

Capital Reporting Company
Chagas Disease Public Meeting 04-28-2015

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FOOD AND DRUG ADMINISTRATION

CHAGAS DISEASE PUBLIC MEETING

ON

PATIENT-FOCUSED DRUG DEVELOPMENT

Tuesday,

April 28, 2015

White Oak Campus

10903 New Hampshire Ave,

Silver Spring, MD

Reported by: Christine Allen,
Capital Reporting Company

(866) 448 - DEPO

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1 A P P E A R A N C E S

2 EXTERNAL PANELISTS:

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4 Service Hospital de Ninos Ricardo Gutierrez,
Buenos Aires, Argentina

5 CARYN BERN, M.D., Professor, Epidemiology and
6 Biostatistics, University of California, San
Francisco

7 DANONG CHEN, Ph.D., Chief Executive Officer
8 MetronomX Therapeutics LLC

9 BARBARA HERWALDT, M.D., Medical
10 Epidemiologist, Division of Parasitic
Diseases, U.S. Centers for Disease Control
and Prevention

11 LOUIS KIRCHHOFF, M.D., Professor, Internal
12 Medicine and Infectious Diseases, University
of Iowa Carver College of Medicine

13 RACHEL MARCUS, M.D., Cardiologist
14 Washington Hospital Center

15 SHEBA MEYMANDI, M.D., Cardiologist, Director,
16 Center of Excellence for the Diagnosis and
Treatment of Chagas Disease, Olive View UCLA
Medical Center

17 ISABELA RIBEIRO, M.D., Head, Chagas Clinical
18 Program, Drugs for Neglected Diseases
Initiative, Geneva, Switzerland

19 ALEJANDRO SCHIJMAN, Ph.D.
20 Laboratory of Molecular Biology of Chagas
Disease, Research Institute of Genetic
21 Engineering and Molecular Biology, Dr. Hector
N. Torres, Buenos Aires, Argentina

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1 A P P E A R A N C E S (continued)

2 SERGIO SOSA-ESTANI, M.D., Director, National
3 Institute of Parasitology, Buenos Aires,
Argentina

4 KILLANA SUZART-WOLSCHNIK, M.D.
5 Senior Epidemiologist, Bayer Healthcare

6 FDA PANELISTS:

7 MARIA ALLENDE, M.D., Medical Officer
8 Division of Anti-Infective Products
9 Center for Drug Evaluation and Research

10 JONCA BULL, M.D., Director, Office of
11 Minority Health, Office of the Commissioner

12 EDWARD COX, M.D., Director, Office of Anti-
13 Microbial Products, Center for Drug
14 Evaluation and Research

15 JOHN FARLEY, M.D., Deputy Director, Office of
16 Anti-Microbial Products, Center for Drug
17 Evaluation and Research

18 SOUJANYA GIAMBONE, MBA, Center for Drug
19 Evaluation and Research, Office of Strategic
20 Programs

21 JONATHON GOLDSMITH, M.D., Acting Associate
22 Director, Rare Disease Program, Office of
New Drugs, Center for Drug Evaluation and
Research

THERESA MULLIN, Ph.D., Director
Office of Strategic Programs, Center for
Drug Evaluation and Research

SUMATHI NAMBIAR, M.D., Director
Division of Anti-Infective Products
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1 A P P E A R A N C E S (continued)

2 THOMAS SMITH, M.D., Medical Team Leader
3 Division of Anti-Infective Products
4 Center for Drug Evaluation and Research

4 JOSEPH TOERNER, M.D., Deputy Director for
5 Safety, Division of Anti-Infective Products
6 Center for Drug Evaluation and Research

6 KATHLEEN WHITAKER, Ph.D., Senior Scientific
7 Reviewer, Division of Microbiology Devices
8 Center for Devices and Radiological Health

8 PATIENT PANELISTS:

9 MARIA ABRIGO (via telephone)

10 MAIRA GUTIERREZ, Patient

11 CANDACE STARK, Patient

12 CARLOS TOBA BEZA, Patient

13 ALSO PRESENT:

14 JEANETTE HIGGINS, Interpreter

15 SARA EGGERS,
16 Office of Strategic Programs, CDER

17 GRAHAM THOMPSON,
18 Office of Strategic Programs, CDER

18 PUJITA VAIDYA,
19 Office of Strategic Programs, CDER

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1 P R O C E E D I N G S

2 (9:00 a.m.)

3 WELCOME AND INTRODUCTIONS

4 MS. GIAMBONE: Good morning, everyone.

5 We will go ahead and get started. My name is
6 Soujanya Giambone. I am with the FDA's Center for
7 Drug Evaluation and Research, Office of Strategic
8 Programs.

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

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

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

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

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

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

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

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

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

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

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

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1 meeting.

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

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

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

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

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

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

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

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

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

22 DR. ALLENDE: Good morning. I'm Maria

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

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

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

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

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

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

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

22 DR. EGGERS: I'm Sara Eggers in the

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1 Office of Strategic Programs here in CDER, FDA.

2 MR. THOMPSON: Graham Thompson, same
3 office.

4 DR. VAIDYA: Pujita Vaidya, same office.

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

8 OPENING REMARKS

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

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

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

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1 meeting.

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

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

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

22 The benefit/risk decision making is an

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

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

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

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

22 This afternoon we are going to have an

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

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

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

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

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

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

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

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

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

7 DR. ALLENDE: (Translating in Spanish.)

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

14 OVERVIEW OF FDA'S PATIENT-FOCUSED
15 DRUG DEVELOPMENT INITIATIVE

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

22 As Dr. Farley mentioned, FDA is

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

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

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

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

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

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

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

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

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

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

7 That's the rationale for this. What we
8 agreed to do in this reauthorized user fee
9 program, which is a five year program that will
10 sunset in 2017 and we will look to renew, is we
11 will conduct at least 20 meetings, each in a
12 different disease area, to try to do this kind of
13 systematic collection of information. Chagas is
14 one of the diseases we are looking at, one of the
15 20.

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

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1 more to go.

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

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

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

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

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

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

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

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

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

8 OVERVIEW OF CHAGAS DISEASE AND AVAILABLE
9 TREATMENT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Chagas Disease with migration in the

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

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

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

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

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

3 Years later, about a third of them, 1 in
4 3, approximately, may develop the chronic phase,
5 which is characterized by heart failure, an
6 enlarged heart not pumping blood well, causing
7 difficulty breathing and leg swelling, irregular
8 heart beats that can cause sudden death, and risk
9 of stroke. Less commonly, problems with digestion
10 and bowel movements.

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

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

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

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

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

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

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1 signs of infection, usually cardiac drugs and
2 pacemakers.

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

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

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

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

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

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

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1 frequent cause of suspension or interruption.

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

9 In this slide, I want to make a summary
10 of all the things I have just talked about.

11 Chagas Disease is a disease that can be
12 transmitted from mother to child, congenitally,
13 even through more than one generation. It is also
14 transmitted through blood transfusion and organ
15 transplants.

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

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

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

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

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

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

20 Thank you all.

21 (Applause.)

22 OVERVIEW OF DISCUSSION FORMAT

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

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

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

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

22 We will then move on to Topic 2, which

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

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

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

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

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

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

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

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

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

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

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

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1 docket, you can find the website right here on
2 this slide, and it is going to be open until June
3 29, so two months from now.

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

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

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

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

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1 encourage you to reach out to them for additional
2 information.

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

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

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

22 Anything again outside the scope of

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

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

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

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

22 PANEL #1 COMMENTS AND DISCUSSION ON TOPIC 1

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

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

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

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

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

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

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

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

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

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

18 (Laughter.)

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

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

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

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

15 I guess really that's about it for me.

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

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

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1 for me to get a letter from the Red Cross.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 (Laughter.)

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

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

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

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

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

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

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

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

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

22 If I could be your guinea pig for you to

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

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

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

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

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

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1 Rachel?

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

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

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

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1 more interesting than what I have to say.

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

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

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

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1 200,000 immigrants from Bolivia, which as everyone
2 here knows is a country that is extremely stricken
3 by this illness.

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

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

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

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

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

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

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

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

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

17 MS. GIAMBONE: Thank you, Rachel.
18 Carlos?

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

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

6 I began with various symptoms. I didn't
7 have an appetite, being dizzy. I came here in
8 2011 to this country. I had vomiting, I was
9 dizzy. I didn't go to the doctor because I didn't
10 have insurance. I went back to El Salvador. I
11 got worse while I was there.

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

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

22 I worked there, talking about it, but I

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

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

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

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

21 MR. THOMPSON: She has not called in
22 yet.

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1 DR. MEYMANDI: (Off microphone.)

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

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

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

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

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

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1 temporizing measure while he is on the heart
2 transplant list.

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

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

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

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

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

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

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

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

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

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

3 MS. GIAMBONE: Thank you, Carlos.

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

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

10 (Applause.)

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

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

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

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

4 (Show of hands.)

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

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

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

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

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

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

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

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

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

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

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

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

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1 MS. GIAMBONE: Yes; absolutely.

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

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

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

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

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

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

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

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

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

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

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

22 Our non-profit just received final IRS

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

4 DR. COX: Congratulations.

5 DR. MARCUS: Thank you.

6 MS. GIAMBONE: Thank you, Rachel.

7 Theresa?

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

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

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

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1 is just not going to be everybody.

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

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

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

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

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1 for eight years, and Maira is mine.

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

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

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

22 We do not want to wait for symptoms.

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

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

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

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

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

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

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

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

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

22 As a matter of fact, just because no one

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

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

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

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

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

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

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

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

16 MR. THOMPSON: Just one comment on the
17 web from Cecilia from Argentina, who said her
18 father was treated for Chagas between the age of
19 18 and 78, but for a large part of that, it was
20 misdiagnosed as congenital cardiomyopathy. She
21 said he suffered a stroke, myocardial infarctions
22 and dysrhythmia until he was prescribed with a

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1 pacemaker later on.

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

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

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

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

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1 worry about that, you don't need treatment.

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

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

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

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

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

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1 clinically? Do you also do any kind of testing?

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

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

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

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

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

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

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

18 SPEAKER: Bolivia as well.

19 MS. GIAMBONE: Thank you, Dr. Meymandi.

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

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

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

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

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

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

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

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

6 (Recess.)

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

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

20 MS. HIGGINS: (Speaking in Spanish.)

21 MS. GIAMBONE: Thank you, Jeanette.

22 Also, a call out to those of you on the web that

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

6 MS. HIGGINS: (Speaking in Spanish.)

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

16 PANEL #2 COMMENTS AND DISCUSSION ON TOPIC 2

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 MS. GIAMBONE: Thank you, Candace.
18 Maira?

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

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

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

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

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

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

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

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

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

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

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

14 MS. GUTIERREZ: Like I said, I was
15 really lucky. I had one side effect, I lost about
16 25 pounds in two months, but I was really happy
17 that I lost 25 pounds.

18 (Laughter.)

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

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

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

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

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

18 DR. MEYMANDI: You had intracardiac
19 electrophysiology.

20 MS. GUTIERREZ: EP?

21 DR. MEYMANDI: EPS.

22 MS. GUTIERREZ: EPS. I had my first one

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

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

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

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

14 MS. GIAMBORN: Carlos?

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

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

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

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

12 MS. GIAMBONE: Rachel?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. ABRIGO: (Interpreted.) Sirolimus

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

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

7 DR. MARCUS: She did.

8 MS. ABRIGO: (Interpreted.) Yes, in
9 2014.

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

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

20 (Applause.)

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

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

11 MS. GIAMBONE: Okay. Thank you,
12 Jonathon.

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

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

22 If they went back a second time to

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

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

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

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

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

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

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

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

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

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

22 DR. MARCUS: The AABB doesn't report to

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1 any organization. They just have published their
2 data recently.

3 MS. GIAMBONE: Thank you.

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

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

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

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

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

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1 notifiable condition, but relatively few
2 conditions are.

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

9 MS. GIAMBONE: Thank you, Barbara.
10 Joseph?

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

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

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1 it's far from perfect.

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

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

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

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1 MS. GIAMBONE: Thank you, Rachel.

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

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

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

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

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

11 MS. GIAMBONE: Thank you.

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

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

22 I'm sitting on the table here with Dr.

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

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

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

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1 treatment response.

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

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

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

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1 day ideally.

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

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

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

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

10 DR. ALTCHER: Hello. My name is Jaime
11 Altcher from Buenos Aires Children's Hospital. We
12 have to see that Chagas Disease is an infectious
13 disease, it is not a cardiac disease. We are
14 talking about sequelae. We have to talk more
15 about infectious disease and less about cardiac
16 disease.

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

20 DR. MEYMANDI: Absolutely agree.

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

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

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

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

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

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1 horrific reaction to it that we just can't use it.

2 So, we need both drugs.

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

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

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

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1 pediatricians, and we have started that.

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

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

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

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

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

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1 (No response.)

2 MS. GIAMBONE: Jonca?

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

7 DR. SOSA-ESTANI: Every child detected
8 with infection in Argentina is treated
9 systematically. The dose, we have two kinds of
10 pills in Argentina now, pill with 100 milligrams
11 and a pill with 50 milligrams. That is a greater
12 opportunity to offer a safer treatment regarding
13 those, and the general dose in children is between
14 5 to 10 milligrams per kilogram per day.

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

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

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

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

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

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

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

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

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

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

18 MS. STARK: Well, thank you.

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

22 The side effects you just read about,

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

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

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

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

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

22 Like I mentioned my kids luckily were

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

6 MS. GIAMBONE: Thank you, Maira. Carlos?

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

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

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

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1 you.

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

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

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

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

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

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

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

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

14 MS. GIAMBONE: Thank you, Dr. Meymandi.

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

22 In our experience, the unique situation

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

7 MS. GIAMBONE: Yes, Maria?

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

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

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

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

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

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

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

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1 they get sent to me.

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

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

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

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

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

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

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

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

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

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

9 MS. GIAMBONE: Thank you, Dr. Meymandi.

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

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

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

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

21 MS. GIAMBONE: Thank you.

22 MR. THOMPSON: We have one comment,

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

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

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

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

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

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

2 (1:03 p.m.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. SUZART-WOISCHNIK: I am Kiliana

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

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

5 DR. ALTCHER: Sorry. My name is Jaime
6 Altcher. I am Chief of Parasitology Services at
7 Buenos Aires Children's Hospital.

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

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

18 She has also published comprehensive
19 reviews of the disease in both NEJM and JAMA.

20 Caryn, we are delighted to have you here today.

21 Thanks.

22 THE EPIDEMIOLOGY AND NATURAL HISTORY

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1 OF CHAGAS DISEASE

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

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

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

22 I want to remind all of us that Chagas

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 An extrapolation from a study of 16
18 blood donors who were apparently infected in the
19 United States suggests the prevalence of one in
20 350,000 donors. That is compared to somewhere
21 between one in 5,000 and one in 10,000 donors from
22 Latin America.

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

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

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

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1 those are probably never diagnosed as being from
2 Chagas Disease.

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

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

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

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

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

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

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

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

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1 based assays, have extremely high sensitivity.

2 This is a very good tool in the acute phase.

3 Congenital T. cruzi, this is an acute

4 infection, but an acute infection in a neonate.

5 If you look at meta-analyses of studies of cohorts

6 of infected women, you find that a median of about

7 six percent of infants who are born to infected

8 women will be infected themselves, but like Chagas

9 Disease in general, most of these are mild or

10 asymptomatic.

11 Most of the babies we see in Bolivia are

12 actually asymptomatic. Rarely, you can have a

13 severe acute phase in a baby and mortality from

14 this is high, but we don't see this very much.

15 What that means is babies need to be

16 screened. First, you need to know the mother is

17 infected, and then once you know the mother is

18 infected, the baby needs to be screened. It is

19 actually not trivial to screen the baby because

20 the test that is usually used in Latin America,

21 what we call the "micro method" or "micro

22 hematocrit method," is microscopy of a

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

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

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

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

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1 months when the maternal IgG has disappeared.

2 This is a difficult screening program.

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

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

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

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

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

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

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

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

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1 that in a minute.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 congestive heart failure.

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

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

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

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

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

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

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

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

22 For liver, it seems to be around 20

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

6 Recommendations that were published in
7 2011 based on these data recommend that kidneys
8 and livers from infected donors can be used,
9 preferably with the knowledge that they are coming
10 from an infected donor, and that presumptive
11 treatment is not recommended, that what is
12 recommended is serial monitoring with PCR, and
13 this is pretty much always done with CDC, which
14 can provide that PCR monitoring, and then a lot of
15 advice over the course of the monitoring of the
16 patient.

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

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

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

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

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

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

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1 reactivation.

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

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

17 This is the first one that came out in
18 2006 from Rodolfo Viotti in Argentina. This was a
19 clinical trial but it was not randomized, and it
20 was not blinded. People knew whether or not they
21 were treated as did their physicians, and they
22 were systematically assigned to treatment or no

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1 treatment.

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

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

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

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1 very impressive.

2 So, 12 of 283 or four percent of those
3 who were treated had progression to a higher
4 Kuschnir class, so that meant they either went
5 from having no signs and symptoms to having an
6 abnormal EKG, or went from having only an abnormal
7 EKG to having signs of cardiac insufficiency, and
8 death was also one of the outcomes, versus 40 of
9 283 or 14 percent of those who were untreated, and
10 this gave an adjusted hazard ratio, adjusted for
11 ejection fraction, that was highly significant.

12 Essentially, if you look at that hazard
13 ratio, what it means is that the treated group had
14 75 percent less progression than the untreated
15 group.

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

22 If you look at the untreated group,

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1 seven percent of those who were indeterminate at
2 baseline progressed to one of the higher classes,
3 but of those who already had EKG changes, it was
4 19 percent, and those of already had signs of
5 cardiac insufficiency, it was 46 percent.

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

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

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

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

7 This study, to me, is a very impressive
8 demonstration, even though it's not a clinical
9 trial, it's a retrospective analysis. There were
10 132 mother/child pairs that were treated versus
11 222 mother/child pairs where the mother was not
12 treated.

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

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

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1 just talked about.

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

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

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

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

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

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

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

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

9 REVIEW CONSIDERATIONS FOR NEW DRUGS IN THE
10 UNITED STATES

11 DR. TOERNER: Thanks, John. In the next
12 10 minutes or so, I'll try to lay the groundwork
13 for what FDA has under consideration when we
14 review new drugs. My talk will cover adequate and
15 well-controlled trials. We will talk about
16 endpoints, and then examples of regulatory
17 approvals.

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

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1 of disease, improvement in symptoms.

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

6 Our statutory guidelines direct us that
7 new drugs for approval must meet the standards for
8 effectiveness and safety. This comes from Section
9 505(d) of our Food, Drug and Cosmetic Act, and the
10 Act was amended in the 1990s to include Section
11 115(a). The Act talks in plural. It talks about
12 trials, plural.

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

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

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

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

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

22 The fourth type of trial design is

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

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

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

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

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

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

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

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

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1 to this Federal Register in a moment.

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

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

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

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

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1 clinician's observation and interpretation.

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

5 An example in the antibacterial world is
6 the reduction in the size of a skin lesion in a
7 patient who has a skin infection. Within a couple
8 of days, the reduction is observed by at least a
9 20 percent reduction.

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

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

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

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

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

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

20 The accelerated approval endpoint in
21 1992, that regulation, was meant to address
22 chronic disease conditions for which therapeutic

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 RECENT, ONGOING, AND PLANNED CLINICAL TRIALS

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1 FOR CHAGAS DISEASE

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

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

15 We have two drugs available, Nifurtimox
16 and Benznidazole, but both of these drugs were
17 actually developed and registered in the 1960s and
18 1970s. Those registrations were based on small
19 case patient series, small trials, actually with
20 data that was generated at a time when you had a
21 number of acute cases also. It's important to
22 consider the timing and the period in which

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1 registration was granted for both of these
2 compounds.

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

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

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

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

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1 observational study from Voitti actually assessing
2 Benznidazole for treatment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 particular.

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

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

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

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

7 These were patients with Chagas, adults,
8 Chagas in the indeterminate phase, they were
9 actually patients with chronic Chagas Disease.
10 Some patients actually had heart disease.

11 Basically, this was randomized, and you had 80 to
12 90 percent of patients randomized with Posaconazol
13 failing treatment at 12 months, and actually six
14 percent of Benznidazole treated actually failed at
15 12 months.

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

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1 that were seen with Posaconazol.

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

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

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

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

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

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

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

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

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

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

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

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

7 What was very interesting on these
8 studies was that actually in both, you had 100
9 percent PCR negative at end of treatment, but when
10 one looks across the blood levels, the blood
11 concentrations, the Benznidazole concentrations in
12 kids, the lower the age group, the lower the blood
13 levels, and when you have patients that are 7 to
14 12 years of age, there was really no significant
15 difference in drug concentrations from adults, but
16 actually kids below seven years of age have a
17 significant difference from adults, but they still
18 have 100 percent PCR response at end of treatment.

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

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1 partially responsible for that.

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

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

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

22 STOP-CHAGAS, another clinical trial.

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

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

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

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

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

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

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

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

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

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1 through the different outcome measures used.

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

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

16 For the main trial, the primary endpoint
17 is a clinical benefit endpoint. Here, you have
18 2,856 patients randomized equally for Benznidazole
19 and placebo, and a primary endpoint that is really
20 evaluating a combination of clinical outcomes of
21 death, cardiac arrest resuscitation, sustained v-
22 tach, need for a pacemaker or defibrillator,

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1 implantation, thromboembolic phenomena or
2 hospitalization for heart failure or heart
3 transplant.

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

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

15 The interesting data in terms of early
16 on drug compliance, you can see very few patients,
17 16 percent in Argentina, 12 percent in Brazil,
18 that actually discontinued, had treatment
19 interrupted at some point, but you had very large
20 and very good compliance overall in terms of
21 treatment. We are very much looking forward to
22 the results.

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

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

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

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

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

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

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

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1 One, the DNDi sponsored trial in collaboration
2 with El Sai, ELEA, Mundo Sano, and also the
3 BERENICE project. There is Nifurtimox in
4 children. This one is efficacy and safety of
5 Nifurtimox in kids. It includes both PCR and
6 serological but primary efficacy response in terms
7 of serological response over time, reduction of
8 titers.

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

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

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

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

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

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

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

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

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

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1 Disease.

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

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

13 Thank you. Thank you very much.

14 (Applause.)

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

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

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

6 PANEL DISCUSSION

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

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

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

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

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

4 DR. FARLEY: About 20 minutes.

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

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

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

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

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

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

22 Dr. Meymandi?

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

3 DR. NAMBIAR: Certainly.

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

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

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

22 Certainly, one consideration that has

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

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

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

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

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

22 DR. MEYMANDI: Do we have access to that

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

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

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

13 DR. MEYMANDI: I agree with that.

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

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1 submit an application, that can manufacture this
2 product, day in, day out, to a quality standard,
3 so it can be approved and it can be available.

4 Does that help?

5 DR. MEYMANDI: Yes. In that direction,
6 we have companies who I know are interested in
7 bringing these drugs forward. We have
8 representation here from those companies. Is this
9 something you guys can get together and move
10 forward or do we have to start at the beginning
11 and redo everything? That's insane.

12 DR. RIBEIRO: I think that is a key
13 question, obviously. I think if we discuss with a
14 number of the investigators that were involved in
15 these clinical trials, I have no doubt you are
16 going to have them making this information
17 available for registration of Benznidazole, for
18 example.

19 In the case of Benznidazole where you
20 have the placebo controlled comparisons done, et
21 cetera, I have no doubt. I think here we have
22 representatives from ELEA, Mundo Sano Foundation.

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1 There are groups that are collaborating on this,
2 and certainly this information could be made
3 available.

4 The issue goes back to perhaps a
5 discussion that we are going to still have, on the
6 issue of the clinical benefit demonstration. If
7 one were able to actually register or seek
8 marketing authorization here based on the outcomes
9 that were selected for this, a number of them have
10 serological response, but now we have PCR data,
11 and if one would be able to support such a filing
12 based on the outcome measures that were selected
13 for these trials, either as a surrogate marker or
14 actually a primary efficacy endpoint.

15 DR. NAMBIAR: That again would depend on
16 how good the data are, one really has to
17 demonstrate the link and make a link between the
18 benefit on the surrogate endpoint translating to a
19 clinically meaningful benefit.

20 DR. MEYMANDI: I'm a positive person,
21 and I'm looking that the data is good, and let's
22 start there instead of again recreating the wheel.

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1 These are two drugs that we are using that we are
2 seeing effective treatment. Again, from a
3 clinician's perspective, let's make this easy. We
4 want it to be safe, obviously.

5 I think everyone here who treats
6 patients has patient safety at heart. If we can
7 do it in an easier fashion than recreating another
8 study design and starting with another patient
9 population that hasn't been treated yet and having
10 a placebo arm versus a treatment arm, and spending
11 five years, ten years doing that, how many
12 patients are we going to lose in that process.

13 DR. COX: A very reasonable goal, and
14 consistent with our thinking on this, too. The
15 real question is trying to gather up the data and
16 identify those that have it and see if they can
17 essentially join up with a manufacturer so that
18 there is a way to try to take advantage of all
19 that has been done, and I agree, why recreate the
20 wheel if the quality data are already out there.

21 It's a very reasonable idea and I think
22 one that several of us are having, and the

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1 question is pulling it together.

2 DR. MEYMANDI: Excellent. Thank you.

3 Done.

4 (Laughter.)

5 DR. NAMBIAR: I guess we can take a

6 break.

7 DR. FARLEY: We're not done. I think

8 that kind of answers the question on Benznidazole

9 and Nifurtimox in terms of what the regulatory

10 pathways might be. Part of our goal of inviting

11 some of the key investigators here was to sort of

12 show them that we really will need access to their

13 data to have the drug approved, particularly in

14 the United States. That's great.

15 I think we had written some of these

16 questions thinking about, for example, a new

17 azole. What would be helpful to us is sort of

18 focusing on a discussion, pretend this is a new

19 azole or a new class, how would you design the

20 trial.

21 We certainly have the right folks here

22 to answer that question, and what population would

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1 you do it in.

2 DR. ALTCHER: About populations, we need
3 studies in children. If you see different
4 presentations, the chronic disease begins after
5 two months of infection. Children present with
6 chronic phase of infection, then children have to
7 be included in all of the studies that we begin
8 about new drugs. This is very, very important.

9 WE have a lot of non-treated children
10 that now are adults. This is the center point.
11 About country groups, this is very difficult to
12 not treat a patient when you diagnose these
13 patients, because we have a lot of information
14 about efficacy of Benznidazole and Nifurtimox. We
15 cannot use placebo for the studies.

16 DR. NAMBIAR: If I can ask you a follow
17 up question. If you are trying to study children,
18 are these children who acquired the infection
19 congenitally, are these children you are picking
20 up in month one or two or are these children that
21 get infected later in life or do you differentiate
22 between the two?

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1 DR. ALTCHER: In places without vector
2 transmission, you have children infected, all the
3 children, with acute infections. In big cities
4 without vector transmission, you have a lot of
5 congenital infected patients.

6 DR. NAMBIAR: Thank you. Dr. Sosa-
7 Estani?

8 DR. SOSA-ESTANI: First of all, I would
9 like to express my complete agreement with the
10 clinical point of view of Sheba, and regarding
11 specifically your question, I think in several
12 presentations, the complexity of the natural
13 history of Chagas Disease, that is infectious
14 disease, chronic infectious disease, with a very
15 late clinical expression, I think as Jaime said,
16 there is enough evidence of benefit. There are
17 some evidence of clinical effect.

18 Personally, I think after benefit trial,
19 to demonstrate clinical effect, is unreasonable,
20 because it is not possible as a design to
21 demonstrate clinical effect after benefit trial.
22 I would like to reinforce that it is necessary to

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1 design clinical trial to demonstrate effect
2 against infection because in addition we have
3 demonstrated that the effect against infection can
4 interrupt one of the main routes of infection,
5 congenital transmission.

6 Regarding the control, I think there is
7 enough evidence that maybe in general would be not
8 recommended use for placebo arm, but in some
9 cases, thinking this is chronic infection, it's
10 possible maybe in some situations thinking a
11 control, delayed treatment.

12 DR. RIBEIRO: Just to answer the
13 specific questions from the panel, I think we have
14 dwelled quite a bit with regard to the populations
15 in which a clinical trial would be feasible and
16 acceptable, and I think we have selected the
17 chronic and indeterminate patients as they
18 represented the highest burden of the disease and
19 where there would not be an issue in terms of
20 recruitment, but also we felt it was important to
21 have a placebo control, and we felt that
22 population would allow us to be able to have a

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1 concurrence type placebo control and a double-
2 blinded design, and therefore, that was considered
3 acceptable as it was represented, as Sergio was
4 indicating, delayed treatment.

5 I think the evaluation of acute cases
6 today is not feasible. I think the incidence is
7 such and it goes so fast that we will not be able
8 to identify cases.

9 Oral Chagas Disease, actually the
10 clusters of oral Chagas are becoming more
11 frequent, at least there is some indication of
12 that, but it is episodic. You cannot predict
13 where they are going to happen.

14 This is a consideration. Kids,
15 certainly children as a population for evaluation.
16 I think there is one element here, just that in
17 one side, there is recruitment as you have pointed
18 out, but as Jaime indicated, I think there are a
19 number of untreated children so far, and
20 therefore, these trials are certainly feasible,
21 but there is the question is it the findings in
22 kids will be representative of an adult

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1 population.

2 If one carries out clinical trials in
3 the children, will the outcomes reflect what one
4 would see in an adult population, the adults being
5 the worse case scenario in a way.

6 Here is where it is actually balancing
7 these two sides, which is really challenging. It's
8 a long answer.

9 DR. NAMBIAR: Do you think these
10 children are identified as part of screening, when
11 serological screening is done routinely in some
12 countries? Is that how they would be picked up?

13 DR. RIBEIRO: Yes, particularly in
14 countries like Argentina and Bolivia, where
15 mothers are actually assessed, so routinely,
16 evaluated in mothers who are Chagas positive.

17 DR. NAMBIAR: Dr. Sosa-Estani?

18 DR. SOSA-ESTANI: I would like to add
19 regarding the design of the clinical trial. We are
20 working for several years, we are really very,
21 very happy to understand and to know with evidence
22 that we can design short clinical trial in

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1 comparison with the past. In the past, we needed
2 at least five or six years to demonstrate efficacy
3 against infection. We can demonstrate the same
4 effect in 12 months.

5 DR. NAMBIAR: You mean because of PCR?

6 DR. SOSA-ESTANI: Yes.

7 DR. SUZART-WOISCHNIK: Just a comment.

8 We did not discuss about the trial design, but my
9 colleagues are trying to put a protocol in place
10 and we have a problem of lost follow up,
11 especially in studies with children with a disease
12 that does not have a phenotype, acute phenotype,
13 it is very difficult after a 60 day treatment to
14 have a long follow up, one year, six months.

15 These poor families will be moving
16 around, these are small countries, and the
17 possibility that we have for full follow up is
18 almost none. It is impossible to predict.

19 This is a risk for us so that we cannot
20 guarantee from the beginning that we will achieve
21 100 percent one-year follow up in order to have
22 our data valuable. Most of the results showed at

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1 least 10 percent or more lost follow up at 12
2 months.

3 DR. CHEN: I think besides that, you
4 have also reinfection, that kids or families went
5 back to the endemic area that you have no control
6 over, and they came back with reinfection. It's
7 very hard to tell. It's very difficult to design,
8 to conduct.

9 DR. RIBEIRO: I think it's worth noting
10 the experience that we had in the clinical trials
11 in Bolivia, where we actually had very good rates
12 of follow up. We actually had at 12 months like
13 three percent lost follow up. Really very little
14 missing data. It's very difficult no doubt.

15 The issue of reinfection is challenging.
16 We actually had linked with programs in order that
17 patients were informed they needed to inform if
18 there was reinfection and so on. It is certainly
19 a question.

20 DR. CHEN: Regarding the control group,
21 it is always hard because you have to treat every
22 single patient, especially in those areas that the

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1 drug is already proved for the last 40 years, and
2 how can you not treat those patients, unless you
3 have a very chronic case and then the
4 recommendation is different.

5 DR. SOSA-ESTANI: Just to reinforce the
6 comment regarding the control and reinfection, it
7 really depends on the size of the trial, of
8 course. In some cases, it is absolutely
9 impossible to design a clinical trial with
10 patients where they are living in areas without
11 vectors or because they are living in an area
12 under surveillance with interruption of
13 transmission.

14 If the trial is huge like the BENEFIT
15 trial, we discussed that, but we assume
16 (speaking in Spanish.)

17 DR. ALLENDE: I want to ask Sergio if
18 the data, the original data from your randomized
19 study would be available to be part of a
20 submission, like the records of each patient, the
21 laboratory results, some kind of record when that
22 study was done, the randomized and the controlled

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1 study in children.

2 DR. SOSA-ESTANI: Yes.

3 DR. ALLENDE: Thank you. I think that
4 would be very important because sometimes in the
5 article when you are reporting a mean GMT
6 reduction or something, median, the actual value,
7 those questions will be very important. Thank you.

8 DR. FARLEY: Thanks very much for that
9 discussion. Just one point for sponsors that may
10 be interested in developing Nifurtimox or
11 Benznidazole. The FDA, following approval,
12 publishes or makes available its reviews on the
13 drugs on the FDA website.

14 One application that may be worth
15 looking at as a recent precedent for reliance upon
16 efficacy trials that you yourself did not conduct
17 would be Miltefosine, approved recently for
18 Leishmaniasis. That may be worth taking a look
19 at.

20 Chagas is challenging in that it's
21 likely we are going to need to understand better
22 the surrogate endpoints that were used in the

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1 trial. By now you know what the FDA calls a
2 "surrogate endpoint," so that is good we are using
3 the same language.

4 We are going to focus on that after the
5 break. We're going to take a break now for 15
6 minutes and reconvene at 3:10. Thanks.

7 (Recess.)

8 DR. FARLEY: We will get started. We
9 are going to turn now to the issue of laboratory
10 monitoring, and our first speaker is Dr. Louis --
11 also known as Vaughn to most of us -- Kirchhoff,
12 Professor of Internal Medicine and Infectious
13 Diseases at the University of Iowa, Carver College
14 of Medicine.

15 He's an expert in laboratory assay
16 development for Chagas Disease. He developed the
17 RIPA assay for Chagas, and is co-author of a large
18 WHO comparative evaluation of serologic assays for
19 Chagas Disease.

20 Vaughn, thanks very much for being here
21 today.

22 LABORATORY MONITORING USING SEROLOGY

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1 DR. KIRCHHOFF: I want to thank the
2 organizers of the meeting for inviting me. I only
3 have three slides and no graphs or pretty
4 pictures. You will understand in a minute.

5 My plan or my charge was to discuss the
6 issues that should be considered by FDA or
7 industry staff when they are considering the
8 design of a trial to evaluate a new drug for
9 Chagas Disease or an old drug.

10 What my three slides show is just really
11 a summary or a list of the issues that I think
12 they would have to think about as they work
13 through this serious challenge, let's say.

14 A bunch of things that are the list here
15 have been mentioned extensively by the earlier
16 speakers, and I will probably skip them. Maybe
17 I'll talk for 8 or 10 minutes, and then cede my
18 time to Dr. Schijman, who is going to talk about
19 PCR.

20 If we can go to the first slide, general
21 issues for evaluating drugs for Chagas Disease,
22 evaluating drugs for Chagas Disease is really a

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1 major challenge as you can see from the meeting
2 here today, but it's not uniquely so. I mean this
3 business of coming up with biomarkers and other
4 indicators that are not clinical or patient based
5 indicators of efficacy, it has come out in HIV a
6 lot, tuberculosis, and many other diseases.

7 In Chagas Disease, as mentioned, there
8 are no clinical related outcomes or no patient
9 related or patient reported outcomes that would
10 come up in a timely fashion that would help or
11 likely help with evaluation of the efficacy of a
12 drug.

13 In terms of the goals, my goal, and I
14 think kind of everyone's goal is parasitologic
15 cure, to simply get rid of all the parasites that
16 infect each person who acts as a host for this
17 infection, but there is this question whether
18 suppression over a period of time is going to
19 affect long term outcomes is kind of running in
20 the background.

21 In terms of what we can look at,
22 parasitologic assays lack sensitivity and

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1 specifically the old time parasitology is with the
2 insect's xenodiagnoses, where the insects are
3 applied in a little cage on one's arm, then you
4 examine the bugs weeks later to see if they have
5 gotten infected from the patient's blood.

6 That is the old time parasitology, and
7 sort of in the middle is hemoculture, take a
8 patient's blood or fractions of it and put it into
9 an appropriate medium to see if the parasites will
10 grow there.

11 They have essentially been replaced by
12 PCR. PCR is much less laborious and can be done
13 in sizable numbers in a relatively short period of
14 time.

15 Moving on to what I'm really charged
16 with here, to talk about serology. This came up
17 this morning in terms of how efficient our system
18 is in the United States these days for screening
19 the U.S. blood supply.

20 I think if you talk to the people, for
21 example, Dr. Susan Stramer, who has been the head
22 of serologic testing for our entire blood supply

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1 in the U.S., ask her about our Chagas Disease
2 assays, and she says they are excellent and they
3 are really just as good as the assays that we have
4 for other infectious diseases that do threaten our
5 blood supply.

6 In a pre-treatment context for screening
7 blood donors and for screening what I think and
8 Dr. Meymandi and others think should be everybody
9 who has any geographic risk for Chagas Disease or
10 maternal risk. All these people should be
11 screened in a pre- treatment situation.

12 We have the serologic tools for doing
13 that. If you want to read about it, there was a
14 comprehensive study financed by WHO that was
15 published in 2009 in Transfusion. The first
16 author was Otani, M.M., and in that, it describes
17 a study of 21 commercially available serologic
18 assays that we use to test blood donor samples,
19 positive and negative ones, from blood banks in 10
20 of the endemic countries.

21 There, it shows many if not most of
22 these assays have sensitivities and specificities

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1 that are in the high 90s. Those are the tests
2 that are used throughout Latin America for
3 screening the blood supply there, and I think they
4 do a good job of it.

5 Here in the United States, there is an
6 Ortho and Abbott test that are used for primary
7 screening essentially of all donated blood or all
8 donors who are not known to be negative by
9 previous testing, and then we do confirmatory
10 testing, second stage testing, either with an
11 Abbott test or with a test that I developed years
12 ago called "Chagas RIPA." We are in good shape for
13 pre-treatment testing.

14 In the context of post-treatment
15 testing, it is much more difficult. I'd summarize
16 it by saying variability and delay in the fall of
17 anti-T. cruzi titers to whatever antigen you pick,
18 after treatment make assessment of drug efficacy a
19 difficult and prolonged process. Both Caryn Bern
20 and Isabela Ribeiro showed slides of how titers
21 fall, but they do so over years, so in evaluating
22 a drug, we really don't have the time to sit

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1 around for four, five, six years until it becomes
2 clear that a drug is useful or not useful enough
3 for us and won't be used.

4 Just a couple of background issues that
5 have been touched on by others. The question is
6 what group of infected persons would be the best
7 ones to include in trials. One of the issues is
8 the data show people who have been infected
9 shorter periods of time, like two years instead of
10 42 years, are more treatable or more curable.

11 If you want to power the test or you
12 want to make it likely that a new drug or a new
13 combination of drugs is shown to be effective, you
14 want to do it on younger patients, just as kind of
15 a general rule.

16 Briefly, this business of reinfection
17 was mentioned, reinfection after treatment.
18 Someone comes in and is determined to be positive,
19 gets in a treatment trial, gets treated, and then
20 goes back to the context in which they got
21 infected in the first place.

22 I don't have strong recommendations on

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1 exactly how to do this now, but I'd say it is
2 something that really needs to be paid attention
3 to because although there have been a lot of
4 studies on the genetics of T. cruzi in recent
5 years, I think at this point it is fair to say we
6 don't have a tool, for example, all the people who
7 seem to be not cured who might have gotten re-
8 infected, we don't have an usable tool yet to look
9 at the genetics of the parasites in those people
10 to make absolutely sure the parasites that they
11 still carry are the old parasites rather than new
12 parasites. That's an issue to think about.

13 Again, in terms of selecting the group,
14 as I mentioned, it is good in terms of serology to
15 have a two-stage process, first, some kind of
16 screening assay, and then followed by a more
17 confirmatory assay.

18 Another issue that is very important, it
19 seems obvious, but I think it merits mention, it
20 is very important to avoid including subjects who
21 are false/positive in serologic assays.
22 Historically, much less so now, but historically

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1 false/positive results in blood tests or serologic
2 tests for Chagas Disease have been a chronic
3 problem.

4 If you're working with an assay that is
5 say 99 percent specific, that means every 100
6 people you look at, you are going to have one
7 person who appears to be positive for some reason
8 unrelated to Chagas infection. If you work that
9 kind of thing through the numbers of your study,
10 in the end, it could turn out to be important and
11 bias your conclusions, your inferences in one way
12 or another. You certainly need to avoid that.

13 Again, I don't have a shopping list here
14 of ways to be 100 percent sure you can avoid the
15 false/positive's, but one thing to think about is
16 what range of titers in the screening assays do
17 you want to include. There is this kind of
18 intuitive thinking that if a patient has just
19 robust titers, that are pretty high, they are more
20 convincingly true positive, and I think that is
21 probably true to a certain degree but not
22 absolutely so. Whether or not to include that

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1 broad range or not is a question.

2 Alternatively, you could just take the
3 top 25 percent in terms of reactivity in the
4 screening assays, and then with either of these
5 options, you could include PCR as a final
6 confirmatory test, but then you are left with the
7 question of whether people who can consistently be
8 demonstrated to be PCR positive, presumably they
9 have more circulating parasites, so either they
10 are different in a biologic sense or in an
11 immunologic sense, or the parasite strain they
12 harbor is different, and there is no real way to
13 sort that out, but either of those issues could
14 conceivably affect the curability of their
15 infection. Those are just issues to think about.

16 Moving on. A quick logistical issue. If
17 you have a study with a large number of people and
18 if you adopt a perspective that you really want to
19 be tight about doing your serological studies, and
20 I think if the idea is instead of looking at the
21 end of three years or four years or something like
22 that, looking at the fall in titers in months or

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1 small number of years, if you're going to hang
2 your hat on specific titers or levels of
3 antibodies, I think it would be good practice to
4 always run all the samples you have head to head
5 in the same plot, in the same plate, and that will
6 get rid of possible lot to lot variations, and it
7 really appeals to me as one that has done a lot of
8 serology to do that kind of thing.

9 The downside of that is if you have 300
10 or 400 people in your study and you draw blood
11 from them every three months and you want to maybe
12 get 10 to 12 aliquots with each one, because you
13 don't want to take the same tube and freeze it and
14 thaw it, freeze it and thaw it, because that can
15 affect titers. All of a sudden you have 10
16 freezers with 30,000 samples and four staff
17 members to take care of it, and all your data up
18 in a Microsoft Cloud. It could certainly be a
19 complication or burden. It's doable and there are
20 obviously computer programs to deal with that kind
21 of data.

22 Another issue is the long term goal is

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1 to detect after treatment, I would think, an early
2 pattern of declining reactivity of antibodies or
3 some other biomarker that in the study or in a
4 study has been shown, that early fall has been
5 shown to be indicative or highly predictive of
6 parasitologic cure.

7 I think that is the goal and a real
8 challenge, in addition to with other biomarkers
9 waiting until they actually go negative.

10 Moving on to targets. There are a
11 number of things to look for. The Ortho test,
12 which is used to screen a good portion of the U.S.
13 blood supply these days, obviously approved by
14 FDA, it's a cut, a size cut of lysates of T. cruzi
15 grown in cultures. It has a broad and undefined
16 mixture of antigen, anything from proteins,
17 glycoproteins, glycolipids, and who knows what
18 else. That is one approach.

19 Another approach that many others and I
20 have taken is mixtures of single or combined
21 recombinant proteins. Wiener Laboratories in
22 Brazil and in Argentina has a 510K FDA approved --

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1 it's called the Wiener "Chagatest recombinante" --
2 that has five or six separately produced
3 recombinant antigens, an approach that I and my
4 co-workers took to do the molecular biology up
5 front and make these strings of coding sequences
6 of antigens that are from different places in the
7 genome.

8 Tests based on the latter is an Abbott
9 Prism Chagas assay, which is used also with Ortho
10 test to screen blood supply. Abbott Architect,
11 and an enzyme strip assay, that also has these
12 recombinant antigens. That is another approach.
13 There are tons of options in which proteins to
14 include.

15 Then there are whole parasites, and what
16 we are particularly referring to here is there is
17 an assay called "Compliment mediated lysate of
18 whole parasites," living parasites, that identify
19 a group of antibodies called "lytic antibodies."
20 These lytic antibodies persist in people who have
21 persistent infections, but when the infections are
22 cured, then as the supporters of this approach

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1 believe, these lytic antibodies actually
2 disappear. There are people who say things like
3 it is widely accepted that assays that measure
4 lytic antibodies are the best approach for
5 assessing the effect of anti-T. cruzi drugs.

6 Why don't we just design a trial in
7 which we do this assay, and I think because it,
8 too, belongs to old time parasitology, it's very
9 complicated. I've never done it, but I think you
10 have to radiate mice, make them immunodeficient,
11 and then you infect the mice with parasites from
12 other mice, and then you eventually harvest blood
13 from these mice. I think by centrifugation,
14 separate the parasites from the mouse blood, and
15 then run your assay. It's complicated.

16 I think certainly in the United States
17 from a regulatory point of view, I think it would
18 be difficult to convince the regulators that this
19 is a good idea to do.

20 For years I've been chair of the
21 institutional Biosafety Committee at the
22 University of Iowa, and I know my colleagues would

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1 raise their eyebrows thinking about all these
2 potentially lethal parasites being carried around
3 between hoods and to the animal room, stuff like
4 that.

5 An option is to clone or molecularly
6 clone the protein essence of what the lytic
7 antibodies bind to, and measure those antibodies
8 that way. People are working on that. They have
9 isolated what is called GP- 160, a glycoprotein,
10 from trypanomastigotes, I assume, and using that as
11 a target. There are papers out there that have
12 used that natural molecule as a target to measure
13 the level of lytic antibodies.

14 I think more work needs to be done, and
15 they are trying to clone it in a molecular sense
16 as well.

17 Lastly, I would say what about all these
18 different approaches looking at both parasite and
19 human biomarkers as indicators of infection status
20 after treatment. I will just finish up with this.

21 There are all sorts of things that
22 people have been doing with big science these

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1 days, including mass spectrometry, with MALDI- TOF
2 and CELDI-TOF, looking at expression of human
3 biomarkers like APOA-1 and FN1, and the list goes
4 on and on.

5 If you're interested in this, this is an
6 18 page paper of which three of our panelists are
7 co-authors, that goes through all of this. I
8 think it is 2014, so it is recent information.
9 I'd say there is a lot going on, but the question
10 is, are any of these approaches ready to go for a
11 new trial?

12 I will just read what the authors say in
13 the conclusion here of this review, and it is
14 antibodies including all other biomarkers. "There
15 are several marker candidates with which together
16 may fulfill acceptable criteria to indicate the
17 efficacy of trypanocidal treatment. Data from
18 ongoing studies are considered essential to
19 improve assessment of existing markers and to
20 identify those for early follow up of treated
21 patients."

22 There is a lot going on there but I

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1 think at this moment there is nothing we can grab
2 and order or bring over to the laboratory in the
3 next month or two to help us address this problem.
4 Thank you.

5 (Applause.)

6 DR. FARLEY: Thanks, Dr. Kirchhoff. We
7 will now move on to the issue of laboratory
8 monitoring using PCR. We have invited Dr.
9 Alejandro Schijman to do that talk. He's head of
10 the Laboratory of Molecular Biology of Chagas
11 Disease at the Research Institute of Genetic
12 Engineering and Molecular Biology in Buenos Aires.

13 He has worked in PCR assay development
14 and exploration of biological markers of Chagas
15 Disease. He's the principal investigator for a
16 WHO international collaborative study conducted by
17 expert PCR laboratories from 16 countries to
18 evaluate the performance of PCR methods in the
19 detection of Trypanosoma cruzi DNA by an external
20 quality evaluation.

21 We are delighted to have you here today.
22 Thanks.

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1 LABORATORY MONITORING USING PCR

2 DR. SCHIJMAN: Thank you for the

3 opportunity to share our experience and results.

4 I'm going to talk on PCR standardization and

5 validation issues in the context of using PCR as a

6 surrogate marker for monitoring treatment

7 efficacy.

8 The validation of PCR was recognized as

9 one of the priorities by the WHO, not only for

10 detection and characterization but also as a test

11 of cure.

12 Since 2007, a series of international

13 meetings were launched to search for a PCR test

14 for monitoring and treatment. Although PCR has

15 been proposed for Chagas Disease since the 1990s,

16 there was a huge variability in sensitivity among

17 the different techniques, so with the aid of PAHO

18 and WHO, we started an international study to

19 search for the most reliable PCR test in all the

20 laboratories with expertise of PCR in the world.

21 For that, our task was to take into

22 account the new knowledge about the genetic

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1 diversity of PCR because we all know the reasons
2 to explain PCR was so valuable in the different
3 regions could be due to the molecular targets used
4 for PCR, which is related to the genetic
5 variability of T. cruzi, and nowadays, T. cruzi is
6 classified into six discrete typing units, with
7 different geographic distribution.

8 Any molecular diagnosis should be
9 analyzed in the context of this because the
10 molecular sequences used for diagnosis have
11 different copy numbers and different mutations in
12 the different strains of the parasite.

13 With this, we started to prepare a blind
14 panel of samples, composed of one panel of DNA
15 purified from strains of different -- a panel of
16 artificial blood samples that were spiked with
17 different quantities of parasites, and a panel of
18 clinical samples from different parts of the
19 world, and we sent these panels on a blind basis
20 to 29 laboratories in the world who wanted to
21 participate in this task. CDC in Atlanta was one
22 of those laboratories that participated in this.

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1 These laboratories sent their results
2 using their own PCR techniques, and we asked them
3 to specify the DNA structure methods, the
4 molecular targets, the names and composition of
5 the primers, and the rest of the protocol of their
6 procedures.

7 We made a statistical analysis to search
8 for the best methods in terms of specificity and
9 sensitivity, asking them to have a sensitivity
10 enough to detect a chronic Chagas patient, it had
11 to be a very high sensitivity.

12 This experience was very useful to allow
13 us to discard a lot of sequences of the parasites
14 that nowadays we know they are not useful for
15 molecular diagnosis. Maybe they are useful for
16 typing parasites of different linages but not for
17 molecular diagnosis. There were two sequences that
18 were useful for molecular diagnosis in terms of
19 sensitivity, kDNA and Satellite of the nuclear
20 genome.

21 Among these sequences and the methods
22 based on these sequences, there were many

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1 laboratories that used the same sequences and the
2 same protocols but the results were not the same.
3 A lot depended on the work of the laboratories.

4 Another important conclusion of this
5 study was that almost none of the laboratories
6 used internal standards for their PCR. They
7 couldn't discriminate between a real negative
8 result because of inhibition of lots of material
9 during the procedure.

10 With the advantage of having not only a
11 sequenced parasitic but also for -- based on the
12 best methods, we set up a duplex PCR. From this
13 method, we wrote a standard procedure that is
14 being used now in the clinical trials with new
15 drugs.

16 In 2011, we made another international
17 study where we transferred this technology to a
18 lot of participants from all over the world who
19 came to Argentina, and they were invited to bring
20 their own clinical samples, samples from chronic
21 and acute patients, and patients infected with
22 different linages, to assess the sensitivity and

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1 specificity and availability of parasitic load in
2 only one laboratory but using the same devices.

3 Following the international guidelines
4 of the Clinical Laboratory Standard Institute, we
5 made all the experiments to have the parameters of
6 the two methods, with limit of infection, limit of
7 quantification, analytical sensitivity for the
8 different strains, and also exclusivity for
9 microbial -- involved in the same samples of
10 patients with Chagas Disease, like patients with
11 Leishmaniasis.

12 Provided the good sensitivity and
13 specificity of these methods, we transferred them,
14 and these are now available for everyone,
15 published, to be used in research and in clinical
16 trials.

17 This is an example of the results. Here
18 you can see the availability of parasitic loads
19 measured by both PCR methods, clinical samples
20 infected with different units, and we can see
21 there is no statistical difference between the
22 measurements used in one or the other PCR method.

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1 Another important issue we found that to
2 perform a good reliable PCR, we must have external
3 control quality standards. We started to provide
4 all the laboratories that wanted to do PCR -- made
5 of different strains with different quantities of
6 parasitic loads, they are composed of seronegative
7 blood infected with cultured parasites, and they
8 have a blind cohort, they are sent to the
9 laboratories, and we asked them to give us the
10 results, and at the same time, we performed our
11 own experiment with the lipids of the same
12 samples.

13 Here you can see for different
14 laboratories, we prepared panels for one year of
15 work, they have to perform the PCR three months,
16 and you can see although there is difference
17 between the values of PCR using different strains,
18 which is natural, because different strains have
19 different copy numbers of the targets, there is no
20 statistical difference between the mean parasitic
21 loads from one panel to the other panel.

22 That means that the blood samples that

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1 are taken, they are very stable at least for a
2 year after getting them, and this is important
3 because in some clinical trials that are made in
4 endemic regions, you have a time before collection
5 of the sample and to the laboratory, and the
6 procedure itself.

7 You can see here different panels, you
8 see the mean values of the parasitic loads are
9 homogeneous, and the differences is due to the
10 multiple strains used, but we know patients are
11 affected by multiple strains, so it is important
12 not to expect results because of this variability.

13 Another issue is the laboratories that
14 participated in this external control, they were
15 able to look at their result sand to improve them.
16 For example, for the samples with less number of
17 parasites which were close to the limit of the
18 method, they had negative results and then after
19 changing the real time device, for example, making
20 some changes, they could detect them. It's an
21 important means while they are working to improve
22 their results.

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1 At last, I wanted to talk about the
2 application of these PCRs and clinical trials.
3 Work we have been doing in collaboration with MSF-
4 DNDi was to improve clinical sensitivity of the
5 test in chronic patients, in particular, in
6 patients from Bolivia, the parasitic loads are
7 very, very low, these chronic patients have
8 parasitic loads that are about the limit of the
9 threshold of the PCR.

10 The way to improve sensitivity was to
11 optimize sampling and we tested 10 milliliters or
12 5 milliliters of blood with a stabilizing agent,
13 taken in the same day, and another one taken seven
14 days after. You know the natural history of the
15 chronic infection, you have peaks and valleys of
16 parasitemia. It depends on the time you get the
17 sample, you could have higher or lower parasitic
18 loads.

19 Of course, use of three samples improved
20 the clinical sensitivity of the PCR from 87
21 percent to 91 percent, so for example, for the
22 E1224 trial, DDI, we chose this strategy because

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1 the patients in Cochabamba had very, very low
2 parasitic loads. This must be studied by a pilot,
3 when one chooses a population, it is good to make
4 a pilot study of the parasitic loads in the
5 region.

6 For example, in Columbia, patients have
7 high parasitic loads. The studies may depend on
8 the region where one is going to do the assay.

9 In this study, we saw there was no
10 difference between 5 and 10 milliliters in blood
11 taken the same day or seven days later, but there
12 was a difference between taking a positive result
13 for a patient, taking one sample, two samples, or
14 three samples.

15 This is the results using the same kind
16 of PCR. You can see as Isabela Ribeiro showed you
17 before, the usefulness in the short term of the
18 PCR to show treatment failure, so this is the main
19 usefulness of PCR because in the short term at
20 least you can say the target is not working. If
21 you have a negative chronic patient, you cannot
22 say the patient is cured because you are always

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1 taking a blood sample, so you are evaluating the
2 parasitic load of the last, but not the ones in
3 the tissues, in the target organs, like heart
4 tissues. If the result is positive, you can say
5 that the treatment is failing.

6 This is another example, looking at the
7 differences using this PCR between placebo, the
8 different arms of E1224.

9 This shows the parasitic loads of the
10 E1224 study, and you can see the placebo arm. The
11 arms with E1224, depending on the dose, they
12 started to relapse after treatment. The follow up
13 with PCR is also a good tool to monitor.

14 From this study, we saw there was an
15 increased hazard of relapse with a certain group,
16 and higher PCR baseline, so the parasitic load
17 also can be an indicator of the prognosis at least
18 in this study, the patients that had higher
19 parasitic loads at baseline had higher hazard to
20 relapse after treatment.

21 That's all. Thank you.

22 (Applause.)

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1 DR. FARLEY: Thanks very much,
2 appreciate it. That was a great talk. I'm going
3 to rearrange the agenda a little bit, and take
4 open public comments at this point, so they can be
5 considered by the panel during the second part of
6 the panel discussion.

7 We have one request for formal open
8 public comment, and that is Mr. Frank Sasinowski,
9 representing Mundo Sano.

10 OPEN PUBLIC COMMENT SESSION

11 MR. SASINOWSKI: Thank you, Dr. Farley.
12 Frank Sasinowski from Hyman, Phelps & McNamara
13 representing Mundo Sano, which means "healthy
14 world," through our work with the
15 Chemopharmaceutical Group.

16 Mundo Sano is a non-profit foundation
17 that was started in Argentina in 1993. Its sole
18 mission when it began was to combat Chagas. It
19 has expanded its mission to include all neglected
20 tropical diseases since then, and it has worked
21 with many international coalitions, and in that
22 work, has worked along side the Gates Foundation,

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1 the World Bank, WHO, PAHO and others.

2 Mundo Sano has two requests for FDA to
3 consider today. First, to consider the use of
4 Subpart (h) for Chagas therapies, and the second
5 to consider recognizing Chagas as a neglected
6 tropical disease.

7 Mundo Sano believes that we have heard
8 here today many reasons why a therapy for Chagas
9 should be considered under FDA's Subpart (h)
10 program. So, what is Subpart (h)?

11 It is also known as accelerated approval
12 or fast track, and FDA created it back in the
13 1980s to respond to the AIDS crisis. It allows
14 the FDA to approve a therapy based on "a surrogate
15 that is reasonably likely to predict" ultimate
16 clinical benefit, but only if the disease is
17 serious, and only if there is an unmet medical
18 need.

19 I think today we have heard that
20 undoubtedly Chagas is a serious disease and it is
21 indeed an unmet medical need where there is no
22 approved therapy here in the U.S.

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1 Why would a therapy for Chagas be based
2 on a surrogate and not on actual clinical benefit?
3 Mundo Sano thinks that because with Chagas, a
4 study to prove the ultimate clinical benefit
5 improves survival would likely take a decade or
6 longer to run.

7 A drug therapy could be approved on a
8 surrogate much sooner and allow patients to access
9 treatment through the normal health delivery
10 system rather than through the compassionate use
11 system.

12 Today, the CDC runs the only such
13 program for Chagas in the U.S., but to get access,
14 a newly diagnosed patient would need to be in the
15 care of a physician who knows Chagas, knows of the
16 CDC program, is willing to invest the time and
17 effort to personally apply for such access.

18 Also, there is a well-known phenomenon
19 that when the FDA approves the first real drug for
20 a disease, the awareness of the disease among
21 physicians and therefore the number of patients
22 diagnosed expands sometimes dramatically.

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1 Recall when Tagamet was first approved
2 for ulcers, when Prozac was first approved for
3 depression, when Betaseron was first approved for
4 multiple sclerosis. The same could be true with
5 the first therapy FDA approves for Chagas.

6 How could FDA apply Subpart (h) to
7 Chagas? FDA could rely upon the findings on a
8 surrogate, such as the quantitative PCR test that
9 Dr. Schijman just described in the recently
10 completed Dr. Molina study out of Barcelona. The
11 FDA could look at that kind of surrogate finding
12 as the basis for accelerated approval within a
13 post-approval or phase four study that would
14 confirm the clinical benefit, such as the reduced
15 incidence of sudden death, thromboembolism, and
16 heart failure, which are the leading causes of
17 death in Chagas heart disease, the most serious
18 and frequent manifestation of chronic Chagas.

19 This use of Subpart (h) would follow
20 many FDA precedents. Since 2010 alone, and just
21 in the anti-infective area, there is Dr. Cox, Dr.
22 Farley, Dr. Nambiar and her colleagues working

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1 just in the area of anti- infective since 2010,
2 the FDA has approved many drugs for HIV and
3 Hepatitis C based upon the results of blood tests
4 for these infections rather than clinical benefit.
5 In December 2012, FDA approved Sirturo to treat
6 MDR TB based on the absence of a pathogen in the
7 sputum coughed up from the lungs.

8 Mundo Sano asks FDA to consider applying
9 Subpart (h) to Chagas therapies in order to
10 accelerate patient access to a therapy for Chagas.
11 If that is done, it will likely result in expanded
12 physician awareness of Chagas, and then that would
13 lead to many new diagnoses of persons in this
14 country infected and at risk.

15 Mundo Sano's second request to FDA is to
16 recognize Chagas as a neglected tropical disease.
17 The original 2007 law that created the list of
18 neglected tropical diseases failed to list Chagas.
19 This law also saddled the FDA with such a
20 cumbersome rulemaking system for adding any new
21 disease to the original list that FDA even found
22 it difficult to add Ebola.

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1 In December 2014, Congress and the
2 President changed the law. They added Ebola, and
3 importantly, gave FDA new authority to add
4 diseases without being encumbered by a rulemaking
5 process.

6 On behalf of all those afflicted with
7 Chagas in this country, both diagnosed and the
8 many more now undiagnosed, Mundo Sano asks the FDA
9 to make Chagas the first disease that FDA adds to
10 the official list of neglected tropical diseases
11 under FDA's new December 2014 authority.

12 In sum, Mundo Sano asks FDA to use
13 Subpart (h) for Chagas, to recognize Chagas as a
14 neglected tropical disease, and on behalf of Mundo
15 Sano, thank you. Gracias.

16 (Applause.)

17 DR. FARLEY: Thanks, Mr. Sasinowski.
18 Just to clarify for the panel, I know he did say
19 that, Subpart (h) that is being referred to is the
20 accelerated approval pathway that Dr. Toerner
21 described in his talk. They are synonymous. That
22 is the subpart that refers to accelerated approval

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1 as a type of approval.

2 We will move on to the panel discussion,
3 and I will turn it over to Dr. Nambiar.

4 PANEL DISCUSSION

5 DR. NAMBIAR: Thank you, John. We have
6 a fair number of questions that we wanted to cover
7 in the second part of our panel discussion, some
8 of them we have already touched upon in the first
9 session.

10 I just want to see if any of the panel
11 members have any lingering comments regarding
12 either the populations or the acceptable control
13 groups. If not, we can go into these sets of
14 questions.

15 (No response.)

16 DR. NAMBIAR: The first question we seek
17 your input on is what are feasible and acceptable
18 clinical trial designs. In Dr. Toerner's
19 presentation, he gave you some options as to the
20 different considerations for a trial to be an
21 adequate and well-controlled trial to meet
22 regulatory requirements. We would welcome

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1 thoughts from the panel members on what might be
2 various trial designs.

3 Dr. Ribeiro?

4 DR. RIBEIRO: I think as we discussed
5 before, we have in the case of adults, a placebo
6 concurrent control, which would be acceptable,
7 depending on the time lines for follow up, so 6 to
8 12 month follow up, I would say that is actually
9 acceptable.

10 In the case of children, I don't think
11 basically a concurrent placebo design is
12 acceptable, and therefore we are discussing here
13 either the option of actually having a dose
14 comparison concurrent design or an active
15 treatment concurrent design, or alternatively, a
16 historical control.

17 In terms of the different target
18 populations, those are my views in terms of
19 adequately and well-controlled.

20 I should mention that for adults,
21 obviously the active therapy concurrent and the
22 dose comparison concurrent designs would also be

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1 acceptable. That's my view.

2 DR. NAMBIAR: Sergio?

3 DR. SOSA-ESTANI: I completely agree
4 with the position of Isabela, and would just like
5 to add blinded if possible.

6 DR. NAMBIAR: Dr. Ribeiro, can I just
7 ask you a clarifying question? You had suggested
8 dose response studies might be an option. I
9 certainly don't know enough. How do you sort of
10 assess what might be potentially useful doses? I
11 think historically we have just used a dose or two
12 and we have gone 60 days. How do you make an
13 assessment of would 30 days be enough, 60 days,
14 and what kinds of doses? Do you base that on
15 animal models or do you have some other way of
16 doing it?

17 DR. RIBEIRO: That's a great question.
18 We have been dwelling with this at this point, and
19 I think there is no clear -- we don't know yet the
20 duration in animal models that would reflect that.
21 In the animal models, if you look at different
22 durations, you have an increasing response, you

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1 have like you test 5 days, 10 days, two weeks, 40
2 days. You may see changes.

3 Obviously, this would depend on the drug
4 and so on. At this point, what we have, right now
5 we are evaluating a design for a Benznidazole
6 trial. We are actually looking at two weeks, four
7 weeks, and eight weeks treatment duration. We are
8 actually following patients, so we have assessment
9 at the end of treatment response and then six
10 months and 12 months, looking at sustained
11 results.

12 I hope I answered your question.

13 DR. NAMBIAR: Yes.

14 DR. RIBEIRO: Now, with the information
15 that we have, in terms of some of the data on
16 quantitative PCR, we are trying to model and
17 trying to develop to actually predict and having
18 model predicted responses. That is actually one of
19 the outcomes that we are going to be looking at
20 particularly for phase two in the future, that we
21 are considering.

22 DR. NAMBIAR: When you had the results

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1 from your azole trial, were you sort of surprised,
2 or did you have enough prior's before you went
3 into the study, sort of predicting what might be
4 the outcome?

5 DR. RIBEIRO: There was quite a bit of
6 information that had been generated on
7 Posaconazole in acute and chronic Chagas models.
8 In the case of E1224, we actually had studies also
9 in a model, mostly 20 day model, with
10 immunosuppression, and actually the response with
11 azoles were excellent, but it looks like there is
12 now some additional data that is actually showing
13 that depending on the strain, you might have
14 translation.

15 For example, there is now data from the
16 CL-Brenner model that one could see one would have
17 failures with this, so now we need to accumulate
18 additional data to really support this will remain
19 translational.

20 DR. NAMBIAR: Dr. Altcheh?

21 DR. ALTCHER: There is no rationale for
22 60 days of treatment. During several years, we

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1 used 90 days of treatment. Afterwards, we used 60
2 days. We can use 30 days of treatment. There are
3 some publications of 30 days of treatment. We
4 have to include 30 days of treatment in all the
5 designs for new drugs because there is a lot of
6 evidence that 30 days could be a good time for
7 treatment, maybe less.

8 The other thing is about doses, nobody
9 knows the doses. We need that. We found that
10 children need lower doses, that we are overdosing
11 for adults, for Benznidazole. We don't have
12 enough information. We will generate new
13 information in a few months.

14 DR. NAMBIAR: It certainly will help
15 make the safety profile better as well.

16 DR. SOSA-ESTANI: As Jaime said, there
17 is a lot of information showing 30 day prevents
18 mortality and reduces antibodies. There were
19 several comments regarding therapy at 60 versus
20 30, five milligrams versus 2.5. These are
21 questions that need to be evaluated.

22 DR. NAMBIAR: Any other comment?

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1 DR. ALTCHER: We need better
2 formulation.

3 DR. NAMBIAR: I don't think you have to
4 convince me on that point. That's easy. If there
5 are no more comments on this question, we can move
6 on to the second question. Again, we have
7 certainly touched upon this already and it came
8 across in the two presentations we had from Dr.
9 Kirchhoff and Dr. Schijman.

10 The question is what would be an
11 appropriate primary endpoint, and again to
12 consider whether a clinical outcome endpoint is
13 feasible and what are the strengths and weaknesses
14 for that, and certainly the timing of the
15 assessment of this endpoint and how long patients
16 would need to be followed up.

17 Maybe we can take it a piece at a time,
18 probably have a discussion on what might be the
19 endpoints, talk about a surrogate endpoint based
20 on a microbiologic criterion as well as a clinical
21 outcome endpoint, which I think for the most part
22 we have heard is difficult to do. Maybe after we

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1 have the results from the BENEFIT trial, it may be
2 even harder to do.

3 I would welcome the panel's thoughts on
4 that.

5 DR. ALTCHER: It is hard to respond to
6 the second question because there are literally
7 more important questions. Regarding the clinical,
8 with the primary, if a clinical endpoint is
9 possible, I think we discussed it a lot, at this
10 moment, it maybe always not possible to use.

11 Regarding the question when should
12 treatment benefit be assessed, I think there are
13 at least at this moment a consensus that during 12
14 months after treatment is an excellent time, and
15 certainly using PCR and serological tests also
16 looking for reduction.

17 It is important to consider to assess
18 failure by PCR and success by reduction of
19 antibodies.

20 Regarding the value of negative PCR, I
21 think that would be very important to be clear
22 that the important result of PCR is the positive

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1 result. Regarding the strength or weakness of
2 serological tests or PCR, personally I think the
3 strength of serological tests is it's more
4 sensitive than PCR in general, and the weakness is
5 the after treatment reduces slowly.

6 PCR is more specific after treatment,
7 and the weakness is the result doesn't mean a
8 cure.

9 DR. NAMBIAR: Dr. Ribeiro?

10 DR. RIBEIRO: I think perhaps that
11 particularly in children, the statement that a
12 negative PCR -- I think a negative PCR should be
13 considered as -- for me, I think it is a cure. In
14 adults, I think the issue of sensitivity of PCR,
15 it's more of an issue, but for example,
16 particularly in children, PCR sensitivity is on
17 the order of 100 percent, and Dr. Altcheh and
18 Alejandro, please correct me, but it is really
19 with pretty good specificity.

20 I just wanted to ask a question in terms
21 of the first question of what primary endpoint
22 would be appropriate for a clinical trial, to

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1 answer such a question, should we take into
2 consideration for a clinical trial for marketing
3 authorization, for efficacy demonstration, that's
4 the consideration of that question?

5 DR. NAMBIAR: Yes.

6 DR. RIBEIRO: From my standpoint, I
7 think it is interesting to think about and I think
8 we did briefly earlier, and I think in that sense
9 the presentation that we had before was on the one
10 hand, are we ready to say PCR, for example, or
11 serology are validated primary efficacy endpoints,
12 and what we will need to consider PCR/reduction of
13 titers across different age groups as a validated
14 primary efficacy endpoint, therefore, one would
15 not need to demonstrate later on clinical benefit,
16 right.

17 I'm so sorry. I preempted the question.
18 I apologize. The other one is in relation to
19 should it be considered more a surrogate marker
20 that will need subsequent demonstration of
21 clinical benefit. I think today we are moving in
22 a position where I am of the position that indeed

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1 it should be considered for children's response,
2 no doubt, I think we are there, and in the case of
3 adults, I think particularly with the BENEFIT
4 trial results, the correlation between the
5 validation of those outcomes will be there.

6 DR. NAMBIAR: Yes, Dr. Kirchhoff?

7 DR. KIRCHHOFF: I'd just like to comment
8 on this serology business, what to do with
9 serology. From the perspective of serology, PCR
10 just looks really kind of simple, one thing, and I
11 realize there are complexities of the strains and
12 things like that.

13 Having spent some time looking over a
14 lot of these studies relating to serology, I would
15 say evidence that change in serology, seronegative
16 or reduction in titers, so antibodies to what. In
17 terms of recombinant antigens, there are just
18 literally dozens of recombinant antigens that go
19 back really to the late 1980s and then there are
20 hybrid recombinant antigens that are combinations
21 of these, and then native antigens, and like I
22 said, size cuts of separated molecules, and we are

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1 talking about a substitute target for the lytic
2 antibodies that is the protein core of the GP60 in
3 recombinant form or isolating native GP60 from
4 trypomastigotes, a list of 38 targets.

5 The question is how to sort that out,
6 and one possibility would be to go back and shake
7 everybody's freezers from trials that have been
8 done before where you have specimens for treated
9 patients, but the problem with that is there are
10 no temperature records, they weren't collected in
11 FDA certified context, they have been frozen and
12 thawed an undetermined number of times, so it's a
13 tough and very heterogeneous group to work with,
14 so that's problematic.

15 At the other end, in a sizable trial,
16 you could just collect lots of specimens and lots
17 of aliquots and take this panel of targets for
18 antibodies and other biomarkers and just do it.

19 It's going to take four years or five
20 years to do. I don't know what the answer is but
21 I just wanted to respond. Evidence that change in
22 serology.

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1 DR. RIBEIRO: (Off microphone.)

2 DR. KIRCHHOFF: Yes, maybe the BENEFIT
3 trial. I don't know how much serology they have.

4 DR. SOSA-ESTANI: The difference between
5 the situation during clinical trial in comparison
6 with point of care. Certainly, for point of care,
7 PCR is the more practical to demonstrate in a
8 short time benefit of treatment, showing there is
9 not failure. In our experience, seeing a patient
10 with higher titer and low titer, all are clearly
11 reactive, their reduction is the same during the
12 first 12 months.

13 Talking about this topic, it is
14 interesting, your position, but maybe can exclude
15 some patients to be included in a clinical trial
16 showing a benefit, even if the titer is low, the
17 reduction would be the same in comparison with
18 patients with higher titers. There is at least
19 three papers or trials showing the significant
20 reduction during the first 12 to 24 months after
21 treatment.

22 Personally, I think PCR may be strong

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1 evidence of effect after treatment, the
2 combination of serological test showing a
3 reduction, a combination to show failure and
4 success at the same time.

5 DR. NAMBIAR: Dr. Kirchhoff, is it hard
6 to sort of standardize it, can we say to enter the
7 trial, you have to be positive on, and you specify
8 the test, then you monitor that same test as an
9 assessment of response, is that an option? Can
10 that be done in a clinical trial setting or that's
11 not an option?

12 DR. KIRCHHOFF: Yes, I think you would
13 certainly want to do that, but the question, like
14 I said, we have very good serologic tests for
15 detecting people pre-treatment or blood donors,
16 but the problem I see is those targets may not be
17 the best targets for being able to say something
18 about cure before they get negative or like is
19 alleged for the lytic antibodies, they would go
20 negative faster. They may not be the right ones.

21 Just hypothetically, if we want to say
22 well, let's go with lytic antibodies, let's say

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1 magically we could come up with enough native GP60
2 to supply that need. We would want to use that
3 for follow up, but I think we wouldn't want to use
4 it for qualification because the FDA hasn't looked
5 at it. They don't know anything about it. I
6 would worry about false negatives and false
7 positives, using something like that that is not
8 carefully tested.

9 I was thinking as Sergio was talking,
10 what are the barriers to doing this grand
11 analysis, with all the different biomarkers and
12 everything like that. The real one is the
13 samples, getting the samples, and getting them
14 organized and into a place where you could run a
15 lot of them quickly.

16 Another barrier is getting the antigens,
17 the recombinant proteins. They are around and
18 some are even available commercially, you can kind
19 of do that, maybe not all of them. I don't think
20 that is a major problem. Beyond that, you just
21 need money to have three or four people in a lab
22 for 6 or 12 months to run this.

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1 Running the test is not the problem.
2 I've done hundreds of ELISA plates, and I've never
3 used an automated system. If someone bought me an
4 automated system, everything could have gone a lot
5 faster.

6 I think the real thing is the samples,
7 getting the samples, good samples that haven't
8 been frozen and thawed 50 times, and the ink on
9 the labels hasn't smeared, and there is more than
10 30 microliters and stuff like that. That's the
11 real challenge.

12 DR. ALTCHER: We have to remember that
13 serology is a surrogate of parasitemia. If we
14 have a very good test of parasitemia like PCR, we
15 have to use PCR. If we are using something that
16 is not -- it takes several years to demonstrate -
17 - that never was set up for chronic patients,
18 never talked about that, this is new information.

19 On the other hand, all the serological
20 tests were set up for diagnosis, not for follow up
21 of the patients. We have some problems when we
22 have to follow up on patients. We have a very

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1 good test and that is PCR.

2 DR. KIRCHHOFF: I don't think anyone is
3 proposing using serology and not PCR or PCR and
4 not serology. I think in the end, all of the
5 above, more information is better. I think the
6 panel kind of agrees with that.

7 DR. FARLEY: Speaking of PCR, here's a
8 question for the panel. I'm noticing quantitative
9 PCR being used in the CHAGASAZOL study, the E1224
10 trial, and then in the BENEFIT trial. Those first
11 two trials, although they may have failed, they
12 actually seemed to have very important data,
13 particularly around Benznidazole.

14 The question is is it the same assay
15 being used in all three trials. We have also been
16 joined by Kathleen Whitaker from Center for
17 Devices here at the FDA, and if she has any
18 comments, I would invite her to join in the
19 discussion.

20 I guess the first question is is it the
21 same assay being used in all three trials?

22 DR. SCHIJMAN: Actually, the same assay

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1 was used in CHAGASAZOL, E1224, and I think in
2 BENEFIT, they started with another assay, and I
3 think they changed because the study started
4 before -- yes.

5 DR. ALLENDE: The number of samples, you
6 said in one study you took one sample and the
7 other three, number of blood samples for
8 PCR.

9 DR. RIBEIRO: Yes, that's an important
10 difference. In the E1224 trial, we did three
11 samples at each point. In the Molina trial, the
12 CHAGASAZOL was one, and we did three samples in
13 triplicates. I think that is part of the reason
14 why they have six percent failure and we have 20
15 percent failures identified, for example, in the
16 Benznidazole arm.

17 That might be related to the number of
18 samples, the number of triplicates. STOP- CHAGAS
19 actually did three samples, I believe. BENEFIT did
20 a single sample.

21 This again was before we had the results
22 of the analysis and evaluation.

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1 DR. SOSA-ESTANI: In STOP-CHAGAS, it was
2 a single sample also. There is a consensus today
3 to use in all new trials, in fact, we are
4 performing some clinical studies, use the
5 validated combination of techniques, and it is
6 very extended, the research team are accepting
7 this protocol to perform PCR to assess treatment
8 in a clinical trial.

9 DR. FARLEY: That protocol may answer my
10 next question, if you had your life to live over
11 again, how would you design a trial incorporating
12 quantitative PCR? It sounds like you all have
13 thought that through and have some
14 recommendations. Is that published for sponsors,
15 that they could access that?

16 DR. RIBEIRO: We have been discussing
17 that. I think we have published the results, and
18 I think there is a publication. There was an
19 abstract -- there was a communication on the use
20 of PCR as a marker. There were two -- go ahead.

21 DR. ALTCHER: We used two milliliters on
22 the four children. This is another point we have

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1 to discuss, volume of blood. We are using one
2 milliliter for newborns and two milliliters for
3 children younger than five years, with very good
4 sensitivity.

5 DR. RIBEIRO: The paper on the MSF trial
6 that compares 5 versus 10 for adults and one
7 versus two versus three samples, it should be
8 published this year. That will be coming out
9 soon.

10 I wanted to go to the question on trial
11 designs. On the weakness and strength and what is
12 the evidence on change in serology, negative PCR
13 or other lab test would actually be predictive of
14 a later clinical outcome. This is actually the
15 issue today, right?

16 I think from the Viotti data, we
17 actually have the serological response being
18 described, in terms of seroconversion, and then
19 you have the clinical outcomes, but that
20 evaluation is not done.

21 I think we are hoping that we are going
22 to have the data from the BENEFIT trials, that we

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1 will be able to see that and perhaps from TRAENA,
2 but I think when you look at negative PCR and
3 clinical outcome, one example that comes to mind
4 for me is one of immunocompromised patients.
5 That's a clinical outcome. You actually have
6 patients that have a positive exam and then they
7 have lesions and then they respond.

8 It is a somewhat different scenario
9 because it is not chronic Chagas in a sense, but
10 it is a relationship between that exam and a
11 clinical response.

12 DR. MEYMANDI: That's actually
13 excellent.

14 DR. RIBEIRO: I think it is important to
15 remember those and also in acute Chagas, you could
16 make those correlations in terms of symptomatology
17 and so on.

18 Those examples, I think, just to keep in
19 mind. I think serology and reduction in titers
20 and the prediction of clinical outcome, it should
21 be said openly that in the two placebo controlled
22 trials that were done, neither of them actually

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1 evaluated clinical benefits. These were trials
2 that actually evaluated the response.

3 Unfortunately, for most of those we
4 don't have today yet the proof of later clinical
5 outcome.

6 DR. BERN: Just related to Viotti, the
7 data are scarce because very few people actually
8 reverted to negative serology, but there was a
9 significant association with reverting to negative
10 serology and not having progression.

11 I can show you the paragraph, the p was
12 0.009, and the hazard ratio for those who remained
13 sero positive in three tests over the course of
14 the follow up, the hazard ratio was 4.9 for
15 progressing.

16 DR. FARLEY: Do we know if the source
17 data from Viotti exists?

18 DR. BERN: Yes.

19 DR. FARLEY: Okay, that's good.

20 DR. WHITAKER: If I could just take a
21 quick step back for John's question. A lot of
22 these PCR assays, we haven't necessarily seen, but

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1 one thing I just wanted everybody to keep in mind,
2 the type of assay used -- if you are looking at an
3 FDA approved assay, our assays are very different
4 whether we are considering blood screening or
5 diagnostic. They have completely different
6 performance. They have completely different --
7 the studies we use. Obviously, a blood screening
8 is just going to be 99.9 percent negative people.

9 We actively go out when we look at a
10 diagnostic for Chagas, whether it is serology or
11 PCR, we actively look at chronic patients, we
12 actively look at acute, try to find acute
13 patients. We do find the results are going to be
14 very different if you're going to utilize a "blood
15 screening test" versus a diagnostic.

16 It is a little thing that people don't
17 necessarily think of, but it is surprising how
18 different the results can be when you look at
19 that.

20 DR. SUZART-WOISCHNIK: In the previous
21 session about lost to follow up, the question is
22 about reduction, so a patient that has been

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1 treated and you have an observed reduction in
2 serologic levels and days of lost follow up, the
3 question is is this a patient with failure or not,
4 and is there a way for us to predict, to continue
5 to observe a curve.

6 This is a practical question that we
7 discussed this morning because we might not be
8 able to follow these patients. Counting these
9 patients as failures will be jeopardizing the
10 results unduly because there is the possibility
11 they are getting better. I would like to know
12 what the FDA thinks about it. Thanks.

13 DR. NAMBIAR: I don't know the specific
14 answer but in general we see minimized lost to
15 follow up because that is what we like, once you
16 lost patients to follow up, it certainly affects
17 the interpretation of the results. I agree, if
18 you classify all of them as failures, you are
19 doing anyone a favor.

20 I think there is a whole publication on
21 how to handle lost to follow up, and I think the
22 best advice is to minimize. There was a report

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1 not too long ago on missing data and how to handle
2 it. I think our advice always is to minimize it
3 as best you can, and it looks like some people
4 have been successful, so there may be some lessons
5 learned from other trials that have been done.
6 This is certainly an issue with diseases of this
7 nature because of the kinds of people and the
8 areas of the world.

9 Typically, in terms of the statistical
10 analysis, it should all be laid out up front how
11 you are going to handle missing data. I don't
12 think there is a straight answer to the question
13 but we are aware of the situation, minimized lost
14 follow up, but clearly specify up front how you
15 plan to handle it. Joe?

16 DR. TOERNER: Just to add that an early
17 time point for establishing treatment success or
18 treatment failure will certainly help to minimize
19 lost to follow up, and I think that is partly why
20 we are persevering on questions about PCR as an
21 endpoint because it would certainly help to
22 minimize lost follow up.

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1 DR. SOSA-ESTANI: There is a correlation
2 between the reduction of antibodies and the
3 clinical benefit in studies in Argentina, at least
4 three studies showing that.

5 In addition, I think personally PCR and
6 the current protocol is robust to show benefit
7 after treatment, but there is some new information
8 like we are talking about reduction of antibodies,
9 the reduction of parasitic load is new information
10 also demonstrated during the first day after
11 treatment and the effect during follow up.

12 Other information is the parasitic load
13 was demonstrated that there is a higher risk for
14 congenital transmission. The effect of treatment
15 is not necessary to become negative or absolutely
16 cured. The effect of reduction of parasitic load
17 is a clear benefit.

18 DR. NAMBIAR: I just want to make sure I
19 understand this clearly, on the presentation that
20 Dr. Schijman made, improvements in the PCR, you
21 have factored in the variability between the
22 different species. That is hopefully not an issue

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1 with the current methodology that you are
2 proposing.

3 DR. RIBEIRO: Yes, we took into
4 consideration, so we have described it. This is
5 well-characterized in terms of safe performance,
6 and for the clinical trials, that was actually
7 taken into consideration.

8 Perhaps I should just add one comment,
9 something that we have done and we have not
10 described, just a matter of detail. We actually
11 did genotyping of all baseline samples. We
12 actually did RFLP, we also did sequencing of
13 baseline samples, and we also did it for all
14 treatment relapses, actually trying to
15 characterize the population and selection. We did
16 that.

17 We actually did hemocultures in all the
18 treatment failures also, looking for really a
19 broader characterization there. In terms of other
20 assays, we actually did besides the lytic
21 serology, conventional serology, we did lytic
22 antibodies. We did the APOA 1. We have that for

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1 all time points. We actually have those frozen
2 samples. They were all saved at once, because
3 that was the recommendations that we received.

4 I know for some of the trials presented
5 this morning, this is all available and could be
6 reviewed. There will be samples also to be
7 analyzed.

8 DR. WHITAKER: When you are looking at
9 the PCR assays and you are validating them, do we
10 have a substantial population or cross section of
11 everybody or have they been mainly validated in
12 either pre-treatment or chronic?

13 DR. SCHIJMAN: Could you repeat that?

14 DR. WHITAKER: I was just wondering when
15 we are talking about accurate validation, when
16 they have been validated, is it primarily in pre-
17 treatment or do we have a nice equivalent section
18 of children, pre-treatment, chronic, acute?

19 DR. SCHIJMAN: We used artificial
20 samples that are spiked with known titers of
21 parasites. If the analysis has a good
22 sensitivity, then we proceed with blind clinical

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1 samples. In the first international study, we
2 worked with chronic Chagas Disease patients.

3 It was no more than 70 percent of the
4 time, the best techniques, one sample per patient,
5 gave no more than 70 percent of sensitivity.

6 Afterward, with the strategy we used for the E1224
7 study, using three samples per patient, we got the
8 sensitivity to 90 percent.

9 DR. WHITAKER: Three samples being three
10 separate blood draws? Three separate PCRs?

11 DR. SCHIJMAN: Yes. There were three
12 samples, and then we performed the PCR by
13 duplicating each one of the samples, and if the
14 sample was negative, we performed a third PCR, and
15 with that we could enhance sensitivity 10 percent.

16 If the patient had at least one PCR
17 result, it was considered positive and was
18 included in the trial.

19 I'm talking only about this study
20 because as I mentioned, this population has very,
21 very low parasitic loads.

22 DR. RIBEIRO: Perhaps to go back to the

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1 question, if there is data across different
2 populations and disease stages, I think basically
3 there is quite a bit of data generated for sure
4 before and after treatment in chronic Chagas, as
5 indicated by Dr. Schijman.

6 There is also data in children using the
7 same technique, different volume, and there is
8 data also in transplant patients. I think there
9 is data also from the foodborne using the same
10 technique, in my understanding.

11 The issue with the oral is because it
12 actually becomes so concentrated that there is a
13 need for dilution, as I understand; right?

14 DR. SCHIJMAN: Yes.

15 DR. RIBEIRO: It inhibits.

16 DR. SCHIJMAN: We had to dilute it, same
17 when you analyze for HIV with very high parasitic
18 loads.

19 DR. RIBEIRO: Clearly, this needs to be
20 presented in such a way that this is altogether,
21 right, as a package, as I understand it, as a
22 device, and treated as such. I understand the

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1 question from that angle.

2 I think perhaps it is worth noting today
3 that there is an effort from the Ministry of
4 Health in Argentina and a funded project for the
5 development of a kit, PCR kit. The initial focus
6 is for congenital Chagas, and there are now
7 discussions on validating -- it is actually in
8 this kit for adult Chagas. This is also under
9 discussion.

10 DR. SOSA-ESTANI: Yes, we are including
11 at this moment the use of PCR in three specific
12 situations, for acute phase, congenital infection
13 during the first three months, if possible, of
14 diagnosis, during treatment, and monitoring for
15 activation in patients with immunocompromise.

16 DR. NAMBIAR: We certainly commend you
17 for all the work you have done. It is the ability
18 to look at all this information, get all the
19 details ironed out before we can actually make a
20 final decision, but we certainly congratulate you
21 for all the work you have done over the years, it
22 is great.

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1 Are there any other comments or
2 questions from the panel members before I turn it
3 over to Dr. Farley? I think we are getting close
4 to wrapping up this interesting day.

5 (No response.)

6 DR. NAMBIAR: Seeing none, I turn it
7 over to you, John.

8 CLOSING REMARKS AND ADJOURN

9 DR. FARLEY: I know a lot of you have
10 traveled quite some distance to be here, and I
11 want to assure you that it was worth it. This has
12 been a very useful day for all of us. I think we
13 in the office here particularly like these
14 workshops because it is a rare opportunity to get
15 all the right people in the same room at the same
16 time actually talking to each other. That tends
17 to advance drug development.

18 We have heard loud and clear from our
19 patients this morning that one of their big needs
20 in the United States is having treatment options
21 available, and more readily available than they
22 currently are.

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1 I want to thank everyone. I want to
2 remind you that if there was something you didn't
3 get to say today, there is an open docket that was
4 made known to you this morning. That is available
5 for your comments.

6 I think this is the start of some
7 dialogues that are going to continue. For drug
8 developers, as you know, the Division is available
9 for meetings under the guidelines set forth under
10 the Prescription Drug User Fee Act, and that
11 happens very often, so just a reminder.

12 I want to wish everyone safe travels,
13 and thank you very much for your time today. It
14 was a great meeting.

15 (Applause.)

16 DR. MEYMANDI: If I could just reiterate
17 again that I'm hoping this is just not dialogue,
18 that we come up with concrete plans to move
19 forward in a rapid fashion so we can get access to
20 these drugs. Thank you.

21 (Applause.)

22 (Whereupon, at 4:57 p.m., the meeting

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was adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

2

I, CHRISTINE ALLEN, the officer before whom the

3

foregoing proceeding was taken, do hereby certify

4

that the proceedings were recorded by me and

5

thereafter reduced to typewriting under my

6

direction; that said proceedings are a true and

7

accurate record to the best of my knowledge,

8

skills, and ability; that I am neither counsel

9

for, related to, nor employed by any of the

10

parties to the action in which this was taken;

11

and, further, that I am not a relative or employee

12

of any counsel or attorney employed by the parties

13

hereto, nor financially or otherwise interested in

14

the outcome of this action.

15

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CHRISTINE ALLEN
Notary Public in and for the
State of Maryland

21

22

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