now and go through a few questions, if there are some out there. Kelly are there any questions? Yeah, I've got the first question here, thank you again for everyone for joining us and for your patience with any technical difficulties you encountered.

The first question is who is the ideal medical professional to connect all the dots associated with symptoms, he or she lists off they're specialists there, but who's the best person to be the quarterback?

That's a great question because so many of you guys fall through the cracks because everybody's playing hot potato, um I think that the short answer is that whoever's going to roll up their sleeves and actually do it is the best one to be the quarterback. Sometimes that's the sarcoidologist and I think that most of the docs in large sarcoidosis centers are comfortable with and familiar with dealing with this issue. And, will kind of file forward and try to sort it out I do think having a neurology input. And sometimes the neurologist is the one who will really own this thing I think that's very valuable.

I think sometimes neurologists tend to look at large fiber disease and if it's not large fiber disease then they move on. But, certainly there are some neurologists who are very fluent with this stuff and then sometimes someone like a rheumatologist or a good internist is the one who can be the quarterback so I'd say whoever does it for you is who you should go with.

Next question comes from Irene, I have lived with sarcoidosis for 49 years and was diagnosed with both peripheral and small fiber neuropathy about 15 years ago. My symptoms have accelerated, I just been diagnosed with axonal polyneuropathy, is this a natural progression of neuropathy?

So, axonal polyneuropathy usually refers to some effect of granulomatous inflammation. So, what we would call is neuro-sarcoidosis assuming that there's not another cause of the polyneuropathy and that's really a large fiber disease which would be different than the small fiber thing that we're talking about.

So, I would make the distinction that when you have, when you have neuro-sarcoidosis that affects either nerve roots near the spinal cord, or affects the spinal cord itself, or even affects the large

nerves as they go from the spinal cord out into the limbs, that's usually inflammation that's caused by granulomas, little clumps of cells from the immune system. And, we usually address that by treating it with traditional sarcoidosis medicines like steroids and all the other medicines that we use. When you don't have those granulomatous problems and it's only localized to the small nerve fibers, you know, that's when we think we're talking about small fiber neuropathy. Next question comes from Heidi, can small fiber neuropathy cause tremors and muscle weakness? Those are not very typical symptoms of small fiber neuropathy. Muscle weakness could be for many, many different things, including if you're really quite debilitated from anything, like small fiber neuropathy.

Maybe there would be disuse weakness but muscle weakness and sarcoidosis could also, be from sarcoidosis involving the muscles. It could be from nerve disease that's affecting the nerves going to the muscles it could be from the effects of steroids which can cause muscle weakness in and of themselves. It could be from other medicines, there are many causes of muscle weakness tremors can be part of muscle weakness too although there are other causes of tremors as well, including brain issues.

The next question pertains to syringe ilia and small fiber neuropathy, could they be related and could drugs under investigation help? Ah, syringe ilia, really, I would think of as a separate entity. I'm not really familiar with that being a manifestation of neuro-sarcoidosis either, so I have to defer to people who know more about Cibinetide than me, about whether it would help but I can't think of an obvious reason why wouldn't.

It doesn't really compute for me. How can you be sure that sarcoidosis is causing the nerve pain and it's not another source? Okay it's a great question and the answer is the traditional way we've done it is to say we're going to look around for other causes of neuropathy and if we don't find anything else and if you have sarcoidosis then we're going to say okay it must be from sarcoidosis, but you could turn the thing that backwards and say, "well how come sarcoidosis has to read a diagnosis of exclusion? Why can't we say once you have sarcoidosis then we're not going to label it as diabetic neuropathy?"

And the answer is, there is no objective test to say patient A had it due to sarcoidosis and patient B had it due to diabetes and patient had it due to B-12 deficiency. Some simple things can be done and should be done for everybody diagnosed with small fiber neuropathy. Those including the anti-nuclear antibody test, some kind of an assessment for diabetes, some screening or at least the history about familial or family neuropathy.

And, maybe a B-12 level and there are other tests to exclude some of the other things I listed on the checklist there. But, a lot of those depend on the history and when there's no history to suggest some of those other diseases, then doing screening tests look for them may or may not be very useful.

What is the method of administration of Cibinetide. It's sub-q, it's a shot. And I several questions related to any ongoing trials or how somebody might be able to participate in the ongoing research.

Well I really appreciate that because um we had people come from all over the country for the Dussehra trial. And when you really start looking at including criteria and exclusion criteria and considering you know. Some of that, you know some of the challenges about being in a trial from the patient perspective: the number of people who can actually do it is not as much as the number that's affected by the disease for sure.

In fact it's a fraction, so everybody who can be involved in a trial, I very much appreciate that and you know it's important that you guys stay active and engaged as much as you can and get in trials

when you can. Right now, there's no trial going on for Cibinetide and sarcoidosis. I hope, and we'll just have to see, time will tell but you know the hope and, you know certainly I think this has got a very nice chance of happening.

Will be that there will be a definitive phase three trial which would allow the FDA, if the trial works out in the right way would allow the FDA to say yes, we like this yes, we'll approve it and yes, sarcoidosis people who have neuropathy can have this.

That's the hope so stay tuned and I'm sure that FSR will be one of several groups who are really trying to make sure that the patient populations, all you guys hear all about this and have a chance to participate and obviously, this would be much more than Cleveland when you're talking about the US. This would be many sites across the U.S.