FOOD AND DRUG ADMINISTRATION

CHAGAS DISEASE PUBLIC MEETING

ON

PATIENT-FOCUSED DRUG DEBELOPMENT

Tuesday,

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White Oak Campus

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Silver Spring, MD

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Capital Reporting Company

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P R O C E E D I N G S

(9:00 a.m.)

WELCOME AND INTRODUCTIONS

MS. GIAMBONE: Good morning, everyone. We will go ahead and get started. My name is Soujanya Giambone. I am with the FDA's Center for Drug Evaluation and Research, Office of Strategic Programs.

On behalf of all my FDA colleagues, I'd like to thank you and welcome you all to our public meeting on Chagas. Thank you for being here. We are really looking forward to a great day of discussion and learning so much from you all.

What I'd like to do is quickly go over the agenda and a few housekeeping items, and then we will get started. You should all have a copy of the agenda, but if you don't, we have extra copies out on the registration desk.

We are going to start off with a few presentations from my FDA colleagues. They will provide some opening remarks, an overview of the

Patient-Focused Drug Development Initiative, and also a background and overview of Chagas Disease and current treatment options. I will come back and review the discussion format for today.

For the first half of the meeting, for the morning part of the meeting, we have two discussion topics. Topic 1 is on the disease symptoms and how they impact your daily life, and what matters most to you as patients. Topic 2 is patient perspectives on current approaches to treating Chagas Disease.

Then we will take a break for lunch. We have an one hour break for lunch. The second half of the day will be a scientific discussion, and we have some wonderful scientific experts here who will be presenting their comments, and we are looking forward to a great discussion there as well.

That will take us to about the last half an hour of the day, which we reserved for open public comments. An open public comment is just a time that we reserve for anybody in the audience,

not just patients or patient representatives or scientific experts, anybody in the audience who would like to present additional thoughts and comments related to our topic today on Chagas Disease.

We encourage you if you would like to speak during open public comment to sign up. We have a registration sheet out on the desk, on the registration desk. We will take a look at how many people signed up and how much time each speaker will have. We will take sign up through lunch time.

Finally, we will wrap up the day with some closing remarks. As you can see, this is a full day of discussion but we are once again very thankful that you are here, that you are all here, and looking forward to a really great day of learning from you.

Just a few additional items. This meeting is being recorded and transcribed. The recording and the transcript will be available on the meeting web page within a few days after the

meeting.

Some housekeeping items. Restrooms are back out into the lobby, and if you make a right and go all the way down the hallway, you will see restrooms there. There is also a kiosk that sells basic sandwiches and snacks and drinks for purchase.

Please feel free at any time if you need to get up to stretch, if you need to take a break or grab a snack, feel free to do so. We want you to be as comfortable as possible for the rest of the day.

One thing that will help regarding the kiosk, any time you want to go out there, if you need to buy some coffee, you can also pre- order your lunch, if you would like to eat right here on Campus. You just let them know what you want, and that way it is ready and prepared for you by the time you get there for lunch time. It will minimize the waiting.

Last but not least, the front three tables have microphones. Just a quick note, they

are very sensitive to sound as you can imagine. If somebody at your table isn't speaking at that point, just turn it off. It is a little slide button for on and off. If you could just keep that on off, and when somebody at your table is going to speak, you can slide it on. It takes about three to five seconds to turn on. Just to give you a head's up on that.

On that note, what I would like to do before we turn it over for my FDA colleagues' presentations, if we could have our FDA introduce yourselves, please.

DR. COX: Good morning. Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

DR. NAMBIAR: Good morning. I'm Sumathi Nambiar, Director, Division of Anti- Infective Products, CDER, FDA.

DR. TOERNER: Good morning. I'm Joe Toerner. I'm the Deputy Director for Safety, Division of Anti-Infective Products, CDER, FDA.

DR. ALLENDE: Good morning. I'm Maria

Allende, Medical Officer at the Division of Anti-Infective Products, CDER, FDA.

DR. SMITH: Tom Smith, Medical Team Leader, Division of Anti-Infective Products, CDER, FDA.

DR. MULLIN: Good morning. I'm Theresa Mullin. I direct the Office of Strategic Programs, CDER, FDA.

DR. GOLDSMITH: Good morning. Jonathan Goldsmith. I'm the Acting Associate Director for the Rare Diseases program in the Office of New Drugs, FDA.

DR. BULL: Good morning. I'm Jonca Bull, Director of the Office of Minority Health in the Office of the Commissioner.

DR. HERWALDT: I'm Barbara Herwaldt from the Centers for Disease Control and Prevention, the Parasitic Diseases Branch.

MS. GIAMBONE: Thank you very much. We also have some FDA colleagues here, if you don't mind introducing yourselves.

DR. EGGERS: I'm Sara Eggers in the

Office of Strategic Programs here in CDER, FDA.

MR. THOMPSON: Graham Thompson, same office.

DR. VAIDYA: Pujita Vaidya, same office.

MS. GIAMBONE: Great. Dr. Farley? I'd like to introduce Dr. Farley for his opening remarks.

OPENING REMARKS

DR. FARLEY: Good morning and welcome everyone. I'm John Farley, Deputy Director, Office of Antimicrobial Products here at the Center for Drug Evaluation and Research, which is often called CDER here at the FDA.

This is a very important meeting today, and we are very excited to be here today to hear from patients about how they think about Chagas and what they look for in Chagas' treatments.

It looks like we have a full room today, and I understand we have representation from patients, caregivers, advocates in the audience, and also joining remotely, folks from the web. Thank you for being here and being a part of this

meeting.

I also note we have representation from industry, academia, and other government partners in the room, and I am glad to see a high level of interest from those of you who also play an important part in the drug development process.

Keep in mind through the discussions today that while FDA plays a critical role in drug development, we are just one part of that process. We protect and promote public health by evaluating the safety and effectiveness of new drugs. While we often provide advice to those who are developing drugs, we at the FDA do not develop drugs ourselves or conduct clinical trials.

Drug companies, sometimes working with researchers or patient communities, are the ones that conduct trials and submit applications for new drugs to the FDA. It is then our responsibility to review the new drug application and ensure that the benefit of the drug outweighs the risks.

The benefit/risk decision making is an

integral part of our review process, and what we hear from patients today can also help us understand how patients view benefits and risks of Chagas' treatment.

This morning is about listening to patients. We want to hear directly from you about how the disease affects your life and what you value in a potential treatment. Having this kind of dialogue is extremely valuable for us because hearing about what patients care about can help us lead the way in figuring out how to best facilitate drug development for Chagas Disease.

We think very carefully about the kinds of things we should be measuring in clinical trials and looking at when evaluating a new drug, and hearing your perspective on this is very important to us.

What we hear from you today can help us understand how to develop better endpoints to measure the aspects of this disease that are important to you.

This afternoon we are going to have an

opportunity to discuss ideas for clinical trials for new drugs for Chagas. We are very grateful that many of the world's experts have agreed to join us today. This discussion of ideas will not result in formal recommendations or a decision on a particular matter by the FDA, and this is not an advisory committee.

Voluntary disclosure by expert panel members are listed in the program materials. In addition, Dr. Ribeiro would like to disclose that she is affiliated with the Drugs for Neglected Diseases Initiative, which has a number of collaborations including licensing agreements to develop new drugs, and has consultancy agreements with Bayer HealthCare and Laboratoria ELEA.

Scientific workshops like this are informal and we encourage participation in the discussion by patients, advocates, and other audience members, in addition to the panel. Those microphones are available and will remain available throughout the day in the front of the room.

This afternoon's scientific workshop is also part of the agency's program to facilitate the development of surrogate endpoints, clinical endpoints, and other scientific methods for predicting clinical benefit. This is in accordance with Section 901 of the Food and Drug Administration Safety and Innovation Act signed into law on July 9, 2012 by President Obama. That section is entitled "Enhancement of Accelerated Patient Access to New Medical Treatments."

This afternoon we will be discussing potential surrogate endpoints, possible clinical endpoints, and their ability to predict clinical benefit.

We will have an FDA Press Officer in attendance at this meeting. Her name is Ms. Lyndsay Meyer. Lyndsay, are you here? Lyndsay, please raise your hand and identify yourself. Most of the industry press folk know Lyndsay already.

We have Spanish translations available for the morning presentation and the morning

discussion questions. Should you be in need of a Spanish presentation, please go out to the registration desk and we will make that available to you.

Maria, do you want to translate what I just said?

DR. ALLENDE: (Translating in Spanish.)

DR. FARLEY: Gracias. Thank you again for your participation and for being here today. I will now turn the podium over to Dr. Theresa Mullin, who will provide background on the FDA's Patient-Focused Drug Development Initiative. Thanks.

OVERVIEW OF FDA'S PATIENT-FOCUSED DRUG DEVELOPMENT INITIATIVE

DR. MULLIN: Thank you, John. That is exactly what I'm going to do. We have this initiative called "Patient-Focused Drug Development." We are having this meeting as one of several in different disease areas. I'll just give you a little bit of background about that.

As Dr. Farley mentioned, FDA is

responsible for conducting that benefit/risk assessment of new drugs and actually looking at drugs throughout what we call their "life cycle," when they are on the market. We continue to evaluate whether the benefits still exceed the risks.

In looking at the evidence of benefit versus risk, it is really critical that we put that in context. What we hear from all of our scientific experts and clinicians is they need to put that in the context of the disease, which is to say what is the severity of this disease, and what is the degree of unmet medical need.

We know the patient perspective is quite critical to really understanding that. The patients are the ones who are living with the disease. They are the ones that are going to gain any benefit there is to gain from the therapies that we have available, and they will experience the harms.

We realized in going into this -- actually, this program was reauthorized at the

same time as the FDA's Safety and Innovation Act that Dr. Farley mentioned in 2012, but we didn't really have a good systematic way to reach out and hear from patients.

We have some very valuable programs, the patient representative program, which allows us to talk to individual patients and bring them into discussions, typically concerning a particular drug and a particular issue, and because those issues are particular, we need to do a fair amount of screening of the patient or the representative to ensure there is no conflict of interest.

That sort of impedes our ability to get a larger sort of range of input from the patients who have the condition or the people who are living with them or taking care of them.

This initiative is meant to just get a broader input from patients by disease not in the context of a particular drug, but really in the context of the patient's experience with it.

We know this input is going to be really helpful to us in understanding the patient's

perspective, and it will be valuable to refer to subsequently when we have conversations with drug sponsors about development programs, when we look at what might be clinical outcome assessment endpoints, patient reported endpoints that would be helpful to consider, and so on.

That's the rationale for this. What we agreed to do in this reauthorized user fee program, which is a five year program that will sunset in 2017 and we will look to renew, is we will conduct at least 20 meetings, each in a different disease area, to try to do this kind of systematic collection of information. Chagas is one of the diseases we are looking at, one of the 20.

We began this process in 2012, as I mentioned. So far, we have 16 diseases. We actually will soon publish the remaining diseases for 2016 and 2017. Here are the diseases that you see tee'ed up for the first three years of the program, the ones we did in 2013, 2014, and here we are, Chagas Disease for 2015, and we have a few

more to go.

We are really looking forward to hearing what you have to tell us today. Each of these meetings is tailored a little bit. We ask consistently a set of questions about the impact of the disease on your daily life and on your life over time that you have had the disease, and what you are doing to treat it currently and how well that is working for you, as Soujanya outlined.

That is exactly the way our meeting flows. It goes through those questions in some depth. We also may ask additional questions, and we tailor each meeting. For example, in this meeting, the afternoon is going to be spent on scientific issues, further advanced development of products in this area.

With that, we have learned that the active engagement of patients and you telling us as much as you can about your experience, your perspective on this, is really helpful when we take that back and look at programs that might be coming through to treat the disease.

We produce a report at the end of these meetings. We have a docket that is open for a while in case people are unable to make it but they are able to submit information to us and to the electronic docket. We leave that open for at least 30 or 60 days following the meeting to gain any other information we can. We add information from people who may be joining us on a webcast.

We produce this report that tries to faithfully follow what we have heard in the meeting regarding what it is like to live with the disease and how well the treatments people are using are working for them.

We think those reports are both useful as a reference tool for patients, is what we have heard from patient groups that have been involved in some of these previous meetings. It is useful as a reference for our reviewers when they subsequently get applications or programs coming in for their review.

We think it will really help us prompt the development of these other measurement

endpoints to better capture patient experiences living with the disease and then with therapy going forward.

Those are the aspirations we have for this program as well. With that, I will turn it over to our next speaker, Maria Allende, who is going to talk about the disease. Thank you.

OVERVIEW OF CHAGAS DISEASE AND AVAILABLE TREATMENT

DR. ALLENDE: Good morning and thank you for being here. My name is Maria Allende. I'm an infectious disease physician and Medical Officer at the Division of Anti- Infective Products. I will talk about an overview of Chagas Disease and available treatment options.

This is my outline. I will talk about what is Chagas Disease, why is it called "Chagas Disease," who can get it, what are the symptoms, how we make the diagnosis, and what are the treatments available - Nifurtimox and Benznidazole. I will also talk about the side effects of the medications.

What is Chagas Disease? It is a disease spread by contact with feces of an infected insect called "kissing bug," "vinchuca" in Spanish or "barbeiro" in Portuguese. This is a blood sucking insect that bites humans and animals, and after it bites, it defecates, and it carries the agent of the disease in its gut, which is a parasite called Trypanosoma cruzi.

The disease can cause serious heart illness, and it also can affect swallowing and digestion. On the bottom part, you see the picture of what the parasite looks like in the blood, because it eventually enters the blood. I will go into this a little later.

The two pictures below is a close up of the bug that measures about one inch to an inch and a half. You can see it over a human hand.

There are two phases of Chagas Disease, the acute phase and the chronic phase. The acute phase lasts a few weeks or months, up to three months after infection, and the chronic phase can last years and even decades after the infection.

Both phases are usually asymptomatic, have no symptoms, and that is the most common form, or in a few cases, can be life threatening.

Spontaneous cures are extremely rare, and once the person is infected, they are infected for life usually, without treatment. Certain people are at higher risk for more serious disease, those with weakened immune systems, such as AIDS, or those receiving treatment after a kidney or organ transplant.

A bit of history here, why is it called "Chagas Disease." It is called after its discoverer, Dr. Carlos Chagas, a Brazilian physician who was studying another outbreak of another insect transmitted disease in Minas Gerais. He discovered the first human case and described it. On the bottom you can see a picture of him with Berenice, a two-year-old girl from Minas Gerais.

He made the connection with the presence of numerous insects in that area and decided to study them, and found the parasite inside the gut

of the insect, and described the cycle of the parasite. He called the parasite Trypanosoma cruzi in order of his mentor, Oswaldo Cruz, and that is why the disease is also called "American Trypanosomiasis."

He took the blood from Berenice and injected it into laboratory animals which died six days later with large amounts of Trypanosoma in their blood, therefore confirming the cause of the disease.

On the right side of the picture you can see the beautiful drawings of his first application in 1909, which are describing entirely the cycle of the parasite and the human disease symptoms, completely unprecedented for his time, that one single investigator described not only the agent, the cycle, the carrier vector, the insect, and the disease in humans.

The disease is also called "Chagas-Mazza." It is well-known in Argentina this way, in honor of the contributions of Dr. Salvador Mazza, who documented widespread cases in Northern

Argentina starting in 1926 with the discovery of this infection in dogs from which the insect was taking the blood and completing the cycle in nature with humans. Dr. Mazza died from a laboratory infection with Trypanosoma cruzi while working with patients' blood.

Who can get Chagas Disease? Most of what we know about Chagas Disease is from the endemic areas where transmission occurs, endemic to Latin America, South and Central America, especially those who live in rural areas, in these houses that you can see in the pictures made of mud and with a roof of straw.

There is a detail of the wall on the bottom, and the insect hides in these crevices on the mud wall during the day, and at night, it comes out to take the blood from humans and animals. You can see in this cartoon from a prevention poster from Brazil that usually the patient is asleep and the only exposed areas are the face and the arms, and the insect bites. It is called "barbeiro" because it bites usually in

the face, and "barbeiro" means barber. "Kissing bug" also because of that.

The person stretches and helps the parasite get into the blood. Also, with the contaminated fingers, it can inoculate the parasite directly into the eyes, nose, and mouth. Therefore, it gains access to the blood and then to the organs.

Also, the disease can be spread from mother to baby, and more than one generation, mother, child, and grandchild, and organ transplants, blood transfusions, too. These modes of transmission are very important in non-rural areas.

Less common transmissions are laboratory accidents and contaminated food and drink. This has been described in tourists going to endemic areas and drinking juices contaminated with sugar that had elements of the feces of the insect. The disease is not spread through casual person to person contact.

Chagas Disease with migration in the

last 20 years or so has spread around the world. In the darker color, you can see the endemic areas, endemic to 21 countries in Latin America, and in the softer color, you can see the infection follows the pattern of migration, to North America and Europe, including Northern Europe, Japan, and Australia.

In these countries, the disease has mainly been described as congenital cases of people, women who were infected and did not know about it, and gave birth to infected children.

What are the symptoms? Days after the contact, the acute phase, a few people can have body aches and fever, swelling of the eyelid or the bite site, like we see in the picture. This is called "Romasign," and it is produced by the site. It's not very common, but when it is found, it is very characteristic of the disease particularly in endemic areas.

The disease in the acute phase can also cause weakness and inflammation of the heart, myocarditis, and inflammation of the brain in a

few patients. As I said before, most people have no symptoms. It is a very silent disease.

Years later, about a third of them, 1 in 3, approximately, may develop the chronic phase, which is characterized by heart failure, an enlarged heart not pumping blood well, causing difficulty breathing and leg swelling, irregular heart beats that can cause sudden death, and risk of stroke. Less commonly, problems with digestion and bowel movements.

In this picture, I illustrate how the parasitic agent produces this disease. It invades the heart tissue with inflammation and infection, and it produces a weakening of the muscle and dilation of the heart, in the large heart, which doesn't pump blood very well, and also that enlargement causes a disruption of the heart beat, which gives rise to severely irregular beats called arrhythmias.

On the bottom half of this slide is the gastrointestinal disease. It produces by the same mechanism dilation of the esophagus called

achalasia, and dilation of the intestine called megacolon, with severe problems with swallowing and constipation.

The diagnosis is made by testing the blood of the patient. There are several blood tests approved by the FDA in the recent past. No single test predicts who will or will not be sick. Usually more than one test is necessary to confirm the diagnosis.

The tests are currently run at the CDC. The doctor sends the patient's blood sample to CDC through the local state health department. Currently, the blood banks and organ donor programs in the U.S. screen for Chagas Disease. Actually, some people find out that they have Chagas Disease when they are trying to donor blood.

What is the treatment? There are two kinds of treatments, anti-parasitic treatment, to kill the parasites with anti-parasitic drugs, and this is the focus of today's meeting, and also symptomatic treatment to manage the symptoms and

signs of infection, usually cardiac drugs and pacemakers.

There are no treatments currently approved by the FDA, but two drugs are available in oral tablets only exclusively through the CDC at a doctor's request. These drugs have been used in endemic countries since the 1960s and 1970s. They are called Nifurtimox and Benznidazole. The treatment consists of taking two or three daily doses by mouth for 60 days.

The CDC and the WHO recommend treatment in the acute phase, which is shortly after infection, and in the young, with or without symptoms. This includes babies infected from their mothers, children and adolescents, women who can get pregnant, patients with weakened immune systems, AIDS, treatments after kidney transplants, and patients less than 50 years of age without severe symptoms of heart disease.

These recommendations rise from the fact that the reported efficacy is higher between 60 and 90 percent reported when the treatment is

given shortly after infection occurs and especially if the patient is young, up to 18 years of age. This is where the treatment has been reported most successful.

The treatment, however, is optional in cases where there is not much certainty of success, such as patients older than 50 years of age without severe symptoms of heart disease, and it is not currently recommended in pregnant women and patients with severe kidney or liver disease because the drugs are contraindicated in these cases, and it is not currently recommended for patients with severe heart disease, although clinical studies are currently ongoing to determine the benefit of treatment in these cases.

In this slide, I have the commonly reported side effects of Nifurtimox and Benznidazole. They have similar toxicities, most commonly for Nifurtimox, loss of appetite and weight loss with nausea and vomiting which sometimes can interrupt or suspend treatment, and with Benznidazole, allergic skin rashes also are a

frequent cause of suspension or interruption.

However, with either drug, the side effects improve after stopping treatment, and in general, the younger the patient is, the better they tolerate the medications, the side effects are more common in older patients, the older they get, but babies and young children tolerate it very well.

In this slide, I want to make a summary of all the things I have just talked about. Chagas Disease is a disease that can be transmitted from mother to child, congenitally, even through more than one generation. It is also transmitted through blood transfusion and organ transplants.

It has an acute and chronic phase, and in both cases, most people do not have symptoms for many years, but they still can transmit the disease. Infections usually last for a lifetime without treatment, and about a third of all infected people get life threatening cardiac disease many years after the infection. In a

small number of people, the acute disease can also be life threatening.

There is no drug approved in the U.S., but treatment is available through a CDC program.

Here are my acknowledgements to the leadership and management of several offices in the FDA, my colleagues, and a special thanks to all the panelists.

Also, I want to express my gratitude to my first mentors at my hospital in Argentina where I first trained and first met patients with Chagas Disease, and to my patients from the past, present, and future on whose behalf we hope to one day eradicate this disease, and this is the picture of my hospital in Bueno Aires, Argentina where I first trained.

Being from Argentina, I have to thank Lionel Messi for being such a good champion for the fight against Chagas Disease.

Thank you all.

(Applause.)

OVERVIEW OF DISCUSSION FORMAT

MS. GIAMBONE: Thank you to my FDA colleagues for your remarks. What I'd like to do now is go over the discussion format. As I mentioned, we have two topics that we will be reviewing today.

Topic 1 is on the symptoms that matter most to you. Here, what we are listening for is what worries you most about your disease, and what are the symptoms that you experience, and how does it impact your daily life.

Are there activities or things that you like to do that you are not able to do as fully as you would like or not able to do at all because of the symptoms you experience. Also, tell us how your symptoms have evolved over time or how they have changed.

We recognize this was a very difficult topic to write about, but we sincerely appreciate our panelists spending the time to really walk us through how they felt and what they are feeling now, so we appreciate that very much.

We will then move on to Topic 2, which

is on the current treatment approaches to Chagas Disease. Here, what we are listening for is what are you currently doing to treat your Chagas Disease, what is your current treatment regimen, and what are the biggest downsides that you are experiencing because of these treatments. Then we will talk about what you look for in an ideal treatment.

We also have some scenarios that we will go over with you when we get to Topic 2 to hear from you and learn from you on how you make decisions regarding these treatment approaches.

First, we are going to hear from a panel of patients, caregivers, and patient representatives, and on that note, could I have my Topic 1 and Topic 2 panelists please come up and have a seat at the panel table. I have been working with our panelists over the last few months. They have been so wonderful and really putting these thoughts down on paper, sharing these stories with us, so thank you for doing that.

The purpose of our panel discussion today is to really set a good foundation for understanding what patients are thinking and what matters to them most. They will set a really good foundation for our greater discussion. They reflect a range of experiences with Chagas, which we will learn in just a bit.

Once they are done speaking, we are then going to broaden the dialogue, and we will encourage other patients on the web or patient representatives on the web and in the audience here today to contribute to this discussion, and we want you to build on what you have heard from the panels.

For those caregivers and patient representatives, physicians and experts in the audience, please also share with us if what you are hearing from the panel is representative of the patient population that you see and that you work with.

Periodically, we will ask some questions, and I will turn to my FDA panel also

for some questions. We invite you to participate in this dialogue. We ask if you could just please raise your hand. You have microphones at your table, but for others, raise your hand, and we will bring a microphone over to you or you can speak into the microphone at your table. Please state your name. That way, we can make sure we have that in our transcript as well.

I understand we also have about 40 participants joining us on the web. Thank you very much to those of you on the webcast for joining us. We can't see you, but we are truly thankful you are here and participating, and you are a very important part of our meeting.

We will check in with the web periodically to see what comments are coming in, and we will also be going to the phones occasionally, and in fact, we do have one panelist that will be joining us on the web also.

We also have another way of continuing this discussion and continuing to hear from you, and that is through the public docket. The public

docket, you can find the website right here on this slide, and it is going to be open until June 29, so two months from now.

The purpose of this public docket is to have you all continue to visit it, share your experiences, share your thoughts and perspectives, and all of these comments will be incorporated into our summary report that Theresa mentioned a few minutes ago.

Anyone is welcome to comment here. We really do encourage you to go there and visit the site often, and continue to share your thoughts there.

We also have a few other resources at FDA that we would like to share with you. The first is the FDA Office of Health and Constituent Affairs, OHCA. The second is the CDER Office of Center Director. We have the Professional Affairs and Stakeholder Engagement group.

Both of these offices and groups are here for you for additional questions. They are really patient representative programs. We

encourage you to reach out to them for additional information.

Last but not least, we do have a few ground rules that we would like to share with everyone. This meeting is really about the patients that are here, the health care providers, the caregivers, and the advocates to share your perspectives, your thoughts, and your experiences.

FDA is here to listen. We know there are also other members of academia and industry and other government agencies here, and we know this is going to be a very important meeting to all of you. We encourage you to stay in listening mode.

The discussion is going to focus on symptoms and treatments. We know there are many, many aspects of Chagas Disease that we will not be covering here today. We really want to hear from you on the symptoms and the treatments and these topic questions because it is really very beneficial for us to learn from.

Anything again outside the scope of

symptoms and treatments that we will be discussing, we encourage you to sign up for open public comment to share those thoughts.

The views expressed here today are personal opinions, and on that note, respect for one another is paramount.

Last but not least, we will have evaluation forms for you closer to the end of the meeting. They are also available on the registration desk. It is really important if you could fill these out and leave them on the desks or put them out on the registration desk after the meeting is over. We really do learn quite a bit from those evaluation forms, and it helps us to know what worked for you today and what we can improve on.

On that note, what I'd like to do is turn it over to our panelists to share your thoughts with us. We will start with Candace. If you could please introduce yourselves when it is your turn, you just have to press the red button.

PANEL #1 COMMENTS AND DISCUSSION ON TOPIC 1

MS. STARK: Good morning. My name is Candace. I'm 51 years old. I'm from Texas. I found out about a year and a half ago that I do have Chagas. I've been tested three times, and the last time was by CDC themselves. I have three children and four grandchildren. I do not live in a mud hut. I live in a brick home, nice neighborhood, and I work in the oil field industry, which is of course not the place to be right now.

On July 2, 2013, when I was 49, I took the opportunity to give blood, donate, and on August 19 I received that letter from Austin that said I had Chagas. Two days later, I had my first doctor's visit with Dr. Rodney. He did not know how to treat it. He went ahead and run all the tests, he did an Echo and some blood work on me.

Then he ended up sending me to a Dr. Lemos, an infectious disease doctor, in College Station. Again, Dr. Lemos didn't know anything about Chagas either, not how to treat it, but he did do the second blood test and it came back

confirmed. He said well, we're going to go ahead and get that medication. As soon as he let CDC know that I had it, they did their own blood work.

It took me 24 weeks from the time I had my first visit with a doctor until I started my medication. That's six months later. I do know the "kissing bug" exists in Texas because I personally have found one, not in my home, but it was already dead and I sent it to College Station, to Texas A&M, and they confirmed it was positive with the antibodies.

As a matter of fact, the Sarah Hamer Lab, Rachel Curtis, those are the two people that I have gotten most of information from on Chagas. They work with animals, not with humans, yet that's where I went and I got my information from them, and I do thank them, and I still stay up with Rachel Curtis.

On my second visit to the physician that did treat me, I asked him if I should go ahead and tell my neighbors, let them know this bug does exist. Of course, no one has ever heard of it.

He looked at me and asked me if I knew who Typhoid Mary was. I don't know if everybody knows who Typhoid Mary is. I was kind of like yeah. He said well, if you want to be Typhoid Mary, then you go ahead and tell them.

So, I have kept quiet. I live in a small town. To this day, only my closest friends and my family know that I have Chagas. To me, he made me feel embarrassed and ashamed, like I had done something nasty and dirty to have gotten this.

I did end up taking Benznidazole for 63 days. I zoomed right through it. The hardest thing about taking that was I couldn't have drinks with my girlfriends in the evening, and I was drinking iced tea and they were drinking Long Island Ice Tea.

(Laughter.)

MS. STARK: As far as my symptoms go, I don't know if the symptoms I have have anything to do with Chagas. I have a lot of anxiety. If my chest is hurting me, is it because I have some

little critter crawling around in me? I don't know. I think a lot of that is anxiety.

I don't sleep well at all. I'm tired. I do go to bed early before it is even night outside. I go to bed before the party starts. I wake up five and six times a night and then go right back to sleep.

I believe that I got Chagas through an open wound in my leg. It took months and months to heal. It happened in May. In July, it actually looked like a large ringworm around this area. In August is when I found out I actually had Chagas, and I just immediately knew that is where it was. I don't know.

I guess really that's about it for me.

MS. GIAMBONE: Thank you so much, Candace. Thank you. Maira?

MS. GUTIERREZ: Good morning, everyone. My name is Maira Gutierrez. I am from El Salvador. I was diagnosed with Chagas in 1997 after donating blood to the Red Cross. From the point that I donated blood, it took a few weeks

for me to get a letter from the Red Cross.

In 1997, there wasn't a lot about Chagas, so I got a very vague letter stating that they couldn't use my blood, call 1-800 number, which kind of freaked me out. I did and I got an answering machine, left a message.

She called me back at work and asked if I was by myself, and so of course, at that time I'm thinking I have AIDS and I'm only 19/20, not even married. Why else would she be asking me if I'm by myself.

She said if I'm not by myself, to go to a room where I was, so I proceeded to go to an office. That's when she told me I had Chagas. I had no idea what Chagas was. She couldn't answer that question because she had no idea. She said I was going to get a booklet in the mail, and it was going to give me an idea, kind of an overview of what it was.

I received that booklet, and it was basically an one page booklet, this is how you get it, this is what it is, this is what the homes

look like. When I saw the picture of the homes, I said that's exactly where I lived when I was a child, I was born and raised in El Salvador, and migrated to the United States in 1981.

I knew that's where I got it from. Did I remember getting bit? No. Did I get any of the signs? Nope. From that point, I did the obvious thing that everyone else would do, I made an appointment, went to my primary care physician. When I told her, her words to me were the only time I've heard of that disease was during medicine school.

She didn't know what to do with me. She didn't know where to send me. Just didn't have a clue. What she did was she sent me to a CDC specialist, which I traveled back and forth, and it took me about 30/40 minutes. I thought I was in good hands with the CDC specialist. Well, I wasn't. The CDC specialist didn't know what to do with me in 1997.

The first question was well, can you swallow. Yeah, I can swallow. Well, then there's

nothing wrong with you. I said but I've heard there is treatment. No, I'm part of this and that of the CDC, if there was treatment, I would know about it. I will let you know.

They proceeded to go through the same thing of retesting me, but sent me back to my primary physician, and the lab didn't know what kind of testing to do. I waited about an hour so they could figure out how to test me to get confirmed that I had Chagas again.

I went back to the CDC specialist once it was confirmed, and he just basically went back to point one, well, can you swallow. I can swallow. I think I did that for six months, then I got tired. I was calling him every week and his nurse. I just didn't want to deal with it any more so I stopped.

I went from 1997 to 2008, where my sister frantically called me one night and said turn on the t.v., turn on the news report on Channel 11. This was back in California. I did. By then, the report had ended, but she was able to

take the information for the Chagas Clinic in Sylmar with Dr. Meymandi.

I called the next day, and within a week, I had met up with her. I had most of my questions answered. I was on my way to get my first treatment. I was still confused. I didn't know how I got it, how, why, what's going to happen.

Luckily, she talked to me, my husband, answered most of my questions. I still have questions, but am I ever going to get an answer? I don't know. It feels like it's so new no one knows a lot about it.

It took 11 years for me to find someone to treat me. I took Nifurtimox. I lost 25 pounds. As a woman, what woman doesn't want to lose weight. I didn't mind. My mother-in-law wanted to take the treatment. She didn't even have Chagas.

(Laughter.)

MS. GUTIERREZ: They were like well, can you just ask your doctor if I can get some.

That's the only side effect. I started the treatment with other patients. Some of them had to be taken away from the treatment. I was very blessed. I've been very blessed to have my doctor, because she has taken me through all the steps of everything. Without her, I don't know where I would be.

Since then, every year I get monitored. We have the only Chagas Clinic in the United States, and I live 10-15 minutes away from it. How lucky am I. Every year, I get monitored. I get the Echo, the CDC, and we started with the heart MRIs.

I feel very blessed. One thing that I learned from this conference is it is the first time that I get to meet other patients. I have always been the only one. I was telling Candace, I was so excited, not that you have the disease, but just to meet someone else that has the disease that I can relate to.

To go back and forth of what to do, questions, I was really happy this morning. I met

another patient, too, that I was excited to meet.

It's been a roller coaster ride. You have your emotions. You don't know what to do, what to expect. A lot of it is unsettling. You don't know. You can go to your doctor. I just actually did, actually, for my physical.

I was telling Candace. I told the doctor, well, I have Chagas. It's 2015. He said Chagas? He said I've never had a patient with Chagas. He wrote it on my comments, I guess I'm anemic, and he said I think it's due to your Chagas. Okay, I don't think it's my Chagas, but if that's what you are going to blame it on.

I was sent to another specialist to get some other testing done last week. That specialist said the same thing. He was more intrigued and asked me all these questions, which I didn't mind, because same thing, he was a gastroenterologist. He's never had a Chagas patient, so he was writing every single thing, question he had, which I didn't mind.

If I could be your guinea pig for you to

learn, by all means, I don't mind at all, go ahead, ask away. If it can help us get better treatment, bring out awareness, why not. It was frustrating for me 11 years.

My daughter was born at seven months. Was it related to Chagas? I don't know. No one can answer the question. I was in the hospital for seven days after I delivered my son because I lost so much blood. My question is is it Chagas related? I don't know. No one knew.

Little things like that makes you wonder is it related to this, is it related to that. It is just the not knowing.

I like to speak because I like to bring awareness. As patients, my doctor can only do so much for me, but if I can speak, it will do much more for ourselves. We have to bring it out.

MS. GIAMBONE: Thank you, Maira. You bring up some really great points that we will definitely be discussing in Topic 2 as well with your treatment regimen and the side effects. Thank you very much, Maira.

Rachel?

DR. MARCUS: Good morning. My name is Rachel Marcus, and I'm here with two hats today. The first is that I'm a clinical cardiologist practicing in Washington, D.C., and through my work, I've had the opportunity to meet a few patients with advanced cardiac illness from Chagas Disease, and I'm hoping to facilitate their discussion with you today.

The other half that I have is being the Medical Director of a non-profit in the Washington, D.C. area called LASOCHA, which is the Latin American Society for Chagas Disease. We are a patient advocacy organization, and I am the Medical Director of this program, and we are screening and treating Latin American immigrants in the D.C. area. I see my President of the organization, Jenny Sanchez, who is in the back of the room.

I wanted to talk a little bit about the work we are doing with LASOCHA, and then turn back to the patient voices, because they are so much

more interesting than what I have to say.

The start of our organization was when Jenny, who came from Bolivia to the United States many years ago, went to the obstetrician when she was pregnant with her first child and asked for a Chagas test. The obstetrician looked confused and said I don't know what that is. Then Jenny went back for her second visit with the obstetrician and said I really would like my Chagas test. The obstetrician said, well, I looked that up, and we don't have that here, that's only in South America so you don't have need it.

It just exemplifies what the two previous panelists have said, which is there is a huge lack of awareness about Chagas Disease in the United States, and for many people, the one and only time they will hear about it in their medical training is in medical school, and then they promptly forget about it.

Well, Jenny realized that there is a huge group of Latin American immigrants in the D.C. area, including somewhere between 70,000 and

200,000 immigrants from Bolivia, which as everyone here knows is a country that is extremely stricken by this illness.

She had the idea to try to come up with a patient advocacy organization, and I was interested in doing clinical work with patients, so we joined forces about two years ago.

I am really honored to be included up here as a care provider, particularly when Sheba Meymandi is in the audience, who has far more clinical experience than I do, and I hope she will have a chance to share her experiences with the clinical care as well.

Some of the frustrations that we have encountered and our patients have encountered are that generally they are poor, they are uninsured, they are Spanish speakers, and frequently they are undocumented. Their access to care to begin with is extremely fraught.

Then they are faced with a medical community that really doesn't know very much about Chagas Disease, and even if they are extremely

well intentioned and want to try to help, when they hear about the fact that the medications are not commercially available, that you have to actually go through the process of signing a consent form to be able to get the medicine, that the medication requires extremely careful follow up, that there are certain costs.

Although the medication is free because it is administered through an IRB, there are costs associated with the follow up care, and unfortunately, small but real risk of very serious side effects that even wonderful free clinics in the Northern Virginia area have chosen not to embark on screening and treatment programs because they feel the issues are so cumbersome.

We see this as well. It's very difficult to take care of patients who have to travel two hours for their treatment and may or may not be able to have immediate access to follow up if they have a side effect, which as everyone knows is really very common with these medications.

We have been trying to do some screening and treatment. It's been successful thus far, although as everyone knows in the room, there are high risks of side effects, and about 85 percent of people will be able to finish their therapy, but it's a little bit scary to do that, and with this particular community, knowing there is a risk of causing them a life threatening complication that they would be in no position to pay for the medical care that follows.

That's what I wanted to say about our program. I'd like to introduce Carlos Toba Beza, and ask him to share his experiences. He currently has a left ventricular assist device to treat him for his Class IV congestive heart failure as a result of Chagas Disease.

MS. GIAMBONE: Thank you, Rachel. Carlos?

MR. BEZA: (Interpreted.) My name is Carlos Toba Beza. I'm here because it is a privilege to be here to speak with all of you to talk about Chagas. I'm also from El Salvador. In

my country, there is a lot of Chagas. During the night, when it gets dark, the insect comes and it bites. I have suffered from this for a long period of time, but I didn't know. In my country, they didn't know that we had this disease.

I began with various symptoms. I didn't have an appetite, being dizzy. I came here in 2011 to this country. I had vomiting, I was dizzy. I didn't go to the doctor because I didn't have insurance. I went back to El Salvador. I got worse while I was there.

In 2011, I went to the doctor, even though I didn't have insurance. I went to Boston. It was there they detected and diagnosed that I had Chagas Disease. I didn't know anything about this disease.

I worked in a health unit in my country for six years. They talked about some of the insects that were there, but they didn't talk about Chagas. We didn't know anything about this disease, and I didn't know I had it.

I worked there, talking about it, but I

didn't know that I had it at the same time I was working. The doctors in Boston said I had Chagas Disease. I don't know exactly how to explain it, I just felt how was it that I was talking about it, bringing awareness to it, and I had it without knowing.

It is very difficult when you have this disease. It's difficult because you have vomiting and you have a lot of different symptoms, so now I'm on a waiting list from Boston. They sent me here to Maryland. I am on a waiting list here in Washington.

If we can help others, it is good to help others, and if we can explain to some of you about the symptoms, if you ask about the symptoms, we are here and we are prepared to help you, whatever we can do to help. Thank you.

MS. GIAMBONE: Thank you so much, Carlos. Thank you. Do we have Maria joining us on the phone?

MR. THOMPSON: She has not called in yet.

DR. MEYMANDI: (Off microphone.)

MS. GIAMBONE: Rachel, if you don't mind, could you just repeat the question so everyone on the web heard it and maybe those sitting in the back of the room?

DR. MARCUS: Thank you, Sheba, for asking that question.

Maybe Mr. Beza can also share with us the symptoms that he was having at the time he had to have this placed. Mr. Beza had very, very severe congestive heart failure and was in the hospital for five months.

The symptoms were refractory to the typical medications that are administered for heart failure therapy, so he had a pump placed into his left ventricle, which basically does the work of the left ventricle for him, and he wears it on a bag on his chest.

He has to change the battery every 2.5 hours. The machine will beep, but he tries to do it before then. He plugs the machine in at night and sleeps attached to the machine. This is a

temporizing measure while he is on the heart transplant list.

There are certain medications that you need to take when you are on this machine. You have to take a blood thinner. He also takes the other medications for heart failure. There is a risk of blood clotting and infection and device failure.

He's done extremely well with this thus far, although I can tell you that he and I walked here, a long walk from the parking lot, and he was making me walk faster than I usually do. It's been a wonderful change for him.

Mr. Beza, can you tell us what your symptoms were like when you were in the hospital, how poorly you felt?

MR. BEZA: (Interpreted.) The symptoms, I had headaches, vomiting, like I had been doing before. Antidepressant. You don't want to talk to anybody and you are just so sad.

I was five months in the hospital, and they were always observing me, and after they gave

me this apparatus, my situation changed. Before that, I couldn't eat because everything I was eating I was vomiting up.

My situation changed. It got better. Before that I couldn't eat because everything that I was eating, I was vomiting up, and I wasn't able to keep anything in, my weight was up and down. With this apparatus, I feel so much better.

I feel better because even though I have to be permanently connected to this battery, I always have in mind when is the battery going to run out so I make sure I change it on time. It only lasts three hours, then you have to change it. During the night, does it stay connected, so I can be connected to it at night. You have to sleep connected to the electricity, and you still have to change it every three hours if you aren't connected.

I still feel so much better, better than I was before. It's so much better. My situation has changed. Even though you have to keep in mind what time it is and you can't let the battery run

out, there is an alarm that will go off, so you have to change it before the alarm goes off.

MS. GIAMBONE: Thank you, Carlos.

Once again, as I mentioned before, we will definitely be spending quite some time on the treatments and certainly the downsides that you experience with those treatments.

First, could we please give our panelists a round of applause for coming here?

(Applause.)

MS. GIAMBONE: Thank you all for being here and sharing these stories with us, especially after telling us it's been hard to talk about this and find others to relate to. I am really glad and we are all very thankful that you are here to share these stories.

What I'd like to do is I am just going to make a call out to my FDA colleagues, and when we do have our final panelist join us, please just let me know and we will definitely go to her.

With the physicians and the scientific experts and those of you joining us, can I just

see maybe by a show of hands how many of you feel what our patients described here is representative of what you also hear in your patient population?

(Show of hands.)

MS. GIAMBONE: What I'd like to do now is just spend a little bit more time learning about the symptoms that you have all mentioned. We heard dizziness, vomiting, anxiety. Talk about what worries you most about your condition and how have these symptoms changed.

Would one of you like to start us off by walking us through have your symptoms changed at all, do you have a good day versus a bad day, does your symptoms ever change based on the day? Carlos, Maira, Candace?

MS. STARK: What worries me the most about my condition is not knowing. I don't know what to expect. If I do have some type of a symptom, are the doctors just going to say well, that's anxiety, it's not your heart, it's heartburn. Nobody that I know in Texas knows anything about Chagas, none of the doctors.

Symptoms, what I've read about Chagas and in talking about symptoms, I've read many times about sleeplessness. I do have that. I am tired. I do go to sleep very easily. I fell asleep a couple of weeks ago in my office with my manager sitting right there. Thank goodness she was in a good mood.

I would say insomnia. I really don't have any of the symptoms that you guys would be looking for at this time. Activities, I do not do a lot of activities. I don't go out and swing a baseball bat or anything like that because I know I don't have the energy. I don't go on trips down the park with the grandkids because I'm scared I'm going to get halfway there and have to turn around and come back.

My symptoms coming and going, I would say no, they don't just come and go. I think they are there. I have anxiety from this, and I have sleeplessness that I think is caused from it also.

MS. GIAMBONE: Thank you, Candace. Just a quick follow up, with the insomnia that you

talked about, is it something where you feel as though you have to nap on a daily basis?

MS. STARK: Do I need a nap? I wake up in the mornings. I'm a morning person. I'm the one that's going to get up and clean the house in the mornings, on the weekends, but by 11:00, if the house is not clean, it's not going to get cleaned the rest of the day. At that time, I'm getting tired, and I can lay down and go to sleep.

By the time I come home from work, I do sit most of the time at work, but by the time I make it home and it's 4:30/5:00, I could just doze right off in the chair. I am in my bed, no kidding, by 6:30 at night. I lay there and watch t.v. for about an hour or so, and I doze off. I may wake up an hour later, but I can't keep my eyes open.

MS. GIAMBONE: Thank you, Candace. Maira? Carlos? Rachel? Do you have insomnia, and how does that impact your life?

DR. MARCUS: Is it all right if I add something?

MS. GIAMBONE: Yes; absolutely.

DR. MARCUS: I think we as providers see some distinct group of patients with Chagas Disease. There is a group of people in the early chronic phase where they don't have any signs of cardiac damage yet but know they have the parasite.

In the patient population that Jenny and I are working with, many of these people are from Bolivia where their worse symptom is profound fear because almost all of the people we identify as having Chagas have loved ones who have died from it. They are faced with this doom diagnosis. It's quite overwhelming, and then they have to try to navigate a system that is not very hospitable to them in order to try to get the care they need.

Then there is a separate group of people who started to have the heart issues that come along with Chagas, including the kinds of symptoms that Mr. Beza was describing, passing out from slow heart rhythms, passing out from fast heart rhythms, needing to get defibrillators that will

give them shocks, which are extremely painful, congestive heart failure with swelling of the legs and shortness of breath that can require hospitalization and ultimately the need for advanced therapies like he has or for heart failure.

Those are the sorts of things that we see. As Dr. Allende mentioned, a lot of patients with Chagas Disease are going to be in the early phase where they don't really have symptoms from the illness itself except for a profound worry about what is going to happen to them because as of right now, we do not know who is going to go on and develop the more worrisome and severe symptoms of heart disease.

MS. GIAMBONE: Thank you, Rachel. FDA panel, did you have any questions? Yes, Dr. Cox?

DR. COX: Hi. Dr. Marcus, you mentioned some work with a patient advocacy group. I was wondering if you could mention that. I'm hearing a lot about the difficulty of obtaining health information and connecting. If you could tell us

the name of the patient advocacy group or resources, that might be helpful.

DR. MARCUS: I'd love to. It is called LASOCHA. L-A-S-O-C-H-A. We have a website that is under construction but it is Lasocha.org, and a Facebook site. We welcome any requests for information and are trying to help get people connected with the medical care they need.

DR. COX: I'm curious, for patients that do come to you, obviously you have a lot of experience, a lot of information you can share with folks, are there other health resources that you recommend to folks where they may be able to get information about Chagas Disease?

DR. MARCUS: I think the CDC has a very comprehensive website, that can be very helpful. PAHA, also, particularly because it is in Spanish, the Pan American Health Association, the World Health Organization. Not everybody I work with has access to the Internet, so it can be more problematic. We are developing printed material.

Our non-profit just received final IRS

approval to start receiving donations, so we are now in a position to come up with more printed material.

DR. COX: Congratulations.

DR. MARCUS: Thank you.

MS. GIAMBONE: Thank you, Rachel. Theresa?

DR. MULLIN: This is partly in listening to the patients, what they are saying. It sounds like you learned about it through blood tests associated with trying to donate blood. It might have been the Red Cross or some other blood bank.

I wondered, from my CDC colleague or maybe Rachel would know, is it now required that a blood donation center that does that test report it? Are we able to collect information about the incidence?

For example, Candace was saying she doesn't know who else. You are probably not the only one in Texas. Are those data being collected now to know better how many cases or they are at least being picked up that say, even though that

is just not going to be everybody.

DR. MARCUS: I think that is a great question. The American Association for Blood Banks, which I believe oversees around 70 percent of the blood banks in the United States, has recently published some of their data from their screening, and as of right now, their blood banks, I believe, screen any first time donor, regardless of country of origin, which is why you were picked up. There had previously been attempts to look to see whether or not someone came from an endemic region.

It's not ubiquitous, like in many countries in Central and South America where all blood donors are screened for the illness.

DR. MEYMANDI: It's not a reportable condition, so if someone is diagnosed as having Chagas, it's not reported to the state, for example.

I'm Sheba Meymandi. I'm a cardiologist, and I work in Los Angeles, and I have the Center of Excellence in Los Angeles. We have been up now

for eight years, and Maira is mine.

Chagas Disease is not a reportable condition. As such, people are diagnosed, they are notified, and that's the end of it. In Los Angeles, when they get diagnosed, currently, they will get our Center's address and phone number to make contact. They can choose to do so or they can choose not to do so.

Often times, people have insurance and they go to their primary care provider and they start that whole going from primary care to infectious disease specialists, then back and forth. I get a lot of calls, and predominately it is from patients themselves who have Internet access, who are savvy enough to go on line and do a search.

I just have one comment that I really think is important. This is fabulous that we are doing this. It's fabulous that we are getting patients to speak and tell us about their experience.

We do not want to wait for symptoms.

This past month alone, I have three patients who like Mr. Beza got transferred to the Cardiac Care Unit at UCLA, and a few are on LVADs, not well enough to leave the hospital because they need suppressor support, additional medications.

I have another patient who has had so many ablations, they have these terrible arrhythmias, ventricular arrhythmias, where we have to go into the heart. There are only a handful of centers in the U.S. that does this. They essentially go in and make cuts to try to burn and cut pathways to stop the arrhythmias.

To have a global impact on Chagas Disease, we need a focus on diagnosing, appropriate screening, and treatment with the current meds we have available. We cannot wait for the Mr. Bezas of the world. We should not. It is outrageous.

You have a cardiologist who is out there doing screening, because I don't want to see the Mr. Bezas in the world, when we can prevent it. I just need everyone to hear that. Again, even

looking at Mr. Beza, he looks rather well, and you don't really see and feel the impact of the disease.

I am sure Dr. Marcus would concur, it's pretty horrific, and if you can treat and cure or at least prevent progression of the disease or slow the progression of the disease, this is what we need to be doing.

MS. GIAMBONE: Thank you, Dr. Meymandi. Jonca?

DR. BULL: I was just wondering from the patients' perspective about the ease by which you have access to medicine from CDC, is that a fairly accessible process or is that a pretty high hurdle?

MS. STARK: As I had said, I understood what she was just saying, but she's talking about with the medicines we have. The fact is the medicine that we have, two different kinds, you don't just walk into CVS and get it. We need to make it to where you can get that medication now.

As a matter of fact, just because no one

knows anything about Chagas, I'm the Internet girl here, and I don't believe everything the Internet says, but I do believe it says the medication that I took should be taken within the first couple of months, first eight weeks or so. I got it 24 weeks later.

Had I just gotten it, I don't know that it is going to make me live any longer, if I happen to be that 30 or 40 percent that it actually does attack.

We need to make sure that we get the medication here. We don't have to go to Argentina or wherever, on the other side of the country there. That's why I'm here. Let's get the medicine here.

DR. MARCUS: If I could answer that as well. I've had an extremely easy time getting the medicine from the CDC, very prompt. The problem in my practice is then going through the consent form, and the way I work with the patients, I make sure I have plenty of time to read the entire consent form to them in Spanish, make sure they

have time to ask questions. That is an exceedingly difficult proposition for anyone in a typical medical practice for whom the 20 minutes of going through that form is quite onerous.

The other thing is for me it was very easy to sign onto the CDC IRB, but if you are associated with an academic institution, it can often be quite difficult because the institution may want you to have a separate IRB.

I think it would be phenomenally easier to deal with this if it was something we could just write a prescription for.

MS. GIAMBONE: Thank you, Rachel. Thank you, Jonca, for your question. Do we have any comments coming in on the web?

MR. THOMPSON: Just one comment on the web from Cecilia from Argentina, who said her father was treated for Chagas between the age of 18 and 78, but for a large part of that, it was misdiagnosed as congenital cardiomyopathy. She said he suffered a stroke, myocardial infarctions and dysrhythmia until he was prescribed with a

pacemaker later on.

MS. GIAMBONE: Thank you, Graham. That brings up a good point. We have heard the difficulty in finding a physician that was able to treat you and diagnose you correctly. This question goes out to you and health care providers in the audience.

Do you find that misdiagnosis is a common theme initially or is it you are not able to find somebody that can diagnose you with Chagas? Is misdiagnosis common?

DR. MEYMANDI: My experience has been it's not a misdiagnosis because no one even thinks of it really for it to be a diagnosis. Often times, for the majority, a lot of the blood donors who find out they have it, then where do they go to get help.

Most often, it is patients going in with oh, I have Chagas, look, I have the letter from the Red Cross, what do I do, and then there is a lack of provider awareness in terms of what has to be done. The majority actually are told oh, don't

worry about that, you don't need treatment.

We have rolled out our screening to the primary care setting where I really strongly feel this needs to be. If you're a Latin American immigrant, you get tested.

With my own providers, I am having challenges because they are telling me, well, you don't need to treat, so now I'm doing this whole education going to the different clinics and discussing it.

In terms of misdiagnosis, I don't think the diagnosis is made. It's not like it is misdiagnosed and they are calling it something else.

MS. GIAMBONE: Thank you, Dr. Meymandi. Any follow up questions? Sumanthi?

DR. NAMBIAR: A couple of questions for you, Dr. Marcus. There are a few of your patients who really are not willing to sign onto the informed consent process and get on any of these medications, so what kind of follow up do you have for them? Is it primarily monitoring them

clinically? Do you also do any kind of testing?

DR. MARCUS: I might have misspoke. The patients that I see are generally extremely incented to get therapy. Most of them are Bolivian, and since they have seen their loved ones die from this illness, Chagas is a very, very serious medical problem in Bolivia, they all want the therapy.

Once they receive the therapy, then there is the ongoing need for follow up to make sure they aren't developing cardiac illness. Most of the patients I've treated through the non-profit are people with the illness who don't at present have significant cardiac damage.

DR. NAMBIAR: Just one other point. Women of child-bearing age, is it routine to screen them for Chagas if they come from endemic areas or have these high risk factors?

DR. MARCUS: Like Dr. Meymandi was saying, nobody thinks of it. There is actually data that I think the American College of Gynecology put out, specifically documented, how

little knowledge there is about both Chagas Disease in the obstetric community and the fact that Chagas Disease can be transmitted congenitally. I don't remember the precise numbers, but it is shockingly high numbers of people who are unaware of it.

There are people like Jenny who came and asked for the test, but by and large, the practitioners in the United States are not going to think of this illness and look for it.

DR. MEYMANDI: If I could just add to what Rachel was saying, in other countries, the one screening that is done, it's not done in the primary care settings, but the people they do screen are the pregnant women. Places like Spain, I think Argentina, they screen pregnant women. That is something we should be doing here also.

SPEAKER: Bolivia as well.

MS. GIAMBONE: Thank you, Dr. Meymandi.

DR. SOSA-ESTANI: Hello. I'm Sergio Sosa-Estani from Argentina. I would like to ask about a very important concept, about the

psychological impact in the patient, and also for the relatives and friends of the patient. I think at this moment there is an opportunity to change the historic situation regarding care of patients.

In our countries, we are feeling at this moment as doctors that we have the opportunity to offer -- we will discuss this afternoon the benefits and how we can demonstrate that benefit, but I would like to add this specific benefit, the psychological benefit to the patient and relatives, if you can offer treatment.

Doctors currently are feeling that we can change the natural history of Chagas Disease, and this is very important regarding the past 10 years ago, the providers are just an inspector of the natural history. At this moment, we can change this history.

MS. GIAMBONE: Thank you very much. The psychological impacts. We also heard social impacts. Candace, you talked about the emotional impacts. Thank you for bringing that up.

At this point, let's take a short break,

and we will come back and dive much digger into the treatments and how you are experiencing them, and hear more from the health care providers also.

Thank you very much. We will take a 10 minute break.

(Recess.)

MS. GIAMBONE: Okay, so we'll go ahead and get started again. If I can have our panelists come back up and have a seat. Jeanette is here providing Spanish interpretation services. For anybody in the audience, if you do require Spanish interpretation, please feel free to come on up and have a seat next to Jeanette and she can help with that.

Also, a call out to those of you on the web, if you need Spanish interpretation or translation services, please type your comment in there, and we will be able to have that translated here.

MS. HIGGINS: (Speaking in Spanish.)

MS. GIAMBONE: Thank you, Jeanette. Also, a call out to those of you on the web that

we will be taking phone calls during this topic. If you had something that you wanted to say during Topic 1 and you didn't get a chance to, please dial in, we will check in with you in just a few moments.

MS. HIGGINS: (Speaking in Spanish.)

MS. GIAMBONE: Thank you. Let's get started with Topic 2. We had a very good discussion with Topic 1. You really have shared so much with us, as Rachel said, the primary symptom being the fear and anxiety, but also some of the other symptoms that you mentioned that you are living with. We thank you for that. Also, thank you to the health care providers in the audience for sharing your perspectives also.

PANEL #2 COMMENTS AND DISCUSSION ON TOPIC 2

MS. GIAMBONE: Now, we'd like to start with Topic 2, which is again a much deeper dive into patient perspectives on your treatment approaches for treating Chagas Disease. Once again, what we are listening for is what are you currently doing to treat your condition, remind us

of your treatment regimen, and if that regimen has at all changed for you at all, what do you feel are the biggest downsides for your treatment regimen, how do you experience them, and what things are you looking for in an ideal treatment for Chagas.

We also encourage you to tell us what worries you the most about this particular treatment that you are taking, is there anything that worries you for the future with the treatment you are on.

With that, I'd like to turn it over to Candace for your comments.

MS. STARK: All right. What am I currently doing? Nothing right now. I did have to ask my physician, my family physician, two weeks ago, to have an Echo done, and to have some blood work done because he doesn't know what to do.

As a matter of fact, I had to get something to make me happy just to get on the airplane. When I went to see him, he told me to

be sure and bring back as much information as I can to provide to him.

If I have Chagas, I know there is more than just myself in my little small town. As I said before, I did find the bug there and it was tested and it is positive. There is going to be a lot more cases. We are going to need the medication very, very soon.

I currently do not experience any symptoms as he does. When I was taking my medication, I was having to travel an hour and a half every two weeks to go and get my medication, because CDC would not allow him to give me 60 days worth of medication. I had to go every Wednesday, have blood work done, home Thursday. Once they seen it was good, on Friday, I would run down another hour and a half to College Station and get my medication for two more weeks. I did well on my medication.

The ideal treatment, I wish there was an ideal treatment. Right now, all you have is two medications that I know of that are in another

country. Ideally, the treatment would be that it was local, and you don't have to go through CDC to get it. I guess that's it.

MS. GIAMBONE: Candace, is there something that worries you about the future with the medication that you have taken or do you foresee your treatment regimen having to take any other medications, and how does that worry you?

MS. STARK: I have not taken any other medications at this time because we don't know what to look for, first of all. I'm going to run back home and I'm going to tell the doctor now, thanks to my neighbor here, and I'm so glad we have met, that I should be seeing a physician at least once a year just to watch for something.

My mother had heart problems. She passed away nine months ago. I did have her tested. She did not have Chagas. She did not pass away from that. I had my dog, which is at my cost, tested. She passed. I also had my son and four year old granddaughter tested because they live with me, and they also do not have it.

Should I get them tested again next year? I don't know.

I can tell you this, I've had several people tell me, and these are the very few people that know I have Chagas, well, I think I'm going to go and give blood, just so I can find out if I have Chagas. That's not good. In Texas, not all that blood is being tested.

If my neighbor over here has it and they happen to be maybe 30 percent that is not tested, then they give it to your husband, wife, or child, we do need to start screening. It is something that needs to be screened. I really feel that way, or you are going to have a lot of people who are just going to run out and start donating blood. We need to get the medication here.

MS. GIAMBONE: Thank you, Candace. Maira?

MS. GUTIERREZ: Hello again. For my treatments, like I said before, I've been really lucky. I've never had any physical symptoms. Three years ago, we started doing - - Dr. Meymandi

started doing a heart MRI. The first one was perfect. The second one two years ago, I got that phone call that I could have a heart attack at any given moment.

Last year it was communicated to my doctor that my first treatment is being considered a fail by the CDC. CDC said -- this was with Nifurtimox. CDC said I need a second treatment with Benznidazole.

I'm all for it. I've been blessed not to have the physical symptoms of it. I do on the other hand have everything that you can't see, which worries me more, because those are usually the bad ones. It's been a year and a half that I have been waiting for Benznidazole because according to the CDC, we have a shortage on that medication, which I found out in November at the conference we did in New Orleans.

I went on line actually and I looked to see what it would cost me to buy Benznidazole myself. It is $225 a jar, and I need about three or four of those.

It is frustrating because I don't have any physical symptoms, which I find myself fortunate that I can tell you about, but I'm worried about everything I can't see. I think by the time we get to a symptom, it's probably too late, if something has already happened that I have to go see a doctor for. By then, you have to treat what is already wrong or keep taking medication to solve that problem.

To me, the ideal treatment will be something that is not so toxic. The medications have been here for so long, but no one is taking anything to try to bring out new medications. I read the side effects of Benznidazole, but they are not any different than the Nifurtimox. They kill the bad, but they also kill the good. Unfortunately, that's the only options we have. We don't have any other options.

One of the reasons why I also got involved is I was really, really lucky that my kids were negative, but if my kids were positive, at that time, I would have to give them an adult

dose, hope not to overdose them with the way the medication was cut.

I believe now we do have a pediatric medication. If we treat the young ones first, I don't think we will get to this level. I'm really hoping overall we start with the little ones, and hopefully overall better medication.

MS. GIAMBONE: Thank you, Maira. Maira, you just mentioned that you experienced some side effects with the medicine you took. You said it took care of the bad but then it also hurt the good. What were some of the side effects you experienced?

MS. GUTIERREZ: Like I said, I was really lucky. I had one side effect, I lost about 25 pounds in two months, but I was really happy that I lost 25 pounds.

(Laughter.)

MS. GUTIERREZ: But then I gained them right back.

MS. GIAMBONE: Maira, one more question for you. You mentioned in your statements that

you put together that you are now undergoing additional procedures because they found some tracks in your heart. Can you share with the audience some of the procedures you are going through now?

MS. GUTIERREZ: Sure. With the addition of adding my heart MRI on an annual basis now, which is a constant battle with my insurance, because my primary physician does not understand why is it you need that, because he doesn't know where to send me, so I have to go to Dr. Meymandi, then they have to request it. My insurance is why do you need that, it's not your primary physician who is requesting it.

In finding the tracks with the heart MRIs, I had to do -- help me, Dr. Meymandi, the procedure to see --

DR. MEYMANDI: You had intracardiac electrophysiology.

MS. GUTIERREZ: EP?

DR. MEYMANDI: EPS.

MS. GUTIERREZ: EPS. I had my first one

done in 2013, and I just had another heart MRI. We are waiting on that, and we will see how that goes. I also listened to her and went to see the gastroenterologist. I get back late tomorrow. I am due at the doctor's office at 10:00 on Thursday for stomach x- rays, to start with that.

If I don't do it myself, no one is there to push.

MS. GIAMBORN: Thank you, Maira. Rachel, did you have any comments? Or we can go to Carlos.

DR. MARCUS: I think Carlos has more interesting things to say.

MS. GIAMBORN: Carlos?

MR. BEZA: (Interpreted.) I wanted to tell you that I've had this apparatus for three years. I have to be under treatment with medication. Every two weeks, they are checking my blood work, so I go to the hospital so they can draw blood, to see if there are any changes in the blood. I'm taking blood thinners and other types of medications. I have to go and be followed

every two weeks. I have to see one doctor every month.

I wanted to let you know that I have felt okay, I've felt good with this treatment they are doing, but you have to make sure you are always taking your medication so that your blood is not getting too thick.

You have to take the medication because if you don't, at night time, you might have some bleeding. You have to be on top of your medication. Thank you.

MS. GIAMBONE: Rachel?

DR. MARCUS: I think it's more interesting to hear directly from the patients, but I can speak for the providers, and I hope Sheba will chime in or all the people who have come from South America where treatment of Chagas is really something they know very much about.

There are some nice studies that show that about 85 percent of adults who begin a treatment regimen with Benznidazole will be able to finish therapy, but that means 15 percent of

them won't, and to me, that is an unacceptably high number of people who are not able to tolerate it.

The side effects that seem to be pretty common are headache, weight loss, and rash. The rash is the scariest one because in a very small number of people, it can progress to a very life threatening complication called Stevens-Johnson Syndrome, which if the patient doesn't die, it is often because they received treatment in an intensive care unit. The risk is very low, and it can be caught in time if there is very, very frequent patient follow up, but that can be burdensome on the patients as you have already discussed.

It is one reason perhaps why your doctor chose to have you come see them every two weeks to get the medicine, because it meant they were able to see you frequently.

It is very cumbersome, it is very burdensome. It is 60 days of therapy for Benznidazole. It is 90 days of therapy for

Nifurtimox, which has other side effects which can include psychosis, and Sheba can speak to this more than I can. There are a lot of problems with the medications. That being said, they are all we have at present.

Then for the more advanced cases of heart failure, like Mr. Beza, there are all the standard medications that we use for the treatment of heart failure, and then if someone is fortunate enough to have insurance or to be able to pay for the advanced therapies that he has, those advanced therapies are very costly and time intensive in terms of the way they are managed.

Ultimately, heart transplant patients are required to take immunosuppressants for life long, they need to be monitored with biopsies. They can have the risk of rejection. They can have the risk of reactivation of their Chagas Disease. It can be a very, very problematic medical condition.

MS. GIAMBONE: Thank you, Rachel. A quick follow up question for Carlos. Carlos,

could you share your thoughts on what would be an ideal treatment for you given what you just described?

MR. BEZA: (Interpreted.) The ideal treatment, maybe I won't be able to give you the explanation that you are looking for, but we always have to be attentive, like in my country where they didn't detect it, so basically what I'm saying is it's not being diagnosed in time. Like I said, in my country, we only get a diagnosis when we have already arrived to a place where we have a serious condition. If we could diagnose it earlier, that would be the ideal treatment, and start treating it earlier.

Life is not easy living with the apparatus that I have to use now. You are looking at me, you say I look good, you think I'm in a happy situation, but it is a very difficult situation I'm living with. There have been a lot of changes in my life. First, your life is happy, and you're happy the treatment is working, but everything changes.

You have all these symptoms like dizziness, you have headaches, body aches, and if you miss any of the medication, then you have other symptoms that are brought on by missing your medication.

It's important to tell communities that they need to have an evaluation for this so they don't end up having the kind of consequences that I am living through now. That's all I wanted to say.

MS. GIAMBONE: Thank you, Carlos. I understand we have somebody joining us on the phone.

MR. THOMPSON: Maria, are you there? We have Maria Abrigo.

MS. GIAMBONE: Hi, Maria. Thank you for joining. Maria, would you like to share your thoughts and experiences, and tell us about your treatment regimen?

MS. ABRIGO: (Interpreted.) It's very important to me to have this opportunity to be able to explain to you the things that are going

on because of Chagas Disease. I just wanted to explain how this all began.

When I was about 12 years old, my family had moved from the place we were in Honduras and we went to a house that had roofing that was sort of made from palm and earthen materials. We saw there were some insects there, but we didn't imagine that this little insect could cause such problems and damage.

When I got to this country, I did have some symptoms, but it just was a cough and it just seemed like an ordinary type of infection. The doctor said it was probably just from a change in climate, I was just experiencing some cold symptoms, things of that nature. My cough became more severe. I started feeling very fatigued and tired, as additional symptoms.

I went back to my doctor because I wasn't getting any better. I was having more frequent visits to the doctor. I was having dizziness. I was having pains, body pains. I was having chills.

They sent me to do some x-rays. They said they thought I had some fluid around the heart, and this was something that they detected after years of these minor symptoms. They told me that my condition was very serious and I had to go to the hospital immediately, and that's what I did.

I went to the hospital and they examined me there also, and they said yes, my condition was very severe, and they could see that it was severe but they didn't know what I had, they didn't give me the overall diagnosis of the condition.

They did a lot of evaluations at the hospital. It was George Mason (sic) in Washington, under Dr. Sable. It took them a while to diagnose, they kept doing a lot of tests that were all coming up negative. They gave me a medication actually that came from Brazil. They said that's what I needed but it took a long time and it never arrived.

While all this was going on, my condition was getting worse and worse. I was

having difficulty breathing. I was having difficulty walking. I had to walk slower and slower.

MS. GIAMBONE: Jeanette, may I ask you to ask Maria what is she taking now and is she experiencing side effects because of what she is taking now.

MS. ABRIGO: (Interpreted.) I'm taking a lot of medication. I have a pacemaker, so I am taking medications that are related to the pacemaker. There is a long list of medications.

MS. GIAMBONE: What would she look for as an ideal treatment? Can you ask her perspectives on that?

MS. ABRIGO: (Interpreted.) What do you mean exactly?

MS. GIAMBONE: With the downsides she is experiencing now, what would she look for in a treatment that would maybe not have certain downsides or something that could be easier for her to take.

MS. ABRIGO: (Interpreted.) Sirolimus

is the only one that gave me any problems or adverse reactions, so they changed that medication. This medication is to do something to the blood.

DR. MEYMANDI: Can you ask her if she had a heart transplant.

DR. MARCUS: She did.

MS. ABRIGO: (Interpreted.) Yes, in 2014.

MS. GIAMBONE: Great. Thank you very much, Maria. We encourage her to stay on the line if she can so she can participate in the discussion.

Once again, thank you to our panelists, and thank you, Maria, joining us on the phone, and thank you, Jeanette, for the interpretation. Again, let's give our panelists a round of applause, and also to Maria joining us on the phone.

(Applause.)

MS. GIAMBONE: Let me look to my FDA panel. Yes, Jonathon?

DR. GOLDSMITH: I would just like to address a comment that was made about blood donor testing in the United States. In point of fact, blood donors are tested for Chagas as part of the donation process. It's an universal test that is applied to donors. I think it has been in place for about eight years. Every unit of blood that is transfused in this country that is collected, the donor is tested, not each unit necessarily, but the donor is tested. Just for clarification.

MS. GIAMBONE: Okay. Thank you, Jonathon.

MS. STARK: I don't understand what you mean by that, the donor is tested, not the blood.

DR. GOLDSMITH: Right. They get a blood specimen from the donor and it is tested in the laboratory for the antibodies that would indicate you had Chagas' exposure in the past, had active infection. That is an one time application to a donor. It is at the first donation. It is "donor testing" rather than each individual unit.

If they went back a second time to

donate, they wouldn't have that Chagas test again because they had a negative test and they were living in the United States.

MS. GIAMBONE: Thank you, Jonathon. Theresa, did you have a comment?

DR. MULLIN: I guess just to understand what Jonathon just said, so I understood what you just said, is there already a rule in place, all donors are screened, all blood banks are screening for Chagas? If they find that initial test they do comes back -- how reliable, I guess the test is very reliable in terms of true positive.

There is a rule in place now those donors would not donate, so the blood supply, I guess what you are suggesting is that the blood supply would be probably not exposed to potential blood from Chagas positive people?

DR. GOLDSMITH: Yes, right. The blood supply would be protected from people donating who were carrying Chagas' organisms, and just to go on a little, they would be on a permanent deferral list.

What happens now is because testing has gotten more sophisticated, the screening test actually has to undergo a supplemental test, and that will help determine if the person has a false positive, the test is not perfect, but if they actually have Chagas infection. That has been done as part of the testing mechanism now, to make sure these people are not part of the blood supply.

MS. GIAMBONE: Thank you, Jonathon. We have two comments here, so we will start with Dr. Meymandi.

DR. MEYMANDI: Most organ transplant programs also are doing Chagas screening.

MS. GIAMBONE: Thank you, Dr. Meymandi. One other comment? No? Theresa?

DR. MULLIN: That's a separate consideration from the other question we had, which is about required reporting, which sounds like that is more recent. The AABB is now reporting when they find those people with --

DR. MARCUS: The AABB doesn't report to

any organization. They just have published their data recently.

MS. GIAMBONE: Thank you.

DR. BERN: Barbara might want to correct me, but the last that I remember it wasn't 100 percent of the blood system that was being screened. I think the FDA guidance is voluntary.

DR. GOLDSMITH: It's universal screening of donors; universal.

DR. BERN: Has it changed since I left CDC?

MS. GIAMBONE: Barbara, did you want to comment on this?

DR. HERWALDT: I think part of the confusion is how to explain this issue of testing a donor once and also what Caryn was referring to. Earlier on, there were slightly different policies, and then also in terms of the reportability issue, there are some distinctions that might be complex to explain. It is a reportable disease in a few states, but in terms of national notifiability, it's not a national

notifiable condition, but relatively few conditions are.

We at CDC have various mechanisms which are far from perfect in terms of tracking, but that is people who come to our attention through physicians such as Dr. Meymandi and Dr. Marcus, and patients who are tested at CDC or get the medication through CDC.

MS. GIAMBONE: Thank you, Barbara. Joseph?

DR. TOERNER: Just changing back to Topic #2, I have a question or maybe some understanding about the early chronic disease and treatment for early chronic disease. What is it that you monitor for treatment? Dr. Marcus, what do you monitor for treatment? To hear from the perspective of Maira and Candace, what is it ideally that you would expect to experience as a result of the treatment?

DR. MARCUS: I think you have asked a really great question, and unfortunately, I can tell you what the clinical experience is now, but

it's far from perfect.

The science, and there are people in this room who know it far better than I do, would suggest that if you treat an adult with indeterminate phase disease, so they don't yet have any markers of damage, cardiac damage on their EKG, with Benznidazole, there will be sero conversion or version of serology to normal in a fairly small percentage of patients.

What isn't 100 percent clear yet in the literature is what that means for the likelihood of developing long term cardiac complications down the line. As a cardiologist, that's really what I'm looking for. I think serial electrocardiograms are appropriate on a yearly basis or every two years, to see whether or not there has been any advancement of disease.

It sounds like Sheba has more assessments that she's doing in her program. We have very limited resources here, and an EKG is a very simple, non-invasive test without any radiation.

MS. GIAMBONE: Thank you, Rachel.

DR. MEYMANDI: What we do is pretty elaborate. We do baseline electrocardiograms. We have baseline titers. We get one chest x- ray at the onset. Baseline labs. We see patients every two weeks for follow up of their labs. At the end of treatment, we get another titer, and then annually we do titers to see when the sero conversion, if it happens, it will happen 8 to 10 years down, that late in the process.

We get echocardiograms every year. If the Echo shows any abnormality, we proceed and get a cardiac MRI, and the reason why we do cardiac MRIs is that cardiac MRIs are incredibly good at showing scar formation. When a tissue dies, when the parasite kills off myocytes, you get a scar on the MRI.

What we then do -- I think I can predict who is going to have cardiac death -- those scars are what triggers the arrhythmias that cause cardiac death. If there is scar, we do need to do a study, and if we can elicit an arrhythmia, they

get a defibrillator. For those that have already lost half their function, two-thirds of their heart function, we put in a defibrillator and we kind of watch them.

The majority of people that we put defibrillators in, unfortunately, use their defibrillators appropriately often, because they have multiple episodes of sudden death, and that's when we get into adding medications and then doing the ablations.

MS. GIAMBONE: Thank you.

DR. RIBEIRO: I think we are going to discuss a little bit of this later on in the day. I think there is going to be a talk from Caryn Bern, also a little bit on natural history. I'm going to summarize some of the more recent data from clinical trials.

I think it is worth noting, I just wanted to make two points. One is in relation to the definitions, and actually when one talks about early chronic and how that is actually understood.

I'm sitting on the table here with Dr.

Sosa-Estani, did a trial on early chronic, and Dr. Altcheh, that is a pediatrician, and we have focused quite a bit of the discussion up to the moment in terms of adults, which are likely to represent, for example, in the United States, the highest burden of the disease, as we understand, although we don't know actually what proportion, and how many kids/children are actually involved.

I think it is important to at least remember this as part of this session, the importance of the disease in kids. I will quote again Dr. Altcheh because he didn't talk, but often an adult is a child that was not treated, and not treating kids is malpractice. I am again quoting.

I think the issue here is when you talk about early chronic, if one is not referring to kids and children, in that case, the response to treatment, there is quite a bit of discussion in terms of the shift, that for centers where one can actually do PCR, and PCR is today in a number of centers actually what they are using to assess

treatment response.

Just a note, not to let this not be mentioned beyond the serological response, et cetera.

There were a number of questions in terms of what would be an ideal treatment. I just wanted to share, I work for Drugs for Neglected Diseases Initiative, and as we started the discussions in the Chagas Disease program, we actually devised like a target product profile, in which we involved experts, also patient representatives. We have a Chagas Disease clinical research platform, where we actually share this information.

From the beginning, the ideal treatment was one that would be at least non- inferior to the current available treatments in terms of safety. I'm sorry, non-inferior in terms of efficacy, but definitely better in terms of safety, and that one could and ideally should have shorter treatment courses, if we can, and one should have an oral treatment administered once a

day ideally.

Anyway, this is actually an exercise that I just wanted to share.

MS. GIAMBONE: Thank you. Would you mind just introducing yourself, Isabela?

DR. RIBEIRO: I'm sorry. I'm Isabela Ribeiro from DNDi.

MS. GIAMBONE: Thank you very much. Let me look to my FDA panel, any follow up questions?

DR. ALTCHEH: Hello. My name is Jaime Altcheh from Buenos Aires Children's Hospital. We have to see that Chagas Disease is an infectious disease, it is not a cardiac disease. We are talking about sequelae. We have to talk more about infectious disease and less about cardiac disease.

When I hear about transplantation as treatment, this is a failure of the health systems.

DR. MEYMANDI: Absolutely agree.

MS. GIAMBONE: Thank you. To the health care providers and other physicians that are

seeing patients, can you tell us anything else that you may have heard from your patient group on what they -- I know, Dr. Ribeiro, you just mentioned some ideal treatments, what is most important to patients for ideal treatments. Would other health care providers like to provide some of the downsides that you are seeing with the treatments that your patients are taking?

DR. MEYMANDI: These drugs are potent drugs. If you're not feeling it, you're probably not taking it. Nifurtimox has its own set of side effects. Some people can't tolerate it at all. We used to use Nifurtimox as our first line here. We are now using Benznidazole.

Regardless of which you use, you need to have the other because there is a population that won't tolerate that one medication. I want to say that first. We have two options, we should have both options on the table for our use here.

Again, we can adjust the dose up and down to get them through a treatment usually, but again, there is that population that has a

horrific reaction to it that we just can't use it. So, we need both drugs.

We have tested over 6,000, we have screened over 6,000 people in Los Angeles. Our prevalence consistently has been around 1.5 percent. You take our Latin American immigrant population in the U.S., one to two percent of those patients will have Chagas.

It is pretty incredible. The fact that you have two cardiologists as the main physicians in the U.S. advocating, treating, screening for Chagas, it is kind of crazy. Dr. Altcheh is absolutely right, this is not a cardiology disease. We do not want this to be a cardiology disease. Again, that is why in Los Angeles we are pushing it into the primary care system. If we can get that awareness out to the community, it will make a huge impact.

Again, the pediatric population responds the best, the younger you catch them, the younger you treat them, the better they do, so again, in terms of primary care, for us, that involves our

pediatricians, and we have started that.

MS. GIAMBONE: Thank you, Dr. Meymandi. Jonca?

DR. BULL: I have a question about outside the United States, in South America, are children screened routinely?

DR. SOSA-ESTANI: Thank you. The national programs in most of the countries in Latin America, specifically Argentina, in our country, the national program and other programs in Latin America, have a systematic activity for vector transmission, and in Argentina, we studied around 30,000 to 130,000 children in communities or in screening before accepting into primary school.

I responded just for children. Additionally, in Argentina, screening a year, almost one million donors, and 800 women during prenatal care.

MS. GIAMBONE: Thank you. Let me just check in very quickly with the web. Do we have any comments coming in? Any phone calls?

(No response.)

MS. GIAMBONE: Jonca?

DR. BULL: As a follow up question as to how children are dosed on the drugs, is there a formulation for pediatrics? How is that managed if they are treated?

DR. SOSA-ESTANI: Every child detected with infection in Argentina is treated systematically. The dose, we have two kinds of pills in Argentina now, pill with 100 milligrams and a pill with 50 milligrams. That is a greater opportunity to offer a safer treatment regarding those, and the general dose in children is between 5 to 10 milligrams per kilogram per day.

MS. GIAMBONE: Thank you. What I'd like to do now, we are actually going to do one scenario so we can hear from our patient panelists. I'm going to read a scenario to you. We know it doesn't contain all of the information that you would need to know, but we want to know what is the first thing that comes to your mind when you hear this.

Imagine that you have been invited to participate in a clinical trial to study an experimental treatment for Chagas Disease. Early research in animals and people shows that this treatment may cure the disease in some people.

The purpose of the study is to better understand how well this treatment works and its safety. The study will enroll 50 adults who have been diagnosed with Chagas Disease but do not show symptoms.

This clinical study will last two years, and clinical visits will occur every two months for the first year, and then once every four months in the second year. Some of these visits may involve blood tests, and more common side effects of this therapy may include nausea, vomiting, and weight loss, but rare but more serious side effects may include changes in sensation and nerve damage and skin rash.

I know that was a lot to take in. Take a minute to go through this again.

MS. STARK: I don't have to think about

it. I've had a year and a half to think about it. I would jump on it. I had written to you at one point and I told you that I think that my purpose in life, like I told you, my kids are not the President, I've never done anything great, but in the last year and a half, all I can think of is maybe this was my purpose.

I'm healthy right now and I want to stay that way, but I also don't want to see someone else -- I don't want someone else to end up with the problems he has. I don't want to end up with them either.

I would jump on it, if they could catch it ahead of time, shoot, yeah, I'm there.

MS. GIAMBONE: Thank you, Candace. I hope you know that what you are doing right now is pretty great, Candace.

MS. STARK: Well, thank you.

MS. GIAMBONE: You were saying you were not that great, but yes, you are, for being here and doing this.

The side effects you just read about,

the nausea, vomiting, and even some of the more serious side effects, nerve damage, skin rash, do they have any impact in this decision? Would you consider them?

MS. STARK: No, not really. Who hasn't had nausea or vomiting. Nerve damage and skin rash, I'll deal with it. I've seen my mother -- my mother passed away recently with Leukemia. I seen her go through a whole lot more than that, just living an extra two years. If she can do that, I can, too. I think it would be worth it.

Like I said, I also did very well on the Benznidazole. Maybe I'm just one of those that I just fly right by.

MS. GIAMBONE: Thank you, Candace. Maira, would you like to share your thoughts?

MS. GUTIERREZ: I totally agree with Candace, they wouldn't have to ask me twice. If it is anything to help any of us out or anyone who has not been diagnosed or just recently diagnosed, if we can help in any way.

Like I mentioned my kids luckily were

negative, but if my kids have been positive, it would never have crossed my mind because you want not only that treatment but eventually and hopefully that cure. If that's what we have to go through, that's what we have to go through.

MS. GIAMBONE: Thank you, Maira. Carlos?

MR. BEZA: (Interpreted.) Just as they say, if we can help someone so they don't have to arrive at the consequences, if we can avoid that, if we can help others, it is good. Before I had cough, I had vomiting, and you begin to cough and cough, and you begin to take medications, and none of that helped.

One doesn't sleep at night. One gets sort of desperate, and one almost feels that if you go to sleep, you're not going to wake up the next day. You're so sad and all this is going on because of the disease. The cough really bothers you.

If we can help somebody else avoid that, we should. We want to help in time so they don't get to these consequences that we have. Thank

you.

MS. GIAMBONE: Thank you, Carlos. I know we are approaching our break time. We will break in five minutes or so. I would like to ask the health care providers in the room and certainly the panelists if you want to provide your perspectives, and Maria, if she is still on the phone.

Looking at this type of scenario, do you think you may have a patient that may decline therapy based on what they are reading here?

DR. MARCUS: May I try to answer that? I'm certain Sheba has an answer to this, too. This looks mostly to me like the conversation we have with every patient that we offer therapy to in the United States right now, essentially we have to tell them that it's part of an investigational protocol.

We do have the benefit of being able to say that some of the doctors in this room have proven that the medicines that we have available can cure children, recently infected patients,

things like that. It is a slightly modified version of this conversation, but right now, this is what we do in order to treat a patient in the United States.

DR. MEYMANDI: The current consent form is much worse than this. Any potential bad outcome is listed and you have to go through that with the patient, so this is nothing.

MS. GIAMBONE: Do you have patients that decline therapy based on what they have heard?

DR. MEYMANDI: I've had one patient decline, and I've treated, I don't know, I've lost count.

MS. GIAMBONE: Thank you, Dr. Meymandi.

DR. SOSA-ESTANI: I'd like to tell you that in our experience, inviting patients for a clinical trial -- the patients need to receive some hope, of course, we describe as necessary the invitation for a clinical trial, but in general, for the clinical trial and for regular care, it is really high.

In our experience, the unique situation

where the patient refused treatment is when you say you can't drink alcohol during therapy, so the patient say can't it wait until after the party, then can I receive the treatment. Of course, but that is the unique situation, and the relative frequency is that the patient not refuse.

MS. GIAMBONE: Yes, Maria?

DR. ALLENDE: I would like to personally thank Dr. Rachel Marcus and Dr. Sheba Meymandi for being here. I want to ask them what is your experience in your communities about referral of patients that have been diagnosed by primary care physicians?

I'm asking this because I imagine you come from an area where doctors from South America are not uncommon. I want to know if early diagnosis or screening is happening in clinics.

DR. MEYMANDI: In Los Angeles, currently no one is doing screening. Most of our referrals are from the Red Cross or they are from patients who themselves have gotten on line and have found me. The majority are those who I screen myself.

As I said, we screen actively. We have outreach programs to go out into the community and do screening. There isn't a large referral base.

Again, there isn't a great awareness of this even being an issue, and that is what we really, really need to work on, getting the awareness out there to the people at risk and to the providers who are taking care of these people.

DR. MARCUS: Just to answer from the Washington, D.C. perspective, it is a little bit different in that I think because of the large Bolivian community, the Bolivians who are here are very well-versed in the disease, so there is a community in Northern Virginia that is a little bit more savvy maybe than the general medical community in the country.

As part of my early work with Jenny and the non-profit I did a lot of in-services at free clinics in Northern Virginia, so I get referrals from those clinics. The NIH Parasitology Branch doesn't have a Chagas program, so if someone calls there and the patient doesn't have means, then

they get sent to me.

You and I have tried to work on this particular problem, and you know how difficult it can be to face --

DR. ALLENDE: Yes, I can witness Rachel's approach to free clinics that deal with a large number of immigrants in the area. One day, we will have more success. Thank you.

MS. GIAMBONE: Thank you, Rachel and Maria. We will take one more question and then we are going to break for lunch.

DR. BULL: I just wanted to find out more, the importance of prevention and how we can bring greater awareness, I was just wondering what recommendations you have along those lines.

DR. MEYMANDI: Yes, I think the key is this is preventative medicine. You go to a primary care provider for your annual check, they check your blood pressure, they check your glucose, they check your cholesterol. If you are a Latin American immigrant, at least once in your lifetime, you should get a Chagas screen.

What we are doing in my area -- I'm trying to make it really, really simple, because if it's not simple, it's not going to happen. In terms of having centers, there need to be referral centers because unless we can get it where you people approve these drugs and make it easy for the rest of us to write prescriptions and not go through the consent forms and all the paperwork, primary care providers in reality will not do this. They won't, and you need to understand that.

I have a coordinator that does that full time. You take a busy practice who has to do all the billing issues, pre- authorizations, et cetera, and you add this on top of it? Forget it. It's not going to happen. We need to be based in reality.

What we are trying to do is make this very simple. Get the screening out to the public. We have them drawing samples. They send us the samples. We currently send the samples to the CDC, but in a year, when we have an electronic medical record system that gives all our patients

an unified medical record number, our lab is going to be the central lab for our area, and the confirmatory testing will be done at the CDC.

Whoever is positive, my facility will treat. We will be a referral center so the primary care provider won't have to deal with that. You have to see the patients every two weeks.

MS. GIAMBONE: Thank you, Dr. Meymandi.

DR. RIBERIO: A couple of comments in relation to the concept of preventative treatment because it is actually treating, to try to avoid the development of a long term disease progression in one way, but there is also the information in recently published studies from Dr. Sosa-Estani and Dr. Altcheh, where you actually show there is indication that you prevent transmission from mother to child.

Actually, the treatment of women of child-bearing age has an impact, has a potential impact, in actually avoiding vertical transmission and perpetuation of the disease.

I think this is important. I think when you look today, today in the United States, it is interesting because you have understanding the magnitude of the problem is an issue, and so the need to scale up diagnosis and treatment is essential in some way if one thinks in terms of public health, but if one looks broadly, it is not only a problem here, if you look in the America's, in Latin America, if you look at the numbers of treatments prescribed, Benznidazole and Nifurtimox in the world, we are talking about much less than one percent of people that are estimated to have the disease that are actually being treated.

In Chagas, when you look, you have one problem where you are scaling up diagnosis and treatment, using the current available treatment, and then the next step is actually trying to find better treatments also. I think we should work with what we have but try to find something better.

MS. GIAMBONE: Thank you.

MR. THOMPSON: We have one comment,

somebody would like to ask our Argentinean colleagues to define what "cured Chagas" means, since they say the current methods are not confirmable and clinical evidence of no proliferation in the target organ is not strong, so maybe we can think about that and talk about it in the afternoon.

Also, we set out all the materials. When you go out, there is going to be a speaker list and printouts of all the slides for the presentations.

MS. GIAMBONE: Thank you. Let's definitely come back to that point for the afternoon session. I'd like to just say thank you so much to all our panelists, to Maria on the phone. Thank you for being here. To the health care providers for all of your perspectives.

Let's meet again in one hour. We will take a lunch break, and we will be back for the scientific discussion.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:03 p.m.)

DR. FARLEY: Good afternoon. Welcome back. Just a word of thanks again from the FDA for our patient panelists from this morning. Your opinions were very rich and wonderful to hear.

I think reviewers and also folks working in the pharmaceutical industry would join with me in saying sometimes we don't get to see the faces connected to the treatments that we might be working on and developing. It makes a huge difference for us. We really appreciate you being here, and you really have made a difference.

Also, it is now time for you to get to ask us questions. I want to begin by asking our scientific panel to introduce themselves. I think we will start with Barbara on that end.

DR. HERWALDT: Hi. I'm Barbara Herwaldt, Centers for Disease Control and Prevention, Parasitic Diseases Branch. I'm honored to be here, thank you.

DR. BERN: I'm Caryn Bern. I'm a

medical epidemiologist. I'm at UCSF now. I used to be at CDC. I do research on Chagas Disease.

DR. CHEN: Hi, I'm Danong Chen. I'm with MetronomX.

DR. SMITH: Tom Smith, Medical Team Leader with the Division of Anti-Infective Products, CDER, FDA.

DR. ALLENDE: Maria Allende, Medical Officer with the Division of Anti-Infective Products, FDA.

DR. NAMBIAR: Sumanthi Nambiar, Director, Division of Anti-Infective Products, CDER, FDA.

DR. COX: Hi, Ed Cox. Director of the Office of Antimicrobial products, CDER, FDA.

DR. FARLEY: I'm John Farley, Deputy Director, Office of Antimicrobial Products.

DR. RIBEIRO: I'm Isabela Ribeiro. I'm an infectious diseases physician, and I head the Chagas Disease area at DNDi, Drugs for Neglected Diseases Initiative.

DR. MEYMANDI: I'm Sheba Meymandi. I'm

the Director of the Center for Excellence for Chagas Disease that is based in Los Angeles. I'm affiliated with Olive View, but a Department of Health Service's facility.

DR. TOERNER: I'm Joe Toerner, Deputy Director for Safety in the Division of Anti-Infective Products, CDER, FDA.

DR. SOSA-ESTANI: Good afternoon. My name is Sergio Sosa-Estani. I'm the Director of the National Institute of Parasitology, Minister of Health, Argentina. Thank you for the invitation.

DR. SCHIJMAN: I am Alejandro Schijman, head of the Laboratory of Molecular Biology of Chagas Disease, and I also sit on the National Council of Science and Technology in Argentina. Thank you.

DR. KIRCHHOFF: I am Louis Kirchhoff. I am an infectious diseases physician at the University of Iowa, and I have a long-standing interest in Chagas Disease.

DR. SUZART-WOISCHNIK: I am Kiliana

Suzart-Woischnik. I'm an epidemiologist at Bayer Pharmaceuticals in Germany.

DR. FARLEY: Jaime, would you like to introduce yourself?

DR. ALTCHEH: Sorry. My name is Jaime Altcheh. I am Chief of Parasitology Services at Buenos Aires Children's Hospital.

DR. FARLEY: Great. Thanks very much. We will have a couple of formal presentations and then a panel discussion. That will be the format for the afternoon.

Our first speaker is Caryn Bern, who is a Professor of Epidemiology and Biostatistics at UCSF. She is a former CDC investigator who has worked in endemic areas of Latin America in disease transmission, diagnosis, treatments, and biomarkers of disease progression.

She has also published comprehensive reviews of the disease in both NEJM and JAMA. Caryn, we are delighted to have you here today. Thanks.

THE EPIDEMIOLOGY AND NATURAL HISTORY

OF CHAGAS DISEASE

DR. BERN: Good afternoon. You see the same picture again. Those of us who work in Chagas Disease have a lot of fun putting together our slides because there are so many amazing historical pictures from the days of Carlos Chagas.

By now, I think you all are aware of the major Trypanosoma cruzi transmission routes. This is to remind us all that the transmission is through the feces of the vector, which actually means it is not very efficient. Most people who are living in an endemic area are exposed to the vector and to the parasite many times over the course of their lives.

Of course, the other modes of transmission which become much more important outside of endemic areas and as vector control becomes better, congenital transfusion, transmission, and through contamination of food or drink.

I want to remind all of us that Chagas

Disease in many ways is a public health success story. Twenty-five years ago in 1990, before the first international control effort in the Southern cone, which means the Southern part of South America, the estimated prevalence of infected individuals throughout the Americas was 18 million, and there were an estimated half a million new cases per year.

The most recent estimates, which were just published by PAHO, now estimate that there are just under six million infected people, and about 40,000 new cases per year.

I'd also like to point out that the way some of these estimates are arrived at is there are sentinel population surveillance in most endemic countries of Latin America, and usually that is done by doing serosurveys in children under the age of five. For example, in Brazil, there are nationwide surveys of children under the age of five, because those are new infections.

This comes back to some of the discussions this morning about the early chronic

phase and what we in the Chagas' world mean when we say that. What we mean is that essentially children with infection have of necessity been infected some time during their lifetime, so more recently than, for example, an adult in an endemic area who could have been infected at any time in the last decades.

This becomes important when we start talking about response to treatment and the assays that we can use for that.

This is extremely rough. This is from the most recent PAHO estimates. You can see there is T. cruzi throughout the Continental Americas, and the most affected countries are Bolivia and Argentina with Ecuador, Paraguay, El Salvador, and Guatemala as sort of the next tier in terms of prevalence.

I also want to say that I come from an endemic country, the U.S. is not a non-endemic country. We don't as far as we know have very many human new infections in the United States each year, but there is certainly an enzootic

cycle that is established across the Southern United States, and we have at least 11 competent vectors in the United States, and many infected reservoir hosts.

We can go into details of this, but just so you're aware, all across the Southern United States, if you test raccoons or possums or wood rats in the Southwestern United States, you will find anywhere from a few percent to 40 percent infected.

This speaks to some of the questions that came up this morning in terms of the blood supply in the United States. In the U.S., most of the U.S. blood supply has been screened since the beginning of 2007. The current reports on the AABB website, which is open access, is there are just a little bit over 2,000 confirmed infections picked up through the blood supply.

You can see that it is almost every state in the nation, but with concentrations in areas where we would expect to find large numbers of Latin American immigrants.

As we mentioned before, the locally acquired Chagas Disease burdening in the United States is undefined because we have never done large scale serosurveys, and those would be very expensive.

There have been seven locally acquired vector-borne human infections documented clearly since 1955, four of those in Texas, and one each in California, Tennessee, and Louisiana. Other than the Louisiana case, all of these were acute infections that were picked up usually because an infected triatomine vector was found near the person who turned out to be infected.

Clearly, there are many more infections that go undetected unless someone gives blood, like the donor we heard from this morning.

An extrapolation from a study of 16 blood donors who were apparently infected in the United States suggests the prevalence of one in 350,000 donors. That is compared to somewhere between one in 5,000 and one in 10,000 donors from Latin America.

We know there are more than 20 million people born in Chagas Disease endemic countries of Latin America who live in the United States, and some years ago, we estimated that would extrapolate to about 300,000 infected immigrants based on the T. cruzi infection prevalence in their countries of origin.

What Sheba was talking about this morning I thought was very interesting, that she is finding about 1.5 percent of prevalence when she goes out and does community based serosurveys, and that would come out to exactly the same estimates. That actually gives me quite a bit of confidence in this estimate that we did in the past. This is infected immigrants.

In case series, including that Sheba's group did and another that was done in New York City, somewhere around 13 to 16 percent of non-ischemic cardiomyopathy in Latin American immigrants can probably be attributed to T. cruzi. We know that there are many people in the United States who have Chagas cardiomyopathy. Most of

those are probably never diagnosed as being from Chagas Disease.

I'd like to just very briefly go through the natural history of the disease. You have heard this once this morning from Maria, but I think it doesn't hurt to go through it again.

After vector exposure, the incubation period is one to two weeks, and then a person or an animal for that matter that has been infected has what is called the acute phase of Chagas Disease.

I'd like to point out for those of you who are clinicians that the incubation period can be very much longer in someone that acquires infection through transfusion or organ transplant. The index of suspicion has to be high.

Fewer than one percent of acute infections are thought to be detected. This doesn't mean they don't occur, it's just that they are not diagnosed as being from Chagas Disease. This is because most people don't have something like the Romasign that this little girl has that

would tip you off, that what this is is Chagas Disease.

Most of the symptoms if they occur are mild, and are very non-specific. Fever, malaise, hepatosplenomegaly, atypical lymphocytosis. Sounds just like mononucleosis.

Very rarely someone in the acute phase will have severe symptoms. Acute meningoencephalitis and/or myocarditis. These are rare but when they occur, they are associated with a very high mortality rate. They tend to occur more either in the extremes of age, so in very young individuals, especially, or in people who are immunocompromised. You are more likely to see this, for example, in an organ recipient.

The hallmark of the acute phase is what we call "patent parasitemia," which means parasitemia that you can see on microscopy. This can either be on a wet prep where you actually see the parasites moving or it can be on a stained smear like the one you see here. It also means that in the acute phase, molecular assays, PCR

based assays, have extremely high sensitivity. This is a very good tool in the acute phase.

Congenital T. cruzi, this is an acute infection, but an acute infection in a neonate. If you look at meta-analyses of studies of cohorts of infected women, you find that a median of about six percent of infants who are born to infected women will be infected themselves, but like Chagas Disease in general, most of these are mild or asymptomatic.

Most of the babies we see in Bolivia are actually asymptomatic. Rarely, you can have a severe acute phase in a baby and mortality from this is high, but we don't see this very much.

What that means is babies need to be screened. First, you need to know the mother is infected, and then once you know the mother is infected, the baby needs to be screened. It is actually not trivial to screen the baby because the test that is usually used in Latin America, what we call the "micro method" or "micro hematocrit method," is microscopy of a

concentrated cord or neonatal blood specimen, and the sensitivity of that in a single specimen is only 50 percent or less.

So, most babies are going to be missed on their first specimen, which means you need to do multiple specimens, and that is not very acceptable to parents.

PCR has higher sensitivity but it is still not 100 percent, especially in cord blood, and that is probably because the parasitemia usually rises after birth, so you may have better sensitivity at one month or two months of age than at birth.

You can see already this is a really complex screening program. For example, Argentina has probably the best screening program for congenital Chagas Disease, but even so, the last evaluation I saw made it clear that many babies were being missed because many babies were not brought for their final follow up at nine months when serology can be done, and that has 99 percent sensitivity, because you have to wait until nine

months when the maternal IgG has disappeared. This is a difficult screening program.

Without treatment, within about eight weeks, people then pass into what is called the chronic phase of T. cruzi infection. The parasitemia falls deeply because of the immune response, so people have to mount essentially an inflammatory immune response to control the parasite. Any acute symptoms, if there were any, will go away spontaneously.

At this point, the blood smear will become negative and PCR sensitivity is variable. I know Alejandro is going to speak a lot about sensitivity of PCR and how to maximize it, so I won't go into any details on that.

The diagnosis at this point relies on IgG serology. There are a number of different tests. There are several different kits for enzyme linked immunoassays, ELISAs, the immunofluorescence antibody test, something called the TESA-blot. In the United States, the reference laboratory is at CDC and CDC will do

reference testing on people who need it for Chagas Disease diagnosis.

Because no one of these tests is perfect, we generally confirm with at least two different tests that the person is truly infected, just like you do in HIV infection, for example.

Although you can't see the parasite in the blood, these people are infectious to the vector, can transmit congenitally or via transplant or transfusion, and can reactivate immunosuppressed.

You have already heard this morning the indeterminate form of the chronic phase is someone who has no cardiac signs or symptoms, no GI signs or symptoms, in a normal electrocardiogram. They may have some subtle abnormalities if you do more advanced testing. At this point, we really don't know the prognostic value of those more subtle signs.

Some experts, especially in Southern South America, will require negative barium enema and barium swallow as well. We will talk about

that in a minute.

As you already heard this morning, this is a life long infection in the absence of treatment.

Most people will remain asymptomatic in what is called the indeterminate form for the rest of their lives. They will never have symptoms. In about 20 to 30 percent, the estimates vary depending on the studies that you look at, will progress to either cardiomyopathy or gastrointestinal Chagas Disease or both.

What is Chagas cardiomyopathy? You have already heard a lot about this this morning. You have already heard from people what their experience is when they have this disease. This is a really bad heart disease, and it has many different manifestations.

Usually, the earliest signs are conduction system defects, what we call a "right bundle-branch block," or a "left anterior hemiblock," so the conduction system is not conducting normally, and later on, higher degree

atrioventricular blocks, so people can develop complete heart block, and that is usually associated with a severe slow heart rate, severe bradycardia, possibly with syncope, or even with sudden death.

The cardiologists can speak to this more than I can, but one of the things that is seen in Chagas heart disease are both slow and fast heart rates, so Brady and tachyarrhythmia's. People get sinus node dysfunction, what we used to call sick sinus syndrome, and severe bradycardia, but they also can get ventricular arrhythmias, they can get atrial flutter and fibrillation. Many different symptoms along with the arrhythmias.

Apical aneurysms are actually quite common in people who have advanced Chagas heart disease, usually in the left ventricle, and they can develop clot/thrombus in the left ventricle or in the aneurysm, and because of that, they can develop strokes.

The end stage, as you have heard from several of the patients this morning, is a dilated

cardiomyopathy and congestive heart failure that eventually may not respond to medical treatment.

I want to touch very briefly because this is talked about in some of the studies of treatment on classification schemes for the severity of Chagas cardiomyopathy. There are really just two components to this. The first are the characteristic EKG changes, the characteristic electrocardiogram changes, right-bundle branch block, left anterior fascicular block, bradycardia's, other heart blocks, flutter, left-bundle branch block, and then signs of cardiac insufficiency and eventually congestive heart failure.

You can do that either with a chest x-ray if it shows heart size or an echocardiogram where you can measure the left ventricular extrasystoles volume and the ejection fraction.

Don't be intimidated by this. This is just four, and I think we are up to six or seven different schemes, but they all really follow that same kind of pattern.

Usually, Class 1 or Class 0 or Class A is indeterminate. People will have a normal electrocardiogram and no signs of congestive heart failure. The second class, so 1, B1, are only EKG changes. Three and four or C and D are people who have cardiac insufficiency, and then frank congestive heart failure.

This really has to do with the prognosis of Chagas cardiomyopathy. Signs of poor prognosis include, as you might imagine, complex ventricular arrhythmias, global or segmental wall motion abnormalities on echocardiogram, sustained or non-sustained ventricular tachycardia, and then the signs of congestive heart failure, and increased left ventricular extrasystoles volume and decreased ejection fraction.

Sudden death from Chagas Disease can occur either earlier or later in the course of disease. Early sudden death is usually from a ventricular arrhythmia or complete heart block, less commonly from an embolus, and then mortality, late mortality tends to be from intractable

congestive heart failure.

I won't spend very much time on gastrointestinal Chagas Disease, but this is the other major manifestation, less common than Chagas heart disease, and tends to be seen in Southern South America, and to be very, very rare in Northern South America and Central America.

Not non-existent, but rarely seen. Even in the Southern cone where it is most common, it seems to be less than 10 percent in contrast with heart disease, which is more like 20 to 30 percent.

Both for the esophagus and the colon, which are the two end organs most commonly involved, it involves disorder parasitosis and eventually a dilation of the organ, so you end up with a megaesophagus or a megacolon, or sometimes both.

We think the geographic patterns have to do with strain differences in the parasites. That has been hard to prove directly. Certainly, there is a difference in the prevalence that you see in

the northern part of the hemisphere versus the southern, and the treatment is largely surgical.

As far as we know, treatment with anti-parasitic drugs will not affect the outcome in terms of gastrointestinal disease, although admittedly, we really have no data on that.

In the United States, I think one of the first things that brought Chagas Disease to our attention was an episode where three recipients of organs from an infected donor developed Trypanosoma cruzi, and at least one of them seems to have died from it. This was in about 2001.

We know now with 15 years of data that T. cruzi transmission risk varies depending on which organ is transplanted. There are pretty good data for kidney transplants, which is the most common transplant, that a minority of people who receive an organ from an infected donor will actually develop T. cruzi infection. Thirteen percent in an U.Scohort, 19 percent in an Argentina cohort.

For liver, it seems to be around 20

percent, although admittedly the data are very sparse. There have been some hearts transplanted from infected donors, and three of the four who received hearts from infected donors developed T. cruzi infection.

Recommendations that were published in 2011 based on these data recommend that kidneys and livers from infected donors can be used, preferably with the knowledge that they are coming from an infected donor, and that presumptive treatment is not recommended, that what is recommended is serial monitoring with PCR, and this is pretty much always done with CDC, which can provide that PCR monitoring, and then a lot of advice over the course of the monitoring of the patient.

What we know since 2006 when there have been quite a number of recipients monitored this way is there are very good outcomes with early detection and treatment.

The other thing I'd like to touch on very briefly is reactivation and immunocompromised

hosts, because we have also seen this in the United States. There are two major settings for reactivation, either a T.

cruzi infected patient that receives a solid organ or bone marrow transplant, so clearly a person who has a heart transplant for end stage Chagas, cardiomyopathy, and then in the setting of HIV, T. cruzi co-infection.

In the transplant recipients, the most common manifestation of reactivation is acute myocarditis, and this is usually picked up when endomyocardial biopsies are done in the course of the monitoring of a heart transplant recipient.

Again, this has a good prognosis with prospective monitoring and treatment. It is a matter of really the physicians having a high index of suspicion. In HIV co-infected patients, the most common manifestation is CNS disease. A mass lesion in the brain and/or meningoencephalitis. This is associated with a very, very high mortality rate. Acute myocarditis is the second most common manifestation of

reactivation.

Treatment in these settings involves antitrypanosomal treatment and optimization of anti-retroviral treatments. It is really unclear at this time what the role for antitrypanosomal prophylaxis is because there haven't been that many of these patients, but usually people are put on secondary prophylaxis if they survive their reactivation.

I'd like to turn now to some of the data on effectiveness of treatment that don't come from clinical trials. Isabela is going to cover the clinical trials, and I'm going to cover a couple of observational studies that have been really key in our thinking about treatment, especially of adults.

This is the first one that came out in 2006 from Rodolfo Viotti in Argentina. This was a clinical trial but it was not randomized, and it was not blinded. People knew whether or not they were treated as did their physicians, and they were systematically assigned to treatment or no

treatment.

The second thing to point out is this was very large. They had 566 patients, half of them treated, and the median follow up time was almost 10 years. The primary outcome in this study was progression of cardiac disease, progression from a lower severity class to a higher severity class, and they used what is called the "Kuschnir Classification," which is the first of those classifications.

As I said, this was non-randomized and not blinded. It had about 20 percent loss to follow up. It went through quite a rigorous review before it was published. They did sensitivity analyses to look at what the effect would have been if the people who were lost to follow up had either progressed or not progressed, depending on which group they were in.

I think the bottom line is they found that the treated group had a significantly lower rate of progression compared to the untreated group. To me, when it came out, this was very,

very impressive.

So, 12 of 283 or four percent of those who were treated had progression to a higher Kuschnir class, so that meant they either went from having no signs and symptoms to having an abnormal EKG, or went from having only an abnormal EKG to having signs of cardiac insufficiency, and death was also one of the outcomes, versus 40 of 283 or 14 percent of those who were untreated, and this gave an adjusted hazard ratio, adjusted for ejection fraction, that was highly significant.

Essentially, if you look at that hazard ratio, what it means is that the treated group had 75 percent less progression than the untreated group.

The other thing that I think for those of us who think about the natural history of Chagas Disease and who also think about clinical trials where an outcome might be clinical progression is that those who had disease already were much more likely to progress.

If you look at the untreated group,

seven percent of those who were indeterminate at baseline progressed to one of the higher classes, but of those who already had EKG changes, it was 19 percent, and those of already had signs of cardiac insufficiency, it was 46 percent.

That actually is part of the thinking behind the benefit trial, which we are all waiting to hear the results of, in which they recruited people who already had EKG changes as being a group that was at highest risk of progression.

The other point that I want to bring up from this study is that the mortality rate was lower in those who were treated than in those who were untreated, and this did not reach statistical significance. The p was .085. Still, I think this is a pretty strong trend to decrease mortality.

The other observational study that I'd like to bring to your attention was done by the group that Sergio is the senior member of in Argentina. This is something that actually eight years ago we put into the recommendations in the

JAMA article that came out of the CDC group, that girls and women, non-pregnant women of child-bearing age, should be prioritized for treatment because we figured it would decrease their chances of transmitting to their infants, but we didn't have any data at that time to prove that.

This study, to me, is a very impressive demonstration, even though it's not a clinical trial, it's a retrospective analysis. There were 132 mother/child pairs that were treated versus 222 mother/child pairs where the mother was not treated.

None of the children of the treated women were infected, compared to 15 percent of the children of the untreated mothers. To me, that was a really important finding and supports what we had recommended back in 2007.

The other question that is going to come up in all of the subsequent presentations, I suspect, is the question of what happens to serology after treatments. I just want to bring up some of the findings in these studies that I've

just talked about.

In the Viotti study, negative seroconversion, conversion to a negative ELISA, occurred in only 15 percent of the treated versus six percent of the untreated. I think that has to do with biological variability in these tests. The median time to negative seroconversion was almost 12 years.

In another study from Sergio's group in Argentina, on the second line, up to 40 percent of those who were treated converted to negative serology versus none of the untreated, but it took up to 30 years.

These data are from the same study of women, treated and untreated women, that I just showed you the flow diagram from, and this is only the treated women, and I found this quite interesting because we have always said this, seroreversion, reversion to negative serology was more rapid or maybe we should say not quite as slow, in those who were treated as children compared to those who were treated as adults.

The dotted line are women who were treated when they were 15 years or younger compared to those who were treated after the age of 15. You can see there was somewhat faster reversion to negative serology, but it still took years, more than 10 years for most people.

That is all I have to say today. I'm happy to answer questions now or later.

DR. FARLEY: Why don't we take questions as part of the panel discussion, if that would be okay. I think as we have our discussions this afternoon, it is very important particularly for the panel that we focus on our goal, which is to have drugs commercially available in the United States. I think our patients articulated what a challenge the current situation is for them.

To that end, I have actually asked Joe Toerner to outline for us what those regulatory standards are and what our review consideration for a new drug would be. Joe is an infectious disease physician trained at Georgetown, was on the faculty at UCSD before joining the agency.

At the FDA, he's worked in basically anything in infectious disease I can think of, started out working with antiviral drug development, moved to vaccine drug development, and we were very lucky about five years ago to recruit him to join us working on antibiotics, antifungals, and antiparasitic agents. Thanks, Joe.

REVIEW CONSIDERATIONS FOR NEW DRUGS IN THE UNITED STATES

DR. TOERNER: Thanks, John. In the next 10 minutes or so, I'll try to lay the groundwork for what FDA has under consideration when we review new drugs. My talk will cover adequate and well-controlled trials. We will talk about endpoints, and then examples of regulatory approvals.

This is a general overview of adequate and well-controlled trials. They are trials designed to show that a new drug is safe and effective for treatment. By "effective" we mean it's the benefit the patient experiences, a cure

of disease, improvement in symptoms.

By "safe," what are the risks of the side effects of the drug. At FDA, as well as clinicians, we always weigh the benefits and the risks of new drugs for treatment.

Our statutory guidelines direct us that new drugs for approval must meet the standards for effectiveness and safety. This comes from Section 505(d) of our Food, Drug and Cosmetic Act, and the Act was amended in the 1990s to include Section 115(a). The Act talks in plural. It talks about trials, plural.

The amendment to the Act, the Modernization Act, clarified that one adequate and well-controlled trial could meet the statutory standards for effectiveness and safety.

The Food, Drug and Cosmetic Act also says that the evidence must come from adequate and well-controlled trials, and our Code of Federal Regulations described those. There are five types of trials that are specifically discussed in the regulations.

The first example is the placebo control trial, and it is where a test drug is compared with a placebo designed to look like the test drug. Success is the test drug is better than placebo. By success, what we are talking about is the statistical inference testing that shows robust evidence of efficacy for the drug.

The second example is a dose comparison trial, and it is where two or more doses of the test drug are compared, and success is one dose of the test drug is better than the different dose. Usually, it's the higher dose is better than the lower dose.

The third example is no treatment concurrent control trial, and it is where a test drug is compared with no treatment. Usually, patients are randomized, you know, the flip of a coin, at the beginning of a trial to receive the test drug or to undergo no treatment, and success, that is defined as the test drug is better than no treatment.

The fourth type of trial design is

described in the regulation as the active treatment control. It is where a test drug is compared to a known effective therapy called "the active control."

Success can be described as the test drug is better than the active control or what we are used to dealing with in many trials of antibacterial drugs, the test drug is similar or what we call non-inferior to the known effective therapy.

In the non-inferiority case, we really have to have clear and convincing evidence of the treatment effect that the known effective therapy has over placebo.

The final type of trial design that is described in the regulation is historical control trial, and this is where a test drug is compared to experiences derived from the historical literature or in the natural history of the course of disease, and then of course, success is the test drug is better than the historical experience.

This is pretty rarely used in the regulatory setting, but the examples that are given in the regulations are where the historical experience shows a very high rate of mortality, and the test drug then would result in a lower mortality.

With an adequate and well-controlled trial, it is going to use an endpoint to demonstrate efficacy. Now, I'm going to go through endpoints and how we define endpoints.

The Code of Federal Regulations defines an efficacy endpoint as the method of assessment of subject's responses are well- defined and reliable. The protocol for the study and the report of the results should explain the variables measured, the methods of observation, and the criteria used to assess response.

Another definition of an efficacy endpoint comes from a Federal Register document from FDA where we say a clinically meaningful endpoint is a direct measure of how a patient feels, functions, or survives. I will come back

to this Federal Register in a moment.

The Biomarkers Definitions Working Group convened a meeting in early 2001 and provided this definition of an efficacy endpoint. It is a characteristic or variable that reflects how a patient feels, functions, or survives. Clinical endpoints are a distinct measurements or analyses of disease characteristics observed in a study or clinical trial that reflect the effect of a therapeutic intervention.

Clinical endpoints are the most credible characteristics are used in the assessment of benefits and risks of a therapeutic intervention in clinical trials.

The Institute of Medicine also used this definition in their report of biomarkers and surrogate endpoints.

What are types of endpoints that we think about in clinical trials? I'll talk about three. The first is the clinician reported outcome. We are very familiar with this. It's an assessment of the patient's condition based on a

clinician's observation and interpretation.

It has a lot of advantages. Often they are standardized, reproducible and consistent, and they are well defined and reliable.

An example in the antibacterial world is the reduction in the size of a skin lesion in a patient who has a skin infection. Within a couple of days, the reduction is observed by at least a 20 percent reduction.

Patient reported endpoint measures are in a report of the status of the patient's health condition that comes directly from the patient, without any interpretation by clinicians about how the patient functions or feels in relation to a health condition or treatment.

An example that we have used in the assessment of efficacy is a patient reported outcome symptom measure used in an inhaled antibacterial drug trial in patients that have cystic fibrosis.

Now, I'll talk about biomarker endpoint measures. In that same Definitions Working Group,

they defined "biomarker" as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.

Usually, we consider this as a surrogate endpoint, and it is rarely used as a primary efficacy measurement, but I'll give you an example.

Another definition of a biomarker endpoint measure comes from our accelerated approval preamble to that new regulation, and a surrogate endpoint or a marker is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives, and is expected to predict the effective therapy.

The accelerated approval endpoint in 1992, that regulation, was meant to address chronic disease conditions for which therapeutic

intervention showed an important difference on a biomarker that was reasonably likely to predict clinical benefit, and then could support approval and make a new promising drug available, while additional clinical trials are ongoing to confirm the clinical benefit.

Some examples of biomarker endpoint measures are HIV viral load. This is an example of a biomarker that has been through quite a bit of rigor to show that it is a direct measure of how a patient feels, functions, or survives.

The second example is a drug for treatment of tuberculosis. The TB culture conversion to no growth is a biomarker that has regulatory meaning, and I will cover this in just a moment.

A third type of biomarker is serologic testing for antibodies to the parasite that causes Chagas Disease.

Now, I'm going to give some examples of regulatory approvals. There are really just two that I will cover, and that is a standard

approval. That is that adequate and well-controlled trials have shown that a drug is safe and effective on the basis of a clinically meaningful endpoint.

An example is a new drug for treatment of skin infection on that endpoint I had just mentioned, the reduction in the size of the lesion that a clinician reports.

The second example is a new drug for treatment of HIV/AIDS that is approved on the basis of reduction in HIV viral load. Although it is a biomarker, multiple clinical trials enrolling tens of thousands of patients have validated this endpoint as being a primary efficacy endpoint that is used to approve new drugs for treatment of HIV/AIDS.

Next is accelerated approval. This is where adequate and well-controlled trials has shown that a drug is safe and effective on the basis of a surrogate marker, and the surrogate marker is one that is reasonably likely to predict clinical benefit.

For a drug approved and marketed under the accelerated approval, the sponsor is obligated to conduct additional trials to confirm the clinical benefit. An example of this is drugs for treatment of tuberculosis, they are approved on the basis of the surrogate endpoint of converting the TB culture to no growth, but then the trials are ongoing to show there is a continued clinical benefit and demonstration of cure of tuberculosis in patients.

In summary, I've gone through some definitions of adequate and well-controlled trials that show substantial evidence of efficacy and safety, and our regulations describe types of trial designs. Endpoints are a measure of how a patient feels, functions, or survives. They are either patient reported or clinician reported outcomes.

A biomarker is usually considered a surrogate marker, reasonably likely to predict clinical benefit, although there are rare examples where a biomarker is used as an efficacy endpoint.

We have standard approval as a regulatory approval pathway, and we also have the accelerated approval where a drug can be approved on the basis of a surrogate endpoint.

Thanks very much. I will be happy to answer questions during the discussion session.

DR. FARLEY: Thanks very much, Joe. We have given Dr. Ribeiro the hardest talk to give. She is head of the Chagas Clinical Program at the Drugs for Neglected Diseases Initiative, and she focuses on drug development for Chagas Disease. She has worked in collaboration with industry and academia in the design, coordination, and overview of safety and efficacy of clinical trials of new drug candidates for the treatment of Chagas Disease, and she has also conducted research and co-authored publications evaluating Chagas Disease progression as well as blood-derived biomarkers.

Thanks very much. She's going to give an overview of clinical trials which have been completed or ongoing or planned.

RECENT, ONGOING, AND PLANNED CLINICAL TRIALS

FOR CHAGAS DISEASE

DR. RIBEIRO: Thank you. It's a privilege to be here and presenting. A number of colleagues around the table have been involved with some of these trials and are involved in some of these trials.

Just really as indicated, providing an overview of where we are in terms of clinical trials for Chagas. Not to belabor the point but it is important to frame the discussion in terms of Chagas Disease as an unmet medical need in terms of the most common parasitic diseases in the Americas, a leading cause of infectious myocarditis worldwide.

We have two drugs available, Nifurtimox and Benznidazole, but both of these drugs were actually developed and registered in the 1960s and 1970s. Those registrations were based on small case patient series, small trials, actually with data that was generated at a time when you had a number of acute cases also. It's important to consider the timing and the period in which

registration was granted for both of these compounds.

The situation today is one discussed earlier, that you have less than one percent of those that are infected that receive treatment, but it's not only because the large majority of patients don't get diagnosed, as the largest burden of the disease are patients that are asymptomatic.

In addition to that, there are the safety and tolerability issues, the long treatment period involved. The result is one of really a great part of those that are affected are not receiving treatment.

It doesn't show very well, I'm sorry, in the screen. I thought it was important to start by the systematic review from the CDC group first authored by Caryn, Barbara was also one of the co-authors, and I think Louis Kirchhoff also.

At that time, showing we had just three randomized controlled clinical trials that had been published, and in addition, there was the

observational study from Voitti actually assessing Benznidazole for treatment.

This is actually from a number of case series, a number of studies, but there were three randomized controlled trials in chronic Chagas Disease in the published literature.

In 2009, another review just basically showing the same, what you have is the same three randomized controlled clinical trials. A number of observational studies where they certainly report the benefit of Benznidazole in terms of the different measurements/ assessments that were used, but essentially randomized trials, we are talking about three.

In two of these trials, again, chronic Chagas, the first of these trials is one from Andrade and colleagues, a clinical trial in Brazil, in children. Serology was used as the endpoint, as the primary endpoint for evaluation of treatment response.

Indeed, there was a significant benefit from Benznidazole versus placebo. This was a

double-blinded placebo controlled study. ELISA was used but also there was serological response over time where another measurement, AT-ELISA, was used, the so-called F23, there are different names for this other type of non-conventional ELISA used as an endpoint.

Indeed, an important response, but no clinical outcomes in a population that is largely children with early chronic infection, largely asymptomatic, but an important response, which together with this other trial, an evaluation also, a second double- blinded randomized controlled trial in children, authored by Sergio Sosa-Estani and the group in Argentina, where again a significant difference in terms of serological response in kids.

The results of these two trials actually prompted the change in policy and the recommendation for treatment of children by the WHO and by a number of different programs.

In the study from Sergio Sosa-Estani, the small graph you can barely see on the screen

is actually showing in the order of five percent persistent positive among patients with Benznidazole. A significant difference across the board with both trials and Benznidazole treated children.

The situation in 2008 was one that you had two randomized clinical trials that were ongoing in adults with chronic Chagas Disease. One, the TRAENA trial, the trial that involved patients with chronic Chagas Disease, in the indeterminate phase but also with cardiac involvement, and the BENEFIT trial.

The BENEFIT trial, double-blinded placebo controlled trial evaluating Benznidazole treatment in patients with early cardiac involvement. By then, in 2008, the situation was really we had decades of no new clinical trials for treatment options in Chagas, and research and development really stalled by really a number of knowledge gaps.

One of the essential and a key gap here was actually how to evaluate treatment response,

particularly in adults, where you have this very long treatment, very long disease evolution period, where a large majority of patients are asymptomatic, and really how to assess treatment response in such a scenario. This is besides a number of other knowledge gaps and technical challenges with the disease.

There were a number of discussions, expert groups, the Chagas Disease platform, clinical research platform. There were groups that got together to really see there is a clear need for new treatment options for patients with chronic Chagas Disease, both adults and older children.

A decision was really to proceed with clinical development and generating scientific information that will help fill existing gaps and inform also future drug development.

PCR was selected as the primary endpoint for these clinical trials, after a number of consultations, and there was at that point standardized methodology that had undergone multi-

center evaluation. Dr. Schijman will discuss this a bit further.

The consensus was as there was concern with the low sensitivity of PCR that one would aim for serial and multiple PCR examinations done sequentially. The rationale for selecting PCR as the endpoint was one that was a plausible biological rationale with the link of parasite persistence with chronic heart inflammation, data from animal models in that support. There was human data from acute Chagas Disease in children and also from reactivation, Chagas Disease transplants, and HIV. Also, some information from observational studies.

There was early regulatory consultations in the region, and agreements in terms of endpoints, trial design, and strategy for development, and we were aiming in this process also to generate pharmacokinetic/ pharmacodynamics data in humans using the different available biomarkers doing parasite genotyping for new candidates but also for Benznidazole in

particular.

There has been progress over these recent years. These discussions actually took us forward. Two studies in children were carried out. Until very recently -- although kids, as we discussed before, there was a recommendation for treatment with Benznidazole in kids, and there was no pediatric formulation, but beyond that, there was no PK information in kids whatsoever. Actually, there was data generated in children on pharmacokinetics.

The azole class of compounds that for 15 to 20 years had been considered the class of compounds with a lot of potential for Chagas, actually three clinical trials were initiated, the CHAGASAZOL trial, STOP-CHAGAS, that is a Merck sponsored trial on Posaconazole, and also E1224, and Benznidazole in adults, a phase two trial in Bolivia. More recently, Fexinidazole for Chagas.

Quite a number of new information being generated. I will talk a little bit about these trials. This is the CHAGASAZOL trial, the results

of which came out in 2012. You had the publication in the New England Journal last year. One cannot emphasize how surprised most of us were when we actually saw these results because Posaconazol basically, two doses of Posaconazol were tested. This was the team from Israel, Molina in Spain.

These were patients with Chagas, adults, Chagas in the indeterminate phase, they were actually patients with chronic Chagas Disease. Some patients actually had heart disease. Basically, this was randomized, and you had 80 to 90 percent of patients randomized with Posaconazol failing treatment at 12 months, and actually six percent of Benznidazole treated actually failed at 12 months.

Basically, the primary endpoint for this trial was PCR. It was actually a sustained response at 12 months. All patients had cleared T. cruzi DNA, and at 12 months, as indicated, six percent of Benznidazole treated patients had failed, so 95 percent had sustained response. This was actually a surprise, the failure rates

that were seen with Posaconazol.

Another study, this is a trial comparing three different doses in duration of treatment with E1224, a Benznidazole arm, and this was designed as a double-blinded placebo controlled randomized clinical trial.

A lot of information on this slide, but essentially a lot of new information here. At the end of treatment, at day 65, when you look at Benznidazole, at the end of treatment, you had 90 percent of patients that had cleared parasitemia, the same across, no difference across the different treatment arms on E1224, but basically at 12 months follow up, you had 81 percent of Benznidazole treated patients had sustained that response, and with about 29 percent in the case of E1224, a high dose. The low dose of E1224 had no difference from placebo.

Here again, the primary endpoint that was selected was actually PCR. We actually had in contrast with the trial from Molina, three PCR examinations at each one of the time points. PCR

was evaluated during treatment and at end of treatment, month 4, 6, and 12.

What was quite interesting from this trial is if you look at the graph on the side where you actually have the results of the PCR during treatment, within seven days of initiation of treatment with Benznidazole, you actually had already a very significant difference in terms of placebo.

Placebo is the flat blue line on the top, and at seven days, you already had Benznidazole here, with two weeks of treatment with Benznidazole, you were below the limit of quantification for PCR. It stayed throughout the treatment period.

If you follow until 12 months, you actually had -- even among Benznidazole failures, you had this sustained, very significant difference from placebo over the one year of follow up.

This is actually the first trial that did the PCR treatment response during treatment,

and we actually had some interesting results in adults. This is quite interesting to see how early the treatment response was, and how this was sustained, and even in those that failed, how different the PCR results were from placebo.

In the case of azole, E1224, you actually had with the high dose this drop, also across the treatment arms with azoles during treatment, you had this important response, but as soon as treatment was discontinued, you actually had the slow return up. The two lower doses of E1224, there were no differences from placebo, but in the case of the high dose, it remained different from placebo.

Lastly, and here you also don't see it too way, but we actually did the AT-ELISA, so therefore, also done in kids, and it is interesting to see that actually at 12 months, there was a significant difference from placebo also demonstrated in adult patients with chronic Chagas Disease. With regard to conventional ELISA, no difference.

At this point, just to talk a little bit about the case studies in kids, the two trials, one in kids from 2 to 12 years old, and one for newborns to 12 years of age. This is actually a single arm perspective Pop PK studies. Dr. Altcheh is the principal investigator.

What was very interesting on these studies was that actually in both, you had 100 percent PCR negative at end of treatment, but when one looks across the blood levels, the blood concentrations, the Benznidazole concentrations in kids, the lower the age group, the lower the blood levels, and when you have patients that are 7 to 12 years of age, there was really no significant difference in drug concentrations from adults, but actually kids below seven years of age have a significant difference from adults, but they still have 100 percent PCR response at end of treatment.

It raises the question have we been overdosing adults all along, and would that be one of the explanations for the safety and tolerability issues that have been at least

partially responsible for that.

Importantly, in some of the pediatric cohorts also from Children's Hospital in Buenos Aires, from Dr. Altcheh, there is an indication that not only the PCR response at end of treatment is actually 100 percent, but that is sustained, for patients for which data is available beyond 12 months, this is actually phased down, it is not that patients are actually becoming positive again, that you actually have late relapses.

This is actually looking at the ELISA over time, and also F23 over time. It is really giving an idea of different outcome measures, and how in some way PCR is really showing an early response outcome assessment.

I will not discuss this because of an issue of time and also because it doesn't show too well, but it was actually just in terms of providing additional information in terms of the clinical trials and the very different clinical trial scenario that we have today.

STOP-CHAGAS, another clinical trial.

This one is a Merck sponsored trial, Dr. Morillo is not here today, but is one of the PIs. It is evaluating actually different doses of Posaconazol versus placebo. It has also Benznidazole and Posaconazol combination arm.

Again, across both the Molina trial, E1224 trial, and this one, as you can see, the design was very similar where the primary endpoint for all these trials were PCR selected as the outcome measures, with evaluated response at end of treatment, but also followed patients for the complete 12 months, and looking at sustained parasitological response at this point.

This trial actually recruited 120 patients, enrollment and follow up has been concluded, and we are expecting over the next month the results to be available.

The TRAENA trial, I have a single slide because there is analysis that is still ongoing on this trial. It is a very important trial, adult patients with chronic Chagas Disease, indeterminate phase, and also with cardiac

involvement. This is a randomized, placebo controlled clinical trial, with actually follow up of patients over 10 years.

This trial has serological response, PCR, and also clinical outcomes, with follow up of basically on the order of about 10 years.

As you can see, 910 patients underwent screening, 764 patients were randomized, 382 placebo, 382 Benznidazole, about 300 completed studied in the Benznidazole arm, 308 in the placebo.

Here you have this very significant difference in the placebo and Benznidazole versus placebo response in terms of PCR outcomes and also serological response over time. Here, we looked at sustained serological response measured by PCR at 12 months, and when you look at the Benznidazole response, it is 86 percent sustained response.

It is really looking at this pattern of quite similar in terms of when one looks at the Benznidazole data across the different studies

through the different outcome measures used.

The BENEFIT trial is a key trial that we are all waiting for the results. There is a pilot study that has actually a co-primary endpoint of negativization of PCR and also an evaluation combined actually with the reduction in the mean burden of the parasite load over time. This is a randomized double- blinded clinical trial. Adults with chronic Chagas Disease but with early cardiac involvement.

The mean time of follow up of these patients was on the order of about 7.5 years. The trial is finishing now. The last visits are being made this April. They are reporting on the order of 1.5 lost follow up.

For the main trial, the primary endpoint is a clinical benefit endpoint. Here, you have 2,856 patients randomized equally for Benznidazole and placebo, and a primary endpoint that is really evaluating a combination of clinical outcomes of death, cardiac arrest resuscitation, sustained v-tach, need for a pacemaker or defibrillator,

implantation, thromboembolic phenomena or hospitalization for heart failure or heart transplant.

It is also a trial that is multi-center, multi-country. You have Argentina, Bolivia, Brazil, Columbia, and El Salvador. It is also taking into consideration the impact of the generic diversity.

As you can see, the large majority of patients in the BENEFIT trial, 75 percent is NYHA Class I, really early stage, and you have about 14 patients that from medical history had already gotten a pacemaker. The large majority, early disease.

The interesting data in terms of early on drug compliance, you can see very few patients, 16 percent in Argentina, 12 percent in Brazil, that actually discontinued, had treatment interrupted at some point, but you had very large and very good compliance overall in terms of treatment. We are very much looking forward to the results.

This is not un-blinded yet, so you can see the PCR baseline is on the order of 60 percent, a single sample, PCR sample was done. This is actually one of the things that is interesting, here you have 60 percent with a single sample. In the case of the E1224, we had on the order of about 86 percent PCR positive at baseline. This is actually the integrated results of PCR over time. Not yet un-blinded but shortly to be done.

Just a few notes to conclude. A couple of clinical trials that are also ongoing. You have a Fexinidazole trial, different doses with different treatment durations, 2, 4, and 8 weeks with a low dose, and the same with the higher dose, and a matching placebo. Again, the same pattern, evaluating response during treatment, end of treatment, and in this case not up to 12 months but actually six months for proof of concept.

This trial treatment recruitment was interrupted. We have 47 patients randomized, and we are in the midst of evaluating the response.

There is this planned trial to be initiated now in October of this year, October/November of this year, where we are actually testing the hypothesis that we discussed before, can we actually shorten the treatment duration with Benznidazole, can we lower the dose with Benznidazole, would combination make a change.

This trial actually looks at new doses and duration of treatment with Benznidazole and also combination of Benznidazole and E1224 in adult patients with chronic indeterminate Chagas Disease.

In terms of future clinical trials in chronic Chagas, there is the planned study of Benznidazole in kids, in children. There is a trial sponsored by ELEA/Chemo group with Mundo Sano Foundation. It is actually assessing efficacy and safety of Benznidazole in children, and the design is under discussion, finalization.

There are two trials on new Benznidazole treatment regimens in adults that are planned.

One, the DNDi sponsored trial in collaboration with Elsai, ELEA, Mundo Sano, and also the BERENICE project. There is Nifurtimox in children. This one is efficacy and safety of Nifurtimox in kids. It includes both PCR and serological but primary efficacy response in terms of serological response over time, reduction of titers.

I will not discuss these results, but I thought it was important. Dr. Caryn Bern already discussed these. It is really very important data from Sergio Sosa-Estani and his group in Argentina, in terms of the impact of treatment of women and preventing the transmission of congenital Chagas.

There is work from Dr. Altcheh that is being published now. In this case, 394 women, and actually 15 pregnancies, 16 children, and again, it really corroborates the finding from Dr. Sosa-Estani, in which there was no congenital Chagas documented post-treatment of girls and women of child bearing age.

I will not take you through the whole design of this. This is actually a non-human primate study that is ongoing looking at how PCR response in the blood correlates with sterile cure. This is a study that is done in naturally infected monkeys, non-human primates, and that are treated, and followed over time, treated with Benznidazole at different doses, treated with placebo, and treated with E1224.

Basically, following treatment, after 12 months of follow up, they are immunosuppressed, and after immunosuppression, animals that did not show reactivation will be actually sacrificed and then one can evaluate tissue, the presence of parasites in the tissues. It is actually to provide data in support of PCR and the rationale for use of PCR as a marker.

The Chagas landscape has changed, has changed significantly with some of these discussions and decisions that were taken forward, but there is a lot to be done. I think fundamentally here, and I come to conclude, that

there was a significant impact of this recent clinical trial data, both in adults and children, in overall Chagas Disease R&D landscape.

This data, key data on Benznidazole, actually leads to a push for scaling up diagnosis and treatment in Chagas, also for improved access to available drugs and formulation, but also points to the use of these markers, including PCR, in terms of evaluation of treatment outcomes, treatment response in Chagas.

There is really work to be done towards new treatments for the chronic form of Chagas, and we need to continue to generate and analyze data on pharmacokinetic and pharmacodynamics for new treatments in Chagas, and we are looking forward to the results of the new proof of concept studies on new treatment regimens for Benznidazole, in therapy and in combination.

It's clear we have come to a clear regulatory framework for registration and marketing authorization of new but also old treatments for patients with chronic Chagas

Disease.

Here we make the case as we come forward, and linking to some of the discussion that we had just before, if PCR or serological response could be used as a basis for registration of compounds for Chagas.

The situation in kids and children, it is simpler somewhat, because of the time lines for follow up. In the case of adults where you have this very long period for demonstration of clinical benefit, this is really particularly challenging.

Thank you. Thank you very much.

(Applause.)

DR. FARLEY: Thanks to all our speakers for excellent talks. We are going to begin the first panel discussion. Sumanthi Nambiar is going to be moderating those panel discussions.

Sumanthi is a pediatrician who practiced pediatrics for some time prior to an infectious disease fellowship at the Children's National Medical Center here in Washington. She joined the

FDA, and we were delighted when she was appointed Director of the Division of Anti-Infective Products a short time ago. That division regulates antibacterial, antifungal, and anti-parasitic drugs.

PANEL DISCUSSION

DR. NAMBIAR: Thank you, John, and thank you Dr. Ribeiro, Dr. Bern, and Dr. Toerner for your presentations, very useful to get the discussion started.

I think as John had mentioned when we started this afternoon's discussion, really the task at hand is how can we get safe and effective therapies available for our patients.

I think as Dr. Ribeiro mentioned, how can we have a reasonable regulatory framework such that these products can be developed. We have heard this morning from patients the difficulties they are encountering because these therapies are not readily available.

To that end, we have sort of split the discussion into two parts, and the first panel

discussion before the break -- we are running a little late, so we will try to wrap this up by 3:00.

DR. FARLEY: About 20 minutes.

DR. NAMBIAR: We will try to focus on what populations we could do these clinical trials and what might be some acceptable control groups. We will take a break and then we will come back and talk about trial designs, endpoints, and then we will have a presentation on laboratory monitoring using various methods.

We have had a lot of discussion internally on these topics. We have been impressed by the interest, trying to bring new products but also trying to make the existing products available in the U.S. market.

One important topic I think we would love to get input from all of you on is what might be the appropriate patient populations. Certainly, we could study acutely infected patients. We could study children. The numbers are probably going to be smaller but there are some benefits in

that you might be able to assess the outcomes at a shorter time period, or do we focus on patients who are in the indeterminate category where we have a larger number of patients, but the problem there is the follow up tends to be much longer unless we are now willing to adopt some of the newer methods, such as PCR, and what are the certainties around it.

I would welcome input from the panel members. I think one key question, and I think this came up in Dr. Bern's presentation, the number of patients with Chagas Disease who were really diagnosed in the acute stage of the disease is very small. Is it feasible, is it practical to even to a study of any reasonable size in that patient population. That is one question we would like to ask.

The second is what are the pro's and con's of trying to study a compound in the indeterminate group, which is probably the largest number.

Dr. Meymandi?

DR. MEYMANDI: May I ask a question? As a non-scientist clinician?

DR. NAMBIAR: Certainly.

DR. MEYMANDI: We are currently using two drugs, Nifurtimox and Benznidazole, neither are FDA approved. We are rather meticulous with our use and our follow up's, and there is ample data that they are effective, they are reasonably effective.

What do we need to do? We are using these drugs currently, but it is restricted. What are you looking for in terms of a study designed trial to show what that we don't already have? I'm really confused.

DR. NAMBIAR: A very valid question. I think as Joe presented in his slides, we need a basis to be able to approve these drugs to say they are safe and effective. What is the evidence? I know there is a lot of clinical experience. We certainly have studies done that we have discussed.

Certainly, one consideration that has

been given is if we in fact have access to the primary data, the data that actually supported these studies, is that something we could consider, but I think one issue is the quality of the data. We just cannot approve drugs based on the publications.

DR. MEYMANDI: That's what I'm trying to understand, what is it that we are trying to do, because you don't want to recreate the wheel.

DR. NAMBIAR: No, we don't. If we are able to get primary patient level data --

DR. MEYMANDI: You're appreciating my level of frustration as a clinician.

DR. NAMBIAR: Yes, certainly. We are aware of it. If we could actually get patient level data, say from some of the studies that have been done, which clearly demonstrates the treatment benefit, that is certainly something we can consider. I think there are instances where we have done that; right? Correct me if I'm wrong.

DR. MEYMANDI: Do we have access to that

data, where we don't have to recreate the wheel and do another study design looking at things that have already been done?

DR. COX: Your question is a good one. We were actually talking about this. There is a lot of data out there. To actually get a drug approved, somebody has to submit an application that has the clinical safety and efficacy data, and also provide information on the manufacturing of the product.

We don't make the drug, somebody else does.

DR. MEYMANDI: I agree with that.

DR. COX: All of these pieces need to come together, but the question you are asking is the same question, I think, we are asking ourselves, too, which is who has this data, can we identify it, are there some primary source records out there that might be able to be audited so we could understand the quality of it, and then that should be paired up with who manufactures the drug, and is there somebody out there that can

submit an application, that can manufacture this product, day in, day out, to a quality standard, so it can be approved and it can be available. Does that help?

DR. MEYMANDI: Yes. In that direction, we have companies who I know are interested in bringing these drugs forward. We have representation here from those companies. Is this something you guys can get together and move forward or do we have to start at the beginning and redo everything? That's insane.

DR. RIBEIRO: I think that is a key question, obviously. I think if we discuss with a number of the investigators that were involved in these clinical trials, I have no doubt you are going to have them making this information available for registration of Benznidazole, for example.

In the case of Benznidazole where you have the placebo controlled comparisons done, et cetera, I have no doubt. I think here we have representatives from ELEA, Mundo Sano Foundation.

There are groups that are collaborating on this, and certainly this information could be made available.

The issue goes back to perhaps a discussion that we are going to still have, on the issue of the clinical benefit demonstration. If one were able to actually register or seek marketing authorization here based on the outcomes that were selected for this, a number of them have serological response, but now we have PCR data, and if one would be able to support such a filing based on the outcome measures that were selected for these trials, either as a surrogate marker or actually a primary efficacy endpoint.

DR. NAMBIAR: That again would depend on how good the data are, one really has to demonstrate the link and make a link between the benefit on the surrogate endpoint translating to a clinically meaningful benefit.

DR. MEYMANDI: I'm a positive person, and I'm looking that the data is good, and let's start there instead of again recreating the wheel.

These are two drugs that we are using that we are seeing effective treatment. Again, from a clinician's perspective, let's make this easy. We want it to be safe, obviously.

I think everyone here who treats patients has patient safety at heart. If we can do it in an easier fashion than recreating another study design and starting with another patient population that hasn't been treated yet and having a placebo arm versus a treatment arm, and spending five years, ten years doing that, how many patients are we going to lose in that process.

DR. COX: A very reasonable goal, and consistent with our thinking on this, too. The real question is trying to gather up the data and identify those that have it and see if they can essentially join up with a manufacturer so that there is a way to try to take advantage of all that has been done, and I agree, why recreate the wheel if the quality data are already out there.

It's a very reasonable idea and I think one that several of us are having, and the

question is pulling it together.

DR. MEYMANDI: Excellent. Thank you. Done.

(Laughter.)

DR. NAMBIAR: I guess we can take a break.

DR. FARLEY: We're not done. I think that kind of answers the question on Benznidazole and Nifurtimox in terms of what the regulatory pathways might be. Part of our goal of inviting some of the key investigators here was to sort of show them that we really will need access to their data to have the drug approved, particularly in the United States. That's great.

I think we had written some of these questions thinking about, for example, a new azole. What would be helpful to us is sort of focusing on a discussion, pretend this is a new azole or a new class, how would you design the trial.

We certainly have the right folks here to answer that question, and what population would

you do it in.

DR. ALTCHEH: About populations, we need studies in children. If you see different presentations, the chronic disease begins after two months of infection. Children present with chronic phase of infection, then children have to be included in all of the studies that we begin about new drugs. This is very, very important.

WE have a lot of non-treated children that now are adults. This is the center point. About country groups, this is very difficult to not treat a patient when you diagnose these patients, because we have a lot of information about efficacy of Benznidazole and Nifurtimox. We cannot use placebo for the studies.

DR. NAMBIAR: If I can ask you a follow up question. If you are trying to study children, are these children who acquired the infection congenitally, are these children you are picking up in month one or two or are these children that get infected later in life or do you differentiate between the two?

DR. ALTCHEH: In places without vector transmission, you have children infected, all the children, with acute infections. In big cities without vector transmission, you have a lot of congenital infected patients.

DR. NAMBIAR: Thank you. Dr. Sosa-Estani?

DR. SOSA-ESTANI: First of all, I would like to express my complete agreement with the clinical point of view of Sheba, and regarding specifically your question, I think in several presentations, the complexity of the natural history of Chagas Disease, that is infectious disease, chronic infectious disease, with a very late clinical expression, I think as Jaime said, there is enough evidence of benefit. There are some evidence of clinical effect.

Personally, I think after benefit trial, to demonstrate clinical effect, is unreasonable, because it is not possible as a design to demonstrate clinical effect after benefit trial. I would like to reinforce that it is necessary to

design clinical trial to demonstrate effect against infection because in addition we have demonstrated that the effect against infection can interrupt one of the main routes of infection, congenital transmission.

Regarding the control, I think there is enough evidence that maybe in general would be not recommended use for placebo arm, but in some cases, thinking this is chronic infection, it's possible maybe in some situations thinking a control, delayed treatment.

DR. RIBEIRO: Just to answer the specific questions from the panel, I think we have dwelled quite a bit with regard to the populations in which a clinical trial would be feasible and acceptable, and I think we have selected the chronic and indeterminate patients as they represented the highest burden of the disease and where there would not be an issue in terms of recruitment, but also we felt it was important to have a placebo control, and we felt that population would allow us to be able to have a

concurrence type placebo control and a double-blinded design, and therefore, that was considered acceptable as it was represented, as Sergio was indicating, delayed treatment.

I think the evaluation of acute cases today is not feasible. I think the incidence is such and it goes so fast that we will not be able to identify cases.

Oral Chagas Disease, actually the clusters of oral Chagas are becoming more frequent, at least there is some indication of that, but it is episodic. You cannot predict where they are going to happen.

This is a consideration. Kids, certainly children as a population for evaluation. I think there is one element here, just that in one side, there is recruitment as you have pointed out, but as Jaime indicated, I think there are a number of untreated children so far, and therefore, these trials are certainly feasible, but there is the question is it the findings in kids will be representative of an adult

population.

If one carries out clinical trials in the children, will the outcomes reflect what one would see in an adult population, the adults being the worse case scenario in a way.

Here is where it is actually balancing these two sides, which is really challenging. It's a long answer.

DR. NAMBIAR: Do you think these children are identified as part of screening, when serological screening is done routinely in some countries? Is that how they would be picked up?

DR. RIBEIRO: Yes, particularly in countries like Argentina and Bolivia, where mothers are actually assessed, so routinely, evaluated in mothers who are Chagas positive.

DR. NAMBIAR: Dr. Sosa-Estani?

DR. SOSA-ESTANI: I would like to add regarding the design of the clinical trial. We are working for several years, we are really very, very happy to understand and to know with evidence that we can design short clinical trial in

comparison with the past. In the past, we needed at least five or six years to demonstrate efficacy against infection. We can demonstrate the same effect in 12 months.

DR. NAMBIAR: You mean because of PCR?

DR. SOSA-ESTANI: Yes.

DR. SUZART-WOISCHNIK: Just a comment. We did not discuss about the trial design, but my colleagues are trying to put a protocol in place and we have a problem of lost follow up, especially in studies with children with a disease that does not have a phenotype, acute phenotype, it is very difficult after a 60 day treatment to have a long follow up, one year, six months.

These poor families will be moving around, these are small countries, and the possibility that we have for full follow up is almost none. It is impossible to predict.

This is a risk for us so that we cannot guarantee from the beginning that we will achieve 100 percent one-year follow up in order to have our data valuable. Most of the results showed at

least 10 percent or more lost follow up at 12 months.

DR. CHEN: I think besides that, you have also reinfection, that kids or families went back to the endemic area that you have no control over, and they came back with reinfection. It's very hard to tell. It's very difficult to design, to conduct.

DR. RIBEIRO: I think it's worth noting the experience that we had in the clinical trials in Bolivia, where we actually had very good rates of follow up. We actually had at 12 months like three percent lost follow up. Really very little missing data. It's very difficult no doubt.

The issue of reinfection is challenging. We actually had linked with programs in order that patients were informed they needed to inform if there was reinfection and so on. It is certainly a question.

DR. CHEN: Regarding the control group, it is always hard because you have to treat every single patient, especially in those areas that the

drug is already proved for the last 40 years, and how can you not treat those patients, unless you have a very chronic case and then the recommendation is different.

DR. SOSA-ESTANI: Just to reinforce the comment regarding the control and reinfection, it really depends on the size of the trial, of course. In some cases, it is absolutely impossible to design a clinical trial with patients where they are living in areas without vectors or because they are living in an area under surveillance with interruption of transmission.

If the trial is huge like the BENEFIT trial, we discussed that, but we assume

(speaking in Spanish.)

DR. ALLENDE: I want to ask Sergio if the data, the original data from your randomized study would be available to be part of a submission, like the records of each patient, the laboratory results, some kind of record when that study was done, the randomized and the controlled

study in children.

DR. SOSA-ESTANI: Yes.

DR. ALLENDE: Thank you. I think that would be very important because sometimes in the article when you are reporting a mean GMT reduction or something, median, the actual value, those questions will be very important. Thank you.

DR. FARLEY: Thanks very much for that discussion. Just one point for sponsors that may be interested in developing Nifurtimox or Benznidazole. The FDA, following approval, publishes or makes available its reviews on the drugs on the FDA website.

One application that may be worth looking at as a recent precedent for reliance upon efficacy trials that you yourself did not conduct would be Miltefosine, approved recently for Leishmaniasis. That may be worth taking a look at.

Chagas is challenging in that it's likely we are going to need to understand better the surrogate endpoints that were used in the

trial. By now you know what the FDA calls a "surrogate endpoint," so that is good we are using the same language.

We are going to focus on that after the break. We're going to take a break now for 15 minutes and reconvene at 3:10. Thanks.

(Recess.)

DR. FARLEY: We will get started. We are going to turn now to the issue of laboratory monitoring, and our first speaker is Dr. Louis -- also known as Vaughn to most of us -- Kirchhoff, Professor of Internal Medicine and Infectious Diseases at the University of Iowa, Carver College of Medicine.

He's an expert in laboratory assay development for Chagas Disease. He developed the RIPA assay for Chagas, and is co-author of a large WHO comparative evaluation of serologic assays for Chagas Disease.

Vaughn, thanks very much for being here today.

LABORATORY MONITORING USING SEROLOGY

DR. KIRCHHOFF: I want to thank the organizers of the meeting for inviting me. I only have three slides and no graphs or pretty pictures. You will understand in a minute.

My plan or my charge was to discuss the issues that should be considered by FDA or industry staff when they are considering the design of a trial to evaluate a new drug for Chagas Disease or an old drug.

What my three slides show is just really a summary or a list of the issues that I think they would have to think about as they work through this serious challenge, let's say.

A bunch of things that are the list here have been mentioned extensively by the earlier speakers, and I will probably skip them. Maybe I'll talk for 8 or 10 minutes, and then cede my time to Dr. Schijman, who is going to talk about PCR.

If we can go to the first slide, general issues for evaluating drugs for Chagas Disease, evaluating drugs for Chagas Disease is really a

major challenge as you can see from the meeting here today, but it's not uniquely so. I mean this business of coming up with biomarkers and other indicators that are not clinical or patient based indicators of efficacy, it has come out in HIV a lot, tuberculosis, and many other diseases.

In Chagas Disease, as mentioned, there are no clinical related outcomes or no patient related or patent reported outcomes that would come up in a timely fashion that would help or likely help with evaluation of the efficacy of a drug.

In terms of the goals, my goal, and I think kind of everyone's goal is parasitologic cure, to simply get rid of all the parasites that infect each person who acts as a host for this infection, but there is this question whether suppression over a period of time is going to affect long term outcomes is kind of running in the background.

In terms of what we can look at, parasitologic assays lack sensitivity and

specifically the old time parasitology is with the insect's xenodiagnoses, where the insects are applied in a little cage on one's arm, then you examine the bugs weeks later to see if they have gotten infected from the patient's blood.

That is the old time parasitology, and sort of in the middle is hemoculture, take a patient's blood or fractions of it and put it into an appropriate medium to see if the parasites will grow there.

They have essentially been replaced by PCR. PCR is much less laborious and can be done in sizable numbers in a relatively short period of time.

Moving on to what I'm really charged with here, to talk about serology. This came up this morning in terms of how efficient our system is in the United States these days for screening the U.S. blood supply.

I think if you talk to the people, for example, Dr. Susan Stramer, who has been the head of serologic testing for our entire blood supply

in the U.S., ask her about our Chagas Disease assays, and she says they are excellent and they are really just as good as the assays that we have for other infectious diseases that do threaten our blood supply.

In a pre-treatment context for screening blood donors and for screening what I think and Dr. Meymandi and others think should be everybody who has any geographic risk for Chagas Disease or maternal risk. All these people should be screened in a pre- treatment situation.

We have the serologic tools for doing that. If you want to read about it, there was a comprehensive study financed by WHO that was published in 2009 in Transfusion. The first author was Otani, M.M., and in that, it describes a study of 21 commercially available serologic assays that we use to test blood donor samples, positive and negative ones, from blood banks in 10 of the endemic countries.

There, it shows many if not most of these assays have sensitivities and specificities

that are in the high 90s. Those are the tests that are used throughout Latin America for screening the blood supply there, and I think they do a good job of it.

Here in the United States, there is an Ortho and Abbott test that are used for primary screening essentially of all donated blood or all donors who are not known to be negative by previous testing, and then we do confirmatory testing, second stage testing, either with an Abbott test or with a test that I developed years ago called "Chagas RIPA." We are in good shape for pre-treatment testing.

In the context of post-treatment testing, it is much more difficult. I'd summarize it by saying variability and delay in the fall of anti-T. cruzi titers to whatever antigen you pick, after treatment make assessment of drug efficacy a difficult and prolonged process. Both Caryn Bern and Isabela Ribeiro showed slides of how titers fall, but they do so over years, so in evaluating a drug, we really don't have the time to sit

around for four, five, six years until it becomes clear that a drug is useful or not useful enough for us and won't be used.

Just a couple of background issues that have been touched on by others. The question is what group of infected persons would be the best ones to include in trials. One of the issues is the data show people who have been infected shorter periods of time, like two years instead of 42 years, are more treatable or more curable.

If you want to power the test or you want to make it likely that a new drug or a new combination of drugs is shown to be effective, you want to do it on younger patients, just as kind of a general rule.

Briefly, this business of reinfection was mentioned, reinfection after treatment. Someone comes in and is determined to be positive, gets in a treatment trial, gets treated, and then goes back to the context in which they got infected in the first place.

I don't have strong recommendations on

exactly how to do this now, but I'd say it is something that really needs to be paid attention to because although there have been a lot of studies on the genetics of T. cruzi in recent years, I think at this point it is fair to say we don't have a tool, for example, all the people who seem to be not cured who might have gotten re-infected, we don't have an usable tool yet to look at the genetics of the parasites in those people to make absolutely sure the parasites that they still carry are the old parasites rather than new parasites. That's an issue to think about.

Again, in terms of selecting the group, as I mentioned, it is good in terms of serology to have a two-stage process, first, some kind of screening assay, and then followed by a more confirmatory assay.

Another issue that is very important, it seems obvious, but I think it merits mention, it is very important to avoid including subjects who are false/positive in serologic assays. Historically, much less so now, but historically

false/positive results in blood tests or serologic tests for Chagas Disease have been a chronic problem.

If you're working with an assay that is say 99 percent specific, that means every 100 people you look at, you are going to have one person who appears to be positive for some reason unrelated to Chagas infection. If you work that kind of thing through the numbers of your study, in the end, it could turn out to be important and bias your conclusions, your inferences in one way or another. You certainly need to avoid that.

Again, I don't have a shopping list here of ways to be 100 percent sure you can avoid the false/positive's, but one thing to think about is what range of titers in the screening assays do you want to include. There is this kind of intuitive thinking that if a patient has just robust titers, that are pretty high, they are more convincingly true positive, and I think that is probably true to a certain degree but not absolutely so. Whether or not to include that

broad range or not is a question.

Alternatively, you could just take the top 25 percent in terms of reactivity in the screening assays, and then with either of these options, you could include PCR as a final confirmatory test, but then you are left with the question of whether people who can consistently be demonstrated to be PCR positive, presumably they have more circulating parasites, so either they are different in a biologic sense or in an immunologic sense, or the parasite strain they harbor is different, and there is no real way to sort that out, but either of those issues could conceivably affect the curability of their infection. Those are just issues to think about.

Moving on. A quick logistical issue. If you have a study with a large number of people and if you adopt a perspective that you really want to be tight about doing your serological studies, and I think if the idea is instead of looking at the end of three years or four years or something like that, looking at the fall in titers in months or

small number of years, if you're going to hang your hat on specific titers or levels of antibodies, I think it would be good practice to always run all the samples you have head to head in the same plot, in the same plate, and that will get rid of possible lot to lot variations, and it really appeals to me as one that has done a lot of serology to do that kind of thing.

The downside of that is if you have 300 or 400 people in your study and you draw blood from them every three months and you want to maybe get 10 to 12 aliquots with each one, because you don't want to take the same tube and freeze it and thaw it, freeze it and thaw it, because that can affect titers. All of a sudden you have 10 freezers with 30,000 samples and four staff members to take care of it, and all your data up in a Microsoft Cloud. It could certainly be a complication or burden. It's doable and there are obviously computer programs to deal with that kind of data.

Another issue is the long term goal is

to detect after treatment, I would think, an early pattern of declining reactivity of antibodies or some other biomarker that in the study or in a study has been shown, that early fall has been shown to be indicative or highly predictive of parasitologic cure.

I think that is the goal and a real challenge, in addition to with other biomarkers waiting until they actually go negative.

Moving on to targets. There are a number of things to look for. The Ortho test, which is used to screen a good portion of the U.S. blood supply these days, obviously approved by FDA, it's a cut, a size cut of lysates of T. cruzi grown in cultures. It has a broad and undefined mixture of antigen, anything from proteins, glycoproteins, glycolipids, and who knows what else. That is one approach.

Another approach that many others and I have taken is mixtures of single or combined recombinant proteins. Wiener Laboratories in Brazil and in Argentina has a 510K FDA approved --

it's called the Wiener "Chagatest recombinante" -- that has five or six separately produced recombinant antigens, an approach that I and my co-workers took to do the molecular biology up front and make these strings of coding sequences of antigens that are from different places in the genome.

Tests based on the latter is an Abbott Prism Chagas assay, which is used also with Ortho test to screen blood supply. Abbott Architect, and an enzyme strip assay, that also has these recombinant antigens. That is another approach. There are tons of options in which proteins to include.

Then there are whole parasites, and what we are particularly referring to here is there is an assay called "Compliment mediated lysate of whole parasites," living parasites, that identify a group of antibodies called "lytic antibodies." These lytic antibodies persist in people who have persistent infections, but when the infections are cured, then as the supporters of this approach

believe, these lytic antibodies actually disappear. There are people who say things like it is widely accepted that assays that measure lytic antibodies are the best approach for assessing the effect of anti-T. cruzi drugs.

Why don't we just design a trial in which we do this assay, and I think because it, too, belongs to old time parasitology, it's very complicated. I've never done it, but I think you have to radiate mice, make them immunodeficient, and then you infect the mice with parasites from other mice, and then you eventually harvest blood from these mice. I think by centrifugation, separate the parasites from the mouse blood, and then run your assay. It's complicated.

I think certainly in the United States from a regulatory point of view, I think it would be difficult to convince the regulators that this is a good idea to do.

For years I've been chair of the institutional Biosafety Committee at the University of Iowa, and I know my colleagues would

raise their eyebrows thinking about all these potentially lethal parasites being carried around between hoods and to the animal room, stuff like that.

An option is to clone or molecularly clone the protein essence of what the lytic antibodies bind to, and measure those antibodies that way. People are working on that. They have isolated what is called GP- 160, a glycoprotein, from trypomastigotes, I assume, and using that as a target. There are papers out there that have used that natural molecule as a target to measure the level of lytic antibodies.

I think more work needs to be done, and they are trying to clone it in a molecular sense as well.

Lastly, I would say what about all these different approaches looking at both parasite and human biomarkers as indicators of infection status after treatment. I will just finish up with this.

There are all sorts of things that people have been doing with big science these

days, including mass spectrometry, with MALDI- TOF and CELDI-TOF, looking at expression of human biomarkers like APOA-1 and FN1, and the list goes on and on.

If you're interested in this, this is an 18 page paper of which three of our panelists are co-authors, that goes through all of this. I think it is 2014, so it is recent information. I'd say there is a lot going on, but the question is, are any of these approaches ready to go for a new trial?

I will just read what the authors say in the conclusion here of this review, and it is antibodies including all other biomarkers. "There are several marker candidates with which together may fulfill acceptable criteria to indicate the efficacy of trypanocidal treatment. Data from ongoing studies are considered essential to improve assessment of existing markers and to identify those for early follow up of treated patients."

There is a lot going on there but I

think at this moment there is nothing we can grab and order or bring over to the laboratory in the next month or two to help us address this problem. Thank you.

(Applause.)

DR. FARLEY: Thanks, Dr. Kirchhoff. We will now move on to the issue of laboratory monitoring using PCR. We have invited Dr. Alejandro Schijman to do that talk. He's head of the Laboratory of Molecular Biology of Chagas Disease at the Research Institute of Genetic Engineering and Molecular Biology in Buenos Aires.

He has worked in PCR assay development and exploration of biological markers of Chagas Disease. He's the principal investigator for a WHO international collaborative study conducted by expert PCR laboratories from 16 countries to evaluate the performance of PCR methods in the detection of Trypanosoma cruzi DNA by an external quality evaluation.

We are delighted to have you here today. Thanks.

LABORATORY MONITORING USING PCR

DR. SCHIJMAN: Thank you for the opportunity to share our experience and results. I'm going to talk on PCR standardization and validation issues in the context of using PCR as a surrogate marker for monitoring treatment efficacy.

The validation of PCR was recognized as one of the priorities by the WHO, not only for detection and characterization but also as a test of cure.

Since 2007, a series of international meetings were launched to search for a PCR test for monitoring and treatment. Although PCR has been proposed for Chagas Disease since the 1990s, there was a huge variability in sensitivity among the different techniques, so with the aid of PAHO and WHO, we started an international study to search for the most reliable PCR test in all the laboratories with expertise of PCR in the world.

For that, our task was to take into account the new knowledge about the genetic

diversity of PCR because we all know the reasons to explain PCR was so valuable in the different regions could be due to the molecular targets used for PCR, which is related to the genetic variability of T. cruzi, and nowadays, T. cruzi is classified into six discrete typing units, with different geographic distribution.

Any molecular diagnosis should be analyzed in the context of this because the molecular sequences used for diagnosis have different copy numbers and different mutations in the different strains of the parasite.

With this, we started to prepare a blind panel of samples, composed of one panel of DNA purified from strains of different -- a panel of artificial blood samples that were spiked with different quantities of parasites, and a panel of clinical samples from different parts of the world, and we sent these panels on a blind basis to 29 laboratories in the world who wanted to participate in this task. CDC in Atlanta was one of those laboratories that participated in this.

These laboratories sent their results using their own PCR techniques, and we asked them to specify the DNA structure methods, the molecular targets, the names and composition of the primers, and the rest of the protocol of their procedures.

We made a statistical analysis to search for the best methods in terms of specificity and sensitivity, asking them to have a sensitivity enough to detect a chronic Chagas patient, it had to be a very high sensitivity.

This experience was very useful to allow us to discard a lot of sequences of the parasites that nowadays we know they are not useful for molecular diagnosis. Maybe they are useful for typing parasites of different linages but not for molecular diagnosis. There were two sequences that were useful for molecular diagnosis in terms of sensitivity, kDNA and Satellite of the nuclear genome.

Among these sequences and the methods based on these sequences, there were many

laboratories that used the same sequences and the same protocols but the results were not the same. A lot depended on the work of the laboratories.

Another important conclusion of this study was that almost none of the laboratories used internal standards for their PCR. They couldn't discriminate between a real negative result because of inhibition of lots of material during the procedure.

With the advantage of having not only a sequenced parasitic but also for -- based on the best methods, we set up a duplex PCR. From this method, we wrote a standard procedure that is being used now in the clinical trials with new drugs.

In 2011, we made another international study where we transferred this technology to a lot of participants from all over the world who came to Argentina, and they were invited to bring their own clinical samples, samples from chronic and acute patients, and patients infected with different linages, to assess the sensitivity and

specificity and availability of parasitic load in only one laboratory but using the same devices.

Following the international guidelines of the Clinical Laboratory Standard Institute, we made all the experiments to have the parameters of the two methods, with limit of infection, limit of quantification, analytical sensitivity for the different strains, and also exclusivity for microbial -- involved in the same samples of patients with Chagas Disease, like patients with Leishmaniasis.

Provided the good sensitivity and specificity of these methods, we transferred them, and these are now available for everyone, published, to be used in research and in clinical trials.

This is an example of the results. Here you can see the availability of parasitic loads measured by both PCR methods, clinical samples infected with different units, and we can see there is no statistical difference between the measurements used in one or the other PCR method.

Another important issue we found that to perform a good reliable PCR, we must have external control quality standards. We started to provide all the laboratories that wanted to do PCR -- made of different strains with different quantities of parasitic loads, they are composed of seronegative blood infected with cultured parasites, and they have a blind cohort, they are sent to the laboratories, and we asked them to give us the results, and at the same time, we performed our own experiment with the lipids of the same samples.

Here you can see for different laboratories, we prepared panels for one year of work, they have to perform the PCR three months, and you can see although there is difference between the values of PCR using different strains, which is natural, because different strains have different copy numbers of the targets, there is no statistical difference between the mean parasitic loads from one panel to the other panel.

That means that the blood samples that

are taken, they are very stable at least for a year after getting them, and this is important because in some clinical trials that are made in endemic regions, you have a time before collection of the sample and to the laboratory, and the procedure itself.

You can see here different panels, you see the mean values of the parasitic loads are homogeneous, and the differences is due to the multiple strains used, but we know patients are affected by multiple strains, so it is important not to expect results because of this variability.

Another issue is the laboratories that participated in this external control, they were able to look at their result sand to improve them. For example, for the samples with less number of parasites which were close to the limit of the method, they had negative results and then after changing the real time device, for example, making some changes, they could detect them. It's an important means while they are working to improve their results.

At last, I wanted to talk about the application of these PCRs and clinical trials. Work we have been doing in collaboration with MSF-DNDi was to improve clinical sensitivity of the test in chronic patients, in particular, in patients from Bolivia, the parasitic loads are very, very low, these chronic patients have parasitic loads that are about the limit of the threshold of the PCR.

The way to improve sensitivity was to optimize sampling and we tested 10 milliliters or 5 milliliters of blood with a stabilizing agent, taken in the same day, and another one taken seven days after. You know the natural history of the chronic infection, you have peaks and valleys of parasitemia. It depends on the time you get the sample, you could have higher or lower parasitic loads.

Of course, use of three samples improved the clinical sensitivity of the PCR from 87 percent to 91 percent, so for example, for the E1224 trial, DDI, we chose this strategy because

the patients in Cochabamba had very, very low parasitic loads. This must be studied by a pilot, when one chooses a population, it is good to make a pilot study of the parasitic loads in the region.

For example, in Columbia, patients have high parasitic loads. The studies may depend on the region where one is going to do the assay.

In this study, we saw there was no difference between 5 and 10 milliliters in blood taken the same day or seven days later, but there was a difference between taking a positive result for a patient, taking one sample, two samples, or three samples.

This is the results using the same kind of PCR. You can see as Isabela Ribeiro showed you before, the usefulness in the short term of the PCR to show treatment failure, so this is the main usefulness of PCR because in the short term at least you can say the target is not working. If you have a negative chronic patient, you cannot say the patient is cured because you are always

taking a blood sample, so you are evaluating the parasitic load of the last, but not the ones in the tissues, in the target organs, like heart tissues. If the result is positive, you can say that the treatment is failing.

This is another example, looking at the differences using this PCR between placebo, the different arms of E1224.

This shows the parasitic loads of the E1224 study, and you can see the placebo arm. The arms with E1224, depending on the dose, they started to relapse after treatment. The follow up with PCR is also a good tool to monitor.

From this study, we saw there was an increased hazard of relapse with a certain group, and higher PCR baseline, so the parasitic load also can be an indicator of the prognosis at least in this study, the patients that had higher parasitic loads at baseline had higher hazard to relapse after treatment.

That's all. Thank you.

(Applause.)

DR. FARLEY: Thanks very much, appreciate it. That was a great talk. I'm going to rearrange the agenda a little bit, and take open public comments at this point, so they can be considered by the panel during the second part of the panel discussion.

We have one request for formal open public comment, and that is Mr. Frank Sasinowski, representing Mundo Sano.

OPEN PUBLIC COMMENT SESSION

MR. SASINOWSKI: Thank you, Dr. Farley. Frank Sasinowski from Hyman, Phelps & McNamara representing Mundo Sano, which means "healthy world," through our work with the Chemopharmaceutical Group.

Mundo Sano is a non-profit foundation that was started in Argentina in 1993. Its sole mission when it began was to combat Chagas. It has expanded its mission to include all neglected tropical diseases since then, and it has worked with many international coalitions, and in that work, has worked along side the Gates Foundation,

the World Bank, WHO, PAHO and others.

Mundo Sano has two requests for FDA to consider today. First, to consider the use of Subpart (h) for Chagas therapies, and the second to consider recognizing Chagas as a neglected tropical disease.

Mundo Sano believes that we have heard here today many reasons why a therapy for Chagas should be considered under FDA's Subpart (h) program. So, what is Subpart (h)?

It is also known as accelerated approval or fast track, and FDA created it back in the 1980s to respond to the AIDS crisis. It allows the FDA to approve a therapy based on "a surrogate that is reasonably likely to predict" ultimate clinical benefit, but only if the disease is serious, and only if there is an unmet medical need.

I think today we have heard that undoubtedly Chagas is a serious disease and it is indeed an unmet medical need where there is no approved therapy here in the U.S.

Why would a therapy for Chagas be based on a surrogate and not on actual clinical benefit? Mundo Sano thinks that because with Chagas, a study to prove the ultimate clinical benefit improves survival would likely take a decade or longer to run.

A drug therapy could be approved on a surrogate much sooner and allow patients to access treatment through the normal health delivery system rather than through the compassionate use system.

Today, the CDC runs the only such program for Chagas in the U.S., but to get access, a newly diagnosed patient would need to be in the care of a physician who knows Chagas, knows of the CDC program, is willing to invest the time and effort to personally apply for such access.

Also, there is a well-known phenomenon that when the FDA approves the first real drug for a disease, the awareness of the disease among physicians and therefore the number of patients diagnosed expands sometimes dramatically.

Recall when Tagamet was first approved for ulcers, when Prozac was first approved for depression, when Betaseron was first approved for multiple sclerosis. The same could be true with the first therapy FDA approves for Chagas.

How could FDA apply Subpart (h) to Chagas? FDA could rely upon the findings on a surrogate, such as the quantitative PCR test that Dr. Schijman just described in the recently completed Dr. Molina study out of Barcelona. The FDA could look at that kind of surrogate finding as the basis for accelerated approval within a post-approval or phase four study that would confirm the clinical benefit, such as the reduced incidence of sudden death, thromboembolism, and heart failure, which are the leading causes of death in Chagas heart disease, the most serious and frequent manifestation of chronic Chagas.

This use of Subpart (h) would follow many FDA precedents. Since 2010 alone, and just in the anti-infective area, there is Dr. Cox, Dr. Farley, Dr. Nambiar and her colleagues working

just in the area of anti- infective since 2010, the FDA has approved many drugs for HIV and Hepatitis C based upon the results of blood tests for these infections rather than clinical benefit. In December 2012, FDA approved Sirturo to treat MDR TB based on the absence of a pathogen in the sputum coughed up from the lungs.

Mundo Sano asks FDA to consider applying Subpart (h) to Chagas therapies in order to accelerate patient access to a therapy for Chagas. If that is done, it will likely result in expanded physician awareness of Chagas, and then that would lead to many new diagnoses of persons in this country infected and at risk.

Mundo Sano's second request to FDA is to recognize Chagas as a neglected tropical disease. The original 2007 law that created the list of neglected tropical diseases failed to list Chagas. This law also saddled the FDA with such a cumbersome rulemaking system for adding any new disease to the original list that FDA even found it difficult to add Ebola.

In December 2014, Congress and the President changed the law. They added Ebola, and importantly, gave FDA new authority to add diseases without being encumbered by a rulemaking process.

On behalf of all those afflicted with Chagas in this country, both diagnosed and the many more now undiagnosed, Mundo Sano asks the FDA to make Chagas the first disease that FDA adds to the official list of neglected tropical diseases under FDA's new December 2014 authority.

In sum, Mundo Sano asks FDA to use Subpart (h) for Chagas, to recognize Chagas as a neglected tropical disease, and on behalf of Mundo Sano, thank you. Gracias.

(Applause.)

DR. FARLEY: Thanks, Mr. Sasinowski. Just to clarify for the panel, I know he did say that, Subpart (h) that is being referred to is the accelerated approval pathway that Dr. Toerner described in his talk. They are synonymous. That is the subpart that refers to accelerated approval

as a type of approval.

We will move on to the panel discussion, and I will turn it over to Dr. Nambiar.

PANEL DISCUSSION

DR. NAMBIAR: Thank you, John. We have a fair number of questions that we wanted to cover in the second part of our panel discussion, some of them we have already touched upon in the first session.

I just want to see if any of the panel members have any lingering comments regarding either the populations or the acceptable control groups. If not, we can go into these sets of questions.

(No response.)

DR. NAMBIAR: The first question we seek your input on is what are feasible and acceptable clinical trial designs. In Dr. Toerner's presentation, he gave you some options as to the different considerations for a trial to be an adequate and well-controlled trial to meet regulatory requirements. We would welcome

thoughts from the panel members on what might be various trial designs.

Dr. Ribeiro?

DR. RIBEIRO: I think as we discussed before, we have in the case of adults, a placebo concurrent control, which would be acceptable, depending on the time lines for follow up, so 6 to 12 month follow up, I would say that is actually acceptable.

In the case of children, I don't think basically a concurrent placebo design is acceptable, and therefore we are discussing here either the option of actually having a dose comparison concurrent design or an active treatment concurrent design, or alternatively, a historical control.

In terms of the different target populations, those are my views in terms of adequately and well-controlled.

I should mention that for adults, obviously the active therapy concurrent and the dose comparison concurrent designs would also be

acceptable. That's my view.

DR. NAMBIAR: Sergio?

DR. SOSA-ESTANI: I completely agree with the position of Isabela, and would just like to add blinded if possible.

DR. NAMBIAR: Dr. Ribeiro, can I just ask you a clarifying question? You had suggested dose response studies might be an option. I certainly don't know enough. How do you sort of assess what might be potentially useful doses? I think historically we have just used a dose or two and we have gone 60 days. How do you make an assessment of would 30 days be enough, 60 days, and what kinds of doses? Do you base that on animal models or do you have some other way of doing it?

DR. RIBEIRO: That's a great question. We have been dwelling with this at this point, and I think there is no clear -- we don't know yet the duration in animal models that would reflect that. In the animal models, if you look at different durations, you have an increasing response, you

have like you test 5 days, 10 days, two weeks, 40 days. You may see changes.

Obviously, this would depend on the drug and so on. At this point, what we have, right now we are evaluating a design for a Benznidazole trial. We are actually looking at two weeks, four weeks, and eight weeks treatment duration. We are actually following patients, so we have assessment at the end of treatment response and then six months and 12 months, looking at sustained results.

I hope I answered your question.

DR. NAMBIAR: Yes.

DR. RIBEIRO: Now, with the information that we have, in terms of some of the data on quantitative PCR, we are trying to model and trying to develop to actually predict and having model predicted responses. That is actually one of the outcomes that we are going to be looking at particularly for phase two in the future, that we are considering.

DR. NAMBIAR: When you had the results

from your azole trial, were you sort of surprised, or did you have enough prior's before you went into the study, sort of predicting what might be the outcome?

DR. RIBEIRO: There was quite a bit of information that had been generated on Posaconazole in acute and chronic Chagas models. In the case of E1224, we actually had studies also in a model, mostly 20 day model, with immunosuppression, and actually the response with azoles were excellent, but it looks like there is now some additional data that is actually showing that depending on the strain, you might have translation.

For example, there is now data from the CL-Brenner model that one could see one would have failures with this, so now we need to accumulate additional data to really support this will remain translational.

DR. NAMBIAR: Dr. Altcheh?

DR. ALTCHEH: There is no rationale for 60 days of treatment. During several years, we

used 90 days of treatment. Afterwards, we used 60 days. We can use 30 days of treatment. There are some publications of 30 days of treatment. We have to include 30 days of treatment in all the designs for new drugs because there is a lot of evidence that 30 days could be a good time for treatment, maybe less.

The other thing is about doses, nobody knows the doses. We need that. We found that children need lower doses, that we are overdosing for adults, for Benznidazole. We don't have enough information. We will generate new information in a few months.

DR. NAMBIAR: It certainly will help make the safety profile better as well.

DR. SOSA-ESTANI: As Jaime said, there is a lot of information showing 30 day prevents mortality and reduces antibodies. There were several comments regarding therapy at 60 versus 30, five milligrams versus 2.5. These are questions that need to be evaluated.

DR. NAMBIAR: Any other comment?

DR. ALTCHEH: We need better formulation.

DR. NAMBIAR: I don't think you have to convince me on that point. That's easy. If there are no more comments on this question, we can move on to the second question. Again, we have certainly touched upon this already and it came across in the two presentations we had from Dr. Kirchhoff and Dr. Schijman.

The question is what would be an appropriate primary endpoint, and again to consider whether a clinical outcome endpoint is feasible and what are the strengths and weaknesses for that, and certainly the timing of the assessment of this endpoint and how long patients would need to be followed up.

Maybe we can take it a piece at a time, probably have a discussion on what might be the endpoints, talk about a surrogate endpoint based on a microbiologic criterion as well as a clinical outcome endpoint, which I think for the most part we have heard is difficult to do. Maybe after we

have the results from the BENEFIT trial, it may be even harder to do.

I would welcome the panel's thoughts on that.

DR. ALTCHEH: It is hard to respond to the second question because there are literally more important questions. Regarding the clinical, with the primary, if a clinical endpoint is possible, I think we discussed it a lot, at this moment, it maybe always not possible to use.

Regarding the question when should treatment benefit be assessed, I think there are at least at this moment a consensus that during 12 months after treatment is an excellent time, and certainly using PCR and serological tests also looking for reduction.

It is important to consider to assess failure by PCR and success by reduction of antibodies.

Regarding the value of negative PCR, I think that would be very important to be clear that the important result of PCR is the positive

result. Regarding the strength or weakness of serological tests or PCR, personally I think the strength of serological tests is it's more sensitive than PCR in general, and the weakness is the after treatment reduces slowly.

PCR is more specific after treatment, and the weakness is the result doesn't mean a cure.

DR. NAMBIAR: Dr. Ribeiro?

DR. RIBEIRO: I think perhaps that particularly in children, the statement that a negative PCR -- I think a negative PCR should be considered as -- for me, I think it is a cure. In adults, I think the issue of sensitivity of PCR, it's more of an issue, but for example, particularly in children, PCR sensitivity is on the order of 100 percent, and Dr. Altcheh and Alejandro, please correct me, but it is really with pretty good specificity.

I just wanted to ask a question in terms of the first question of what primary endpoint would be appropriate for a clinical trial, to

answer such a question, should we take into consideration for a clinical trial for marketing authorization, for efficacy demonstration, that's the consideration of that question?

DR. NAMBIAR: Yes.

DR. RIBEIRO: From my standpoint, I think it is interesting to think about and I think we did briefly earlier, and I think in that sense the presentation that we had before was on the one hand, are we ready to say PCR, for example, or serology are validated primary efficacy endpoints, and what we will need to consider PCR/reduction of titers across different age groups as a validated primary efficacy endpoint, therefore, one would not need to demonstrate later on clinical benefit, right.

I'm so sorry. I preempted the question. I apologize. The other one is in relation to should it be considered more a surrogate marker that will need subsequent demonstration of clinical benefit. I think today we are moving in a position where I am of the position that indeed

it should be considered for children's response, no doubt, I think we are there, and in the case of adults, I think particularly with the BENEFIT trial results, the correlation between the validation of those outcomes will be there.

DR. NAMBIAR: Yes, Dr. Kirchhoff?

DR. KIRCHHOFF: I'd just like to comment on this serology business, what to do with serology. From the perspective of serology, PCR just looks really kind of simple, one thing, and I realize there are complexities of the strains and things like that.

Having spent some time looking over a lot of these studies relating to serology, I would say evidence that change in serology, seronegative or reduction in titers, so antibodies to what. In terms of recombinant antigens, there are just literally dozens of recombinant antigens that go back really to the late 1980s and then there are hybrid recombinant antigens that are combinations of these, and then native antigens, and like I said, size cuts of separated molecules, and we are

talking about a substitute target for the lytic antibodies that is the protein core of the GP60 in recombinant form or isolating native GP60 from trypomastigotes, a list of 38 targets.

The question is how to sort that out, and one possibility would be to go back and shake everybody's freezers from trials that have been done before where you have specimens for treated patients, but the problem with that is there are no temperature records, they weren't collected in FDA certified context, they have been frozen and thawed an undetermined number of times, so it's a tough and very heterogeneous group to work with, so that's problematic.

At the other end, in a sizable trial, you could just collect lots of specimens and lots of aliquots and take this panel of targets for antibodies and other biomarkers and just do it.

It's going to take four years or five years to do. I don't know what the answer is but I just wanted to respond. Evidence that change in serology.

DR. RIBEIRO: (Off microphone.)

DR. KIRCHHOFF: Yes, maybe the BENEFIT trial. I don't know how much serology they have.

DR. SOSA-ESTANI: The difference between the situation during clinical trial in comparison with point of care. Certainly, for point of care, PCR is the more practical to demonstrate in a short time benefit of treatment, showing there is not failure. In our experience, seeing a patient with higher titer and low titer, all are clearly reactive, their reduction is the same during the first 12 months.

Talking about this topic, it is interesting, your position, but maybe can exclude some patients to be included in a clinical trial showing a benefit, even if the titer is low, the reduction would be the same in comparison with patients with higher titers. There is at least three papers or trials showing the significant reduction during the first 12 to 24 months after treatment.

Personally, I think PCR may be strong

evidence of effect after treatment, the combination of serological test showing a reduction, a combination to show failure and success at the same time.

DR. NAMBIAR: Dr. Kirchhoff, is it hard to sort of standardize it, can we say to enter the trial, you have to be positive on, and you specify the test, then you monitor that same test as an assessment of response, is that an option? Can that be done in a clinical trial setting or that's not an option?

DR. KIRCHHOFF: Yes, I think you would certainly want to do that, but the question, like I said, we have very good serologic tests for detecting people pre-treatment or blood donors, but the problem I see is those targets may not be the best targets for being able to say something about cure before they get negative or like is alleged for the lytic antibodies, they would go negative faster. They may not be the right ones.

Just hypothetically, if we want to say well, let's go with lytic antibodies, let's say

magically we could come up with enough native GP60 to supply that need. We would want to use that for follow up, but I think we wouldn't want to use it for qualification because the FDA hasn't looked at it. They don't know anything about it. I would worry about false negatives and false positives, using something like that that is not carefully tested.

I was thinking as Sergio was talking, what are the barriers to doing this grand analysis, with all the different biomarkers and everything like that. The real one is the samples, getting the samples, and getting them organized and into a place where you could run a lot of them quickly.

Another barrier is getting the antigens, the recombinant proteins. They are around and some are even available commercially, you can kind of do that, maybe not all of them. I don't think that is a major problem. Beyond that, you just need money to have three or four people in a lab for 6 or 12 months to run this.

Running the test is not the problem. I've done hundreds of ELISA plates, and I've never used an automated system. If someone bought me an automated system, everything could have gone a lot faster.

I think the real thing is the samples, getting the samples, good samples that haven't been frozen and thawed 50 times, and the ink on the labels hasn't smeared, and there is more than 30 microliters and stuff like that. That's the real challenge.

DR. ALTCHEH: We have to remember that serology is a surrogate of parasitemia. If we have a very good test of parasitemia like PCR, we have to use PCR. If we are using something that is not -- it takes several years to demonstrate -- that never was set up for chronic patients, never talked about that, this is new information.

On the other hand, all the serological tests were set up for diagnosis, not for follow up of the patients. We have some problems when we have to follow up on patients. We have a very

good test and that is PCR.

DR. KIRCHHOFF: I don't think anyone is proposing using serology and not PCR or PCR and not serology. I think in the end, all of the above, more information is better. I think the panel kind of agrees with that.

DR. FARLEY: Speaking of PCR, here's a question for the panel. I'm noticing quantitative PCR being used in the CHAGASAZOL study, the E1224 trial, and then in the BENEFIT trial. Those first two trials, although they may have failed, they actually seemed to have very important data, particularly around Benznidazole.

The question is is it the same assay being used in all three trials. We have also been joined by Kathleen Whitaker from Center for Devices here at the FDA, and if she has any comments, I would invite her to join in the discussion.

I guess the first question is is it the same assay being used in all three trials?

DR. SCHIJMAN: Actually, the same assay

was used in CHAGASAZOL, E1224, and I think in BENEFIT, they started with another assay, and I think they changed because the study started before -- yes.

DR. ALLENDE: The number of samples, you said in one study you took one sample and the other three, number of blood samples for PCR.

DR. RIBEIRO: Yes, that's an important difference. In the E1224 trial, we did three samples at each point. In the Molina trial, the CHAGASAZOL was one, and we did three samples in triplicates. I think that is part of the reason why they have six percent failure and we have 20 percent failures identified, for example, in the Benznidazole arm.

That might be related to the number of samples, the number of triplicates. STOP- CHAGAS actually did three samples, I believe. BENEFIT did a single sample.

This again was before we had the results of the analysis and evaluation.

DR. SOSA-ESTANI: In STOP-CHAGAS, it was a single sample also. There is a consensus today to use in all new trials, in fact, we are performing some clinical studies, use the validated combination of techniques, and it is very extended, the research team are accepting this protocol to perform PCR to assess treatment in a clinical trial.

DR. FARLEY: That protocol may answer my next question, if you had your life to live over again, how would you design a trial incorporating quantitative PCR? It sounds like you all have thought that through and have some recommendations. Is that published for sponsors, that they could access that?

DR. RIBEIRO: We have been discussing that. I think we have published the results, and I think there is a publication. There was an abstract -- there was a communication on the use of PCR as a marker. There were two -- go ahead.

DR. ALTCHEH: We used two milliliters on the four children. This is another point we have

to discuss, volume of blood. We are using one milliliter for newborns and two milliliters for children younger than five years, with very good sensitivity.

DR. RIBEIRO: The paper on the MSF trial that compares 5 versus 10 for adults and one versus two versus three samples, it should be published this year. That will be coming out soon.

I wanted to go to the question on trial designs. On the weakness and strength and what is the evidence on change in serology, negative PCR or other lab test would actually be predictive of a later clinical outcome. This is actually the issue today, right?

I think from the Viotti data, we actually have the serological response being described, in terms of seroconversion, and then you have the clinical outcomes, but that evaluation is not done.

I think we are hoping that we are going to have the data from the BENEFIT trials, that we

will be able to see that and perhaps from TRAENA, but I think when you look at negative PCR and clinical outcome, one example that comes to mind for me is one of immunocompromised patients. That's a clinical outcome. You actually have patients that have a positive exam and then they have lesions and then they respond.

It is a somewhat different scenario because it is not chronic Chagas in a sense, but it is a relationship between that exam and a clinical response.

DR. MEYMANDI: That's actually excellent.

DR. RIBEIRO: I think it is important to remember those and also in acute Chagas, you could make those correlations in terms of symptomatology and so on.

Those examples, I think, just to keep in mind. I think serology and reduction in titers and the prediction of clinical outcome, it should be said openly that in the two placebo controlled trials that were done, neither of them actually

evaluated clinical benefits. These were trials that actually evaluated the response.

Unfortunately, for most of those we don't have today yet the proof of later clinical outcome.

DR. BERN: Just related to Viotti, the data are scarce because very few people actually reverted to negative serology, but there was a significant association with reverting to negative serology and not having progression.

I can show you the paragraph, the p was 0.009, and the hazard ratio for those who remained sero positive in three tests over the course of the follow up, the hazard ratio was 4.9 for progressing.

DR. FARLEY: Do we know if the source data from Viotti exists?

DR. BERN: Yes.

DR. FARLEY: Okay, that's good.

DR. WHITAKER: If I could just take a quick step back for John's question. A lot of these PCR assays, we haven't necessarily seen, but

one thing I just wanted everybody to keep in mind, the type of assay used -- if you are looking at an FDA approved assay, our assays are very different whether we are considering blood screening or diagnostic. They have completely different performance. They have completely different -- the studies we use. Obviously, a blood screening is just going to be 99.9 percent negative people.

We actively go out when we look at a diagnostic for Chagas, whether it is serology or PCR, we actively look at chronic patients, we actively look at acute, try to find acute patients. We do find the results are going to be very different if you're going to utilize a "blood screening test" versus a diagnostic.

It is a little thing that people don't necessarily think of, but it is surprising how different the results can be when you look at that.

DR. SUZART-WOISCHNIK: In the previous session about lost to follow up, the question is about reduction, so a patient that has been

treated and you have an observed reduction in serologic levels and days of lost follow up, the question is is this a patient with failure or not, and is there a way for us to predict, to continue to observe a curve.

This is a practical question that we discussed this morning because we might not be able to follow these patients. Counting these patients as failures will be jeopardizing the results unduly because there is the possibility they are getting better. I would like to know what the FDA thinks about it. Thanks.

DR. NAMBIAR: I don't know the specific answer but in general we see minimized lost to follow up because that is what we like, once you lost patients to follow up, it certainly affects the interpretation of the results. I agree, if you classify all of them as failures, you are doing anyone a favor.

I think there is a whole publication on how to handle lost to follow up, and I think the best advice is to minimize. There was a report

not too long ago on missing data and how to handle it. I think our advice always is to minimize it as best you can, and it looks like some people have been successful, so there may be some lessons learned from other trials that have been done. This is certainly an issue with diseases of this nature because of the kinds of people and the areas of the world.

Typically, in terms of the statistical analysis, it should all be laid out up front how you are going to handle missing data. I don't think there is a straight answer to the question but we are aware of the situation, minimized lost follow up, but clearly specify up front how you plan to handle it. Joe?

DR. TOERNER: Just to add that an early time point for establishing treatment success or treatment failure will certainly help to minimize lost to follow up, and I think that is partly why we are persevering on questions about PCR as an endpoint because it would certainly help to minimize lost follow up.

DR. SOSA-ESTANI: There is a correlation between the reduction of antibodies and the clinical benefit in studies in Argentina, at least three studies showing that.

In addition, I think personally PCR and the current protocol is robust to show benefit after treatment, but there is some new information like we are talking about reduction of antibodies, the reduction of parasitic load is new information also demonstrated during the first day after treatment and the effect during follow up.

Other information is the parasitic load was demonstrated that there is a higher risk for congenital transmission. The effect of treatment is not necessary to become negative or absolutely cured. The effect of reduction of parasitic load is a clear benefit.

DR. NAMBIAR: I just want to make sure I understand this clearly, on the presentation that Dr. Schijman made, improvements in the PCR, you have factored in the variability between the different species. That is hopefully not an issue

with the current methodology that you are proposing.

DR. RIBEIRO: Yes, we took into consideration, so we have described it. This is well-characterized in terms of safe performance, and for the clinical trials, that was actually taken into consideration.

Perhaps I should just add one comment, something that we have done and we have not described, just a matter of detail. We actually did genotyping of all baseline samples. We actually did RFLP, we also did sequencing of baseline samples, and we also did it for all treatment relapses, actually trying to characterize the population and selection. We did that.

We actually did hemocultures in all the treatment failures also, looking for really a broader characterization there. In terms of other assays, we actually did besides the lytic serology, conventional serology, we did lytic antibodies. We did the APOA 1. We have that for

all time points. We actually have those frozen samples. They were all saved at once, because that was the recommendations that we received.

I know for some of the trials presented this morning, this is all available and could be reviewed. There will be samples also to be analyzed.

DR. WHITAKER: When you are looking at the PCR assays and you are validating them, do we have a substantial population or cross section of everybody or have they been mainly validated in either pre-treatment or chronic?

DR. SCHIJMAN: Could you repeat that?

DR. WHITAKER: I was just wondering when we are talking about accurate validation, when they have been validated, is it primarily in pre-treatment or do we have a nice equivalent section of children, pre-treatment, chronic, acute?

DR. SCHIJMAN: We used artificial samples that are spiked with known titers of parasites. If the analysis has a good sensitivity, then we proceed with blind clinical

samples. In the first international study, we worked with chronic Chagas Disease patients.

It was no more than 70 percent of the time, the best techniques, one sample per patient, gave no more than 70 percent of sensitivity. Afterward, with the strategy we used for the E1224 study, using three samples per patient, we got the sensitivity to 90 percent.

DR. WHITAKER: Three samples being three separate blood draws? Three separate PCRs?

DR. SCHIJMAN: Yes. There were three samples, and then we performed the PCR by duplicating each one of the samples, and if the sample was negative, we performed a third PCR, and with that we could enhance sensitivity 10 percent.

If the patient had at least one PCR result, it was considered positive and was included in the trial.

I'm talking only about this study because as I mentioned, this population has very, very low parasitic loads.

DR. RIBEIRO: Perhaps to go back to the

question, if there is data across different populations and disease stages, I think basically there is quite a bit of data generated for sure before and after treatment in chronic Chagas, as indicated by Dr. Schijman.

There is also data in children using the same technique, different volume, and there is data also in transplant patients. I think there is data also from the foodborne using the same technique, in my understanding.

The issue with the oral is because it actually becomes so concentrated that there is a need for dilution, as I understand; right?

DR. SCHIJMAN: Yes.

DR. RIBEIRO: It inhibits.

DR. SCHIJMAN: We had to dilute it, same when you analyze for HIV with very high parasitic loads.

DR. RIBEIRO: Clearly, this needs to be presented in such a way that this is altogether, right, as a package, as I understand it, as a device, and treated as such. I understand the

question from that angle.

I think perhaps it is worth noting today that there is an effort from the Ministry of Health in Argentina and a funded project for the development of a kit, PCR kit. The initial focus is for congenital Chagas, and there are now discussions on validating -- it is actually in this kit for adult Chagas. This is also under discussion.

DR. SOSA-ESTANI: Yes, we are including at this moment the use of PCR in three specific situations, for acute phase, congenital infection during the first three months, if possible, of diagnosis, during treatment, and monitoring for activation in patients with immunocompromise.

DR. NAMBIAR: We certainly commend you for all the work you have done. It is the ability to look at all this information, get all the details ironed out before we can actually make a final decision, but we certainly congratulate you for all the work you have done over the years, it is great.

Are there any other comments or questions from the panel members before I turn it over to Dr. Farley? I think we are getting close to wrapping up this interesting day.

(No response.)

DR. NAMBIAR: Seeing none, I turn it over to you, John.

CLOSING REMARKS AND ADJOURN

DR. FARLEY: I know a lot of you have traveled quite some distance to be here, and I want to assure you that it was worth it. This has been a very useful day for all of us. I think we in the office here particularly like these workshops because it is a rare opportunity to get all the right people in the same room at the same time actually talking to each other. That tends to advance drug development.

We have heard loud and clear from our patients this morning that one of their big needs in the United States is having treatment options available, and more readily available than they currently are.

I want to thank everyone. I want to remind you that if there was something you didn't get to say today, there is an open docket that was made known to you this morning. That is available for your comments.

I think this is the start of some dialogues that are going to continue. For drug developers, as you know, the Division is available for meetings under the guidelines set forth under the Prescription Drug User Fee Act, and that happens very often, so just a reminder.

I want to wish everyone safe travels, and thank you very much for your time today. It was a great meeting.

(Applause.)

DR. MEYMANDI: If I could just reiterate again that I'm hoping this is just not dialogue, that we come up with concrete plans to move forward in a rapid fashion so we can get access to these drugs. Thank you.

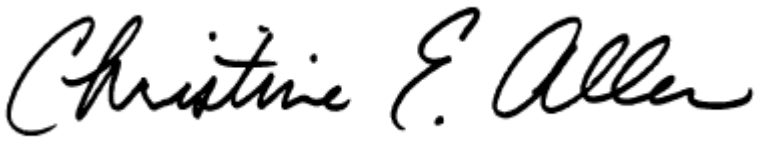
(Applause.)

(Whereupon, at 4:57 p.m., the meeting

was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, CHRISTINE ALLEN, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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