



U.S. Food and Drug Administration

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH
(CDER)

+ + + +

PUBLIC HEARING

+ + + +

EXPANDED ACCESS TO DIRECT-ACTING
ANTIVIRAL AGENTS FOR THE TREATMENT OF
CHRONIC HEPATITIS C INFECTION
IN PATIENTS WITH UNMET MEDICAL NEED

+ + + +

FRIDAY, APRIL 30, 2010

The hearing convened in the Regency Conference Room of the Rockville Hilton, located at 1750 Rockville Pike, Rockville, Maryland, at 9:00 a.m., Jeffrey Murray, MD, Chair, presiding.

PANEL MEMBERS:

JEFFREY MURRAY, MD, Deputy Director, DAVP,
OAP, CDER
DEBRA BIRNKRANT, MD, Director, DAVP, OAP, CDER
EDWARD COX, MD, Director, OAP, CDER
RUSSELL FLEISCHER, PA-C, MPH, Senior Clinical
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PATRICK HARRINGTON, PhD, Virology Reviewer,
DAVP, OAP, CDER
LINDA LEWIS, MD, Medical Officer Team Leader,
DAVP, OAP, CDER
JULIAN O'REAR, PhD, Lead Virologist, DAVP,
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KIMBERLY STRUBLE, PharmD, Medical Team Leader,
DAVP, OAP, CDER
WILLIAM TAUBER, MD, Medical Officer, DAVP,
OAP, CDER

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OPENING REMARKS:

PETER LURIE, MD, MPH, Office of the
Commissioner, FDA

PRESENTERS:

JANICE K. ALBRECHT, PhD, Vice President
Hepatology Clinical Research, Merck
MARK ANTELL, People with Bleeding Disorders
and HCV
DAVID APELIAN, MD, PhD, MBA, Senior Vice-
President of Research and Development and
Chief Medical Officer, GlobeImmune, Inc.
PAUL BRAYSHAW, People with Bleeding Disorders
and HCV
LYNDA DEE, Executive Director of AIDS Action
Baltimore, Co-Chair of the Maryland Hepatitis
Coalition
VICTOR DE GRUTTOLA, ScD, Chair and Professor
of Biostatistics, Harvard School of
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FRANK DUFF, MD, Vice President, Product
Development, Virology Genentech
MARGO HEATH-CHIOZZI, MD, Vice President,
Global Regulatory Strategy, Virology and
Oncology, Bristol-Myers Squibb Company
CHARLES HOWELL, MD, University of Maryland
School of Medicine
ROBERT KAUFFMAN, MD, PhD, Chief Medical
Officer, Vertex Pharmaceuticals, Inc.
JULES LEVIN, Executive Director, NATAP
PATRICIA LUPOLE, Executive Director,
HCVets.com
DOUGLAS L. MAYERS, MD, CMO, Idenix
Pharmaceuticals, Inc.
MARIBEL RODRIGUEZ-TORRES, MD, Chief Medical
Officer, Fundacion de Investigacion de Diego
TRACY SWAN, Hepatitis/HIV Project Director,
Treatment Action Group
DIANA L. SYLVESTRE, MD, Assistant Clinical
Professor of Medicine, University of
California, San Francisco, Executive
Director and Founder, OASIS

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

2 9:00 a.m.

3 CHAIR MURRAY: While we're
4 finishing up with some of the audio visual
5 issues, I think I'm going to go over some
6 logistics for this meeting, and then we're
7 going to have some brief opening remarks from
8 Dr. Peter Lurie, from the Office of the
9 Commissioner.

10 I'm the Deputy Director for the
11 Division of Antiviral Drug Products in the
12 Center for Drug Evaluation and Research in
13 FDA, and I'm the presiding officer for this
14 public hearing today. And I'm going to ask
15 the panel members, which are all FDA people,
16 to introduce themselves, and we'll begin on my
17 right.

18 DR. O'REAR: Jules O'Rear, Virology
19 Team Leader, Antiviral Drugs.

20 DR. HARRINGTON: Pat Harrington,
21 Virology Reviewer, Antiviral Drugs.

22 DR. BIRNKRANT: Debbie Birnkrant,

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1 Director, Division of Antiviral Products.

2 Ms. STRUBLE: Kim Struble, Medical
3 Team Leader, Antivirals.

4 DR. COX: Ed Cox, Director of the
5 Office of Antimicrobial Products.

6 MR. FLEISCHER: Russ Fleischer,
7 Clinical Reviewer, Antiviral Products.

8 DR. LEWIS: Linda Lewis, Medical
9 Team Leader, Antivirals.

10 CHAIR MURRAY: Okay, so welcome,
11 and this is actually the first Part 15 hearing
12 that the Division of Antiviral Products has
13 had in its history, and the topic is Expanded
14 Access to Direct Acting Antiviral Agents for
15 the Treatment of Chronic Hepatitis C Infection
16 in Patients with Unmet Medical Need.

17 So the agenda is as follows. We're
18 going to have opening remarks from Dr. Lurie,
19 as I stated. Then I'm going to open up with
20 an informational presentation on expanded
21 access, regulations, and specific issues
22 relating to the development of hepatitis C

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1 products, and then following my presentation,
2 I will take -- there will be a short time for
3 some clarifying questions from the audience.

4 But after that, then the clarifying
5 questions of the rest of the presentations
6 will come from the FDA panel, and there are
7 white index cards out at the desk, where, if
8 the audience wants to ask clarifying questions
9 of any panel member, they can. And then -- or
10 any presenter, they can write it on a card.

11 You can pass it back to the desk,
12 and we can get to your questions later. The
13 panel will then get to your questions later on
14 in the day to ask presenters, if we -- if we
15 see fit.

16 So we have 16 speakers who pre-
17 registered to speak at today's hearing. So
18 the agenda is packed. We'll also provide time
19 at the end of the day, it's on the agenda, for
20 anybody who has not spoken or pre-registered
21 to speak, and provide their views.

22 If you want to do that, again, make

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1 a request. Write your name down on one of the
2 white cards out at the desk, and we'll divvy
3 up time for that period at the end of the day.

4 So Susie Dill over there is the
5 person that you will hand the cards to or can
6 ask questions on how to do that. We're also
7 welcoming written submissions for the record.

8 At the end of the agenda, we have included
9 the web address for an FDA web page that
10 includes information on today's hearing. The
11 record will remain open until June 25th, 2010.

12 So we've been able to accommodate
13 most requests for the amount of time that
14 speakers have requested. At the beginning of
15 each time, I'll remind you that you have
16 allotted time. We try to give everybody the
17 time they asked, up to a limit of 15 minutes
18 because of the number of speakers.

19 So are the -- speaker lights
20 working? Yes. All right, so, we have speaker
21 lights, and the light will flash yellow when
22 you have one minute to go and red when your

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1 time is officially up.

2 After each presentation has been
3 completed, there will be approximately three
4 minutes for clarifying questions from the
5 panel, and, again, the audience if you have
6 clarifying questions, write them on a card,
7 and we'll try to get to them at some point in
8 the -- during the meeting.

9 So no participant may interrupt the
10 presentation of another participant, and only
11 the presiding officer and the panel members
12 may question any person at the conclusion of
13 each presentation.

14 A little bit more. Public hearings
15 under Part 15 are subject to FDA's policies
16 and procedures for electronic media coverage
17 of the FDA's public administrative
18 proceedings. Representatives of the
19 electronic media may be permitted, subject to
20 certain limitations, to videotape, film, or
21 otherwise record FDA public administrative
22 proceedings, including presentations by the

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1 participants.

2 The hearing will be transcribed.
3 So please remember to introduce yourself prior
4 to speaking. Copies of the transcript and
5 today's presentations may be accessed on the
6 internet. The web link is also provided on
7 the agenda. Please refer to the site for
8 additional information.

9 So we're very happy to have this
10 meeting. It's very timely. Hepatitis C drug
11 development is exciting. We're looking
12 forward to hearing views on a wide spectrum of
13 issues, and we hope for a very productive
14 session.

15 With that, Dr. Lurie, if you would
16 like to start with some opening remarks?

17 DR. LURIE: Good morning,
18 everybody. I first want to thank Jeff Murray
19 and Susie Dill for setting up this meeting and
20 for giving me the opportunity to deliver these
21 comments. It's actually my first comments as
22 a relatively new employee at FDA. So I'm

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1 excited for the opportunity.

2 I want to use my few minutes to
3 accomplish just two goals. First, to let you
4 know a little bit about some other government
5 activities that are going on with respect to
6 hepatitis C and hepatitis B, and secondly, to
7 help set the stage for the important
8 discussions you'll be having this morning and
9 this afternoon.

10 I just want to apologize in advance
11 for having to run off to give my second speech
12 as an FDA employee at 10:45.

13 So the most recent impetus for
14 government action on a chronic hepatitis
15 infection is the Institute of Medicine report,
16 which many of you, I think, will be familiar
17 with. It was entitled hepatitis and Liver
18 Cancer: A National Strategy for Prevention and
19 Control of hepatitis B and C, and was released
20 just in January of this year.

21 The report made the usual
22 estimates: 2.5 million and -- between 2.5 and

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1 5.3 million people infected chronically with
2 either hepatitis B or C, and 15,000 people who
3 die annually either from chronic disease or
4 from virally induced liver cancer.

5 It concluded that, quote, "The
6 current approach to the prevention and control
7 of chronic hepatitis B and C is not working."

8 And went on to recommend a series of
9 improvements in public health awareness,
10 surveillance, and integration of services.

11 Since the release of that report,
12 the Assistant Secretary for Health, Dr. Howard
13 Koh, has convened and is leading a viral
14 hepatitis interagency workgroup that has been
15 developing a strategy for the Department of
16 Health and Human Services to address the
17 public health problem of viral hepatitis.

18 The group has begun by cataloging
19 the various activities related to hepatitis in
20 all the different DHHS agencies. And as you
21 know, for FDA these range from reviewing
22 diagnostic tests to setting standards for the

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1 protection of the blood supply, to reviewing
2 vaccines that prevent hepatitis, and drugs
3 that treat it.

4 Particularly relevant to this
5 meeting, the agency is also developing, as
6 many well know, the guidance for industry for
7 the development of drugs to treat hepatitis C.

8 And we fervently hope that this will
9 facilitate the review and approval of new,
10 effective treatments for that infection.

11 The interagency workgroup has now
12 turned its attention to developing an overall
13 government approach to viral hepatitis,
14 building on the recommendations of the IOM
15 report.

16 My second point relates to expanded
17 access. As you all know, one of the most
18 consistent challenges that the agency has
19 faced over the years has been the balancing of
20 the desire of patients, particularly those
21 with serious or life-threatening conditions
22 like hepatitis B or C, for access to the

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1 newest therapies with the need to maintain the
2 integrity of the product approval system on
3 the one hand, and the desire to protect
4 patients from the risks of unproven therapies.

5 Until 1987, there was no formal
6 recognition of what was called treatment use
7 in the FDA's investigational new drug, or IND,
8 regulations. But drugs were informally made
9 available for treatment use if certain
10 conditions were met.

11 That system was significantly
12 reworked in the late 1980s, when the
13 combination of a growing epidemic of AIDS, a
14 fatal disease among the young, combined with
15 the forces of AIDS activism to force a
16 reconsideration of the issue. The new
17 regulations explicitly recognized the
18 treatment IND for the first time and
19 implicitly acknowledged treatment uses for
20 individual patients.

21 The agency's policies were again
22 recalibrated very recently in the form of two

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1 regulations released in August of 2009. The
2 first laid out three separate formalized
3 expanded access approaches. One for
4 individual patients; two, for the old
5 treatment IND approach that dated back to
6 1987, and it also created a third path in
7 between those two paths that was for
8 intermediate sized populations.

9 The second rule clarified the
10 circumstances under which sponsors could
11 charge patients for the costs incurred in
12 trials conducted on INDs, a provision also
13 intended to expand access. Jeff Murray will
14 provide more details on these regulations in
15 his presentation.

16 All of this bring us to today.
17 This meeting is in part the result of a
18 citizen petition filed in September 2009 on
19 behalf of patients with hemophilia infected
20 with hepatitis C. Petitioners sought a public
21 hearing, as well as expanded pre-approval
22 access to promising drugs for hepatitis C.

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1 This meeting will address those
2 issues. More broadly, one can think of
3 today's meeting as yet another stage in FDA's
4 ongoing consideration of its expanded access
5 policies. Today's discussion will bring a new
6 level of sophistication and complexity to bear
7 on the question of expanded access.

8 For one thing, it will focus on a
9 single disease, not on the more generic
10 questions of access that were raised by the
11 aforementioned regulations, which were
12 designed for all serious or life-threatening
13 conditions.

14 For another, it will require
15 consideration of an aspect of expanded access
16 that has not typically been part of the
17 equation. The public health prerogative of
18 avoiding the induction of drug resistance in
19 patients who enroll in expanded access
20 programs, particularly those involving only a
21 single direct acting antiviral agent.

22 I'm sure we're all looking to an

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1 interesting and productive day. Thank you.

2 CHAIR MURRAY: Thank you, Dr.
3 Lurie. Okay, I want to start out with a
4 definition. We've been using the term DAA,
5 direct acting antivirals, and these are also
6 sometimes called STAT-C drugs. And our
7 definition of a direct acting antiviral is an
8 agent that interferes with specific steps in
9 the HCV replication cycle through a direct
10 interaction with the HCV polyprotein and its
11 cleavage products.

12 Today I'm going to tell you a
13 little bit about Part 15 hearings, talk about
14 expanded access regulations, briefly discuss
15 what happened with HIV in expanded access so
16 perhaps we can learn from that historical
17 perspective.

18 I want to discuss important
19 considerations for expanded access of DAAs for
20 HCV, and I want -- at the end, I'm going to
21 wrap up with the summary of the issues for
22 public comment that was published in the

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1 Federal Register.

2 So what is a Part 15 hearing? It's
3 really one of the two types of public meetings
4 that FDA can host and convene. One is an
5 advisory committee, which probably most people
6 are more familiar with. This is the other,
7 and this really is an opportunity -- a Part 15
8 hearing is an opportunity for FDA to listen to
9 opinion from any stakeholder on important
10 issues.

11 There is no screen process.
12 There's not a voting panel or conflict of
13 interest screening of experts. So really
14 anybody can talk.

15 So the goals for today's meeting
16 are really fairly simple, to listen and learn,
17 to start a dialog between the many
18 stakeholders. We have to realize that this
19 won't be the last discussion on these issues.

20 There's other meetings planned with other
21 groups, including the forum that does a lot of
22 meetings on HIV, doing some meetings for HCV

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1 now as well.

2 Also there may be another advisory
3 committee to discuss issues, an FDA advisory
4 committee to discuss hepatitis C development
5 issues. And we hope to get a guidance out
6 fairly soon.

7 So today we hope to gain enough
8 insight to help move the HCV drug development
9 field a few steps in a positive direction, and
10 today it's not a task force meeting. We're
11 not here to get commitments or negotiate, or
12 to strike up deals.

13 I just wanted to review some of the
14 new expanded access regulations that came out
15 at the end of last year, now under Subpart I
16 of the regulations, and really it just
17 consolidates treatment use into a separate
18 subpart, and establishes some parameters,
19 lists some requirements, and it really defines
20 three categories of expanded access.

21 One might consider expanded access
22 now may be a misnomer. Could just be

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1 preapproval access because some of the
2 expanded access does not have -- do not have
3 to be expansive programs.

4 So there's individual, intermediate
5 and treatment IND, and I'll go over these
6 quickly. So what is expanded access again?
7 It's treatment access outside of a clinical
8 trial to investigational drugs. Like I said,
9 it doesn't have to be a huge, multi-thousand
10 patient program. It is for patients with
11 serious, life-threatening diseases or
12 conditions, and when there is no comparable
13 alternative therapy to diagnose, monitor,
14 treat disease or condition.

15 So, what's some -- what are some of
16 the principals or expanded access programs?
17 First of all, we believe that approved drug
18 products provide the greatest access to the
19 greatest number of patients who need effective
20 therapies.

21 Really, you can't think of expanded
22 access without thinking of -- of drug

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1 development at the same time because you have
2 to continue to have drug development while
3 you're doing expanded access, because getting
4 that information for any -- any individual who
5 might use the drug, including those with
6 special health needs, it is important that
7 that continue as part of drug development,
8 even if you have an expanded access program.
9 So expanded access should not jeopardize drug
10 development, and, again, drug development
11 system provides the greatest evidence of a
12 product's benefit.

13 Also, there has not ever been and
14 there isn't now any prohibitions against use
15 of multiple investigational agents, either in
16 a clinical trial or expanded access program.
17 And this could be done in multiple ways, by
18 having two investigational agents in one
19 program, or co-enrollment in multiple programs
20 from different sources.

21 So I mentioned that there were
22 three basic categories of expanded access, and

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1 they -- it's a whole range from one patient to
2 thousands of patients. So an individual
3 patient, either single or emergency -- a
4 single IND or emergency use. Intermediate,
5 what is meant by intermediate? Talk about
6 that a little bit. Roughly 100 patients. No
7 one is wedded to that exact number. And then
8 treatment INDs, which with HIV we've run
9 anywhere from hundreds to many tens of
10 thousands of patients.

11 So we weigh the risk and potential
12 benefits for each expanded access type
13 request. So for an individual patient risk,
14 individual patient expanded access program,
15 the risk benefit ratio is a little bit
16 different. The hurdle is a little bit lower.

17 So for this case, physician
18 determines that the probable risk from the
19 drug does not exceed that from their disease,
20 and FDA determines that the patient cannot
21 obtain access under another type of IND or
22 protocol. Like I said, it can be emergency

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1 use, if it's emergent, or a single use.

2 Safety and risk for intermediate
3 size population can be sufficient evidence to
4 assess whether the drug is safe at the
5 proposed dose and duration, and to justify the
6 size of the exposed population. So, if it's
7 50 or 200, should be justified by the
8 preliminary safety and efficacy data that is
9 available at the time to pick a sufficient
10 dose that we think is reasonably safe and
11 active in some way.

12 Some additional safeguards for the
13 intermediate size population requires an
14 explanation of why the drug cannot be -- why
15 patients cannot be enrolled in a clinical
16 trial, or -- and also, there will be an annual
17 review to determine whether a treatment use
18 IND would be more appropriate if the
19 population appears to be getting larger and
20 larger.

21 So for treatment use, and this is
22 probably what we're most familiar with with

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1 HIV, usually the drug is being investigated in
2 a clinical trial to support marketing, or
3 trials are already complete.

4 So usually, we're looking for, you
5 know, a serious disease, evidence from Phase
6 III or compelling data from Phase II. For
7 immediately life-threatening diseases, it
8 could be earlier evidence from Phase II, or it
9 could be based on more preliminary clinical
10 evidence.

11 And the additional safeguards for
12 this type of expanded access is there's a 30-
13 day post-submission waiting period of the
14 protocol before initiating. So, it's like
15 initiating a new IND. Of course, there's a
16 monitoring as there would be for other
17 protocols, at least for serious and unexpected
18 adverse events.

19 So some historical perspective:
20 prior meetings on expanded access for HIV.
21 Well, we didn't have a Part 15 hearing, but we
22 had one that was similar in conduct to a Part

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1 15 hearing back in '94 September. We had a
2 meeting on expanded access of HIV drugs, and
3 this was actually before the protease
4 inhibitors were kind of reaching prime time.

5 And we had an open public hearing
6 format where we had a lot of people give their
7 views, like today. Although at that time, we
8 did have the panel there, the Advisory
9 Committee panel there as well.

10 There was other meetings on
11 expanded access that occurred later by a group
12 called, if anyone remembers this, the National
13 Task Force on AIDS Drug Development. I
14 vaguely remember being at that meeting.

15 The National AIDS Task Force was a
16 15-member task force formed in '93. It lasted
17 for two years, and it was a kind of heavy
18 hitting task force. It had the heads of NIH
19 and FDA. It included prominent AIDS
20 activities, pharmaceutical executives, top
21 researchers, and the assistant secretary of
22 health.

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1 And the task force was charged with
2 identifying obstacles to development of drugs
3 for HIV, and to formulate ways to address
4 those obstacles.

5 In February '95, they had a meeting
6 really to discuss if there was enough drug
7 available from the manufacturers and from the
8 manufacturing process to allow expanded access
9 of protease inhibitors, while at the same time
10 being able to complete the Phase III trials,
11 which were well under way.

12 My recollection of the outcome of
13 this meeting is that it may have influenced
14 sponsors to agree to expanded access in a more
15 timely manner.

16 Right now, we don't have a multi-
17 agency task force for hepatitis C drug
18 development, but we do have flexible
19 regulations for expanded access, and -- but
20 new regulations beyond this, what I've
21 outlined for you, would require more
22 legislation from higher levels.

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1 So what did we learn from HIV
2 access programs? Some lessons learned? Well,
3 for the short-term, I'm sure there was a lot
4 of clinical benefit. It was even life
5 prolonging, I'm sure, in many cases. There
6 was probably durable viral suppression in some
7 expanded access programs when there were other
8 drugs that were available for a complete
9 regimen for those people participating.

10 For the long-term, we did realize
11 some down sides. There was emergence of
12 resistance when taken without support of a
13 suppressive regimen. It was essentially what
14 amounted to functional monotherapy
15 sequentially, and what we were left with was a
16 cohort of people who had multi drug class
17 resistance, and people needing salvage
18 therapy, and today, people who need what is
19 often called deep salvage therapy.

20 So, recently, there has been some
21 meetings discussing reinventing of expanded
22 access for HIV. So reinventing HIV expanded

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1 access, what is that new paradigm all about?

2 Well, it's really focusing on
3 combination therapy whenever possible, with
4 approved or unapproved drugs. Whatever you
5 can patch together, basically. It's thinking
6 about co-enrollment in multiple expanded
7 access programs, if you can get them to
8 converge, which always isn't easy. And
9 thinking about protocols, maybe even smaller
10 protocols, like intermediate size protocols,
11 that it could include more than one
12 investigational agent.

13 So these protocols could be from
14 NIH, from an academic sponsor, from a
15 researcher in the community, or from
16 collaboration of two or more sponsors. Any
17 mix, really.

18 So what about drug access for HCV
19 treatments? Well, what are some of the
20 requirements or prerequisites? Well, we need
21 willingness of a pharmaceutical sponsor.
22 There is no mandate from FDA that expanded

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1 access program has to occur. There's nothing
2 in the regulations for that.

3 There also needs to be sufficient
4 data available to reasonably characterize a
5 safe and active dose, if you're giving it to
6 more than just one or two patients in single
7 or emergency INDs.

8 Thinking about treatment INDs, if
9 we're thinking that thousands of patients
10 might be participating, I think the preference
11 would be this to occur during or after Phase
12 III trials are fully enrolled, or well
13 underway, so as -- we're sure that development
14 is not going to be interfered with.

15 Like I said, there's plenty of
16 alternatives for treating people earlier in
17 smaller protocols, single protocols, single
18 patient protocols, and this could really occur
19 almost at any stage of drug development.

20 And, again, multiple agents are
21 fine, and actually multiple agents are needed,
22 especially those people who can no longer take

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1 interferon ribavirin or for whom interferon
2 and ribavirin is contraindicated. And that's
3 one of the big issues for today and for which
4 we need more discussion.

5 What is the appropriate populations
6 for expanded access with direct acting
7 antivirals? So what are some of the
8 recommendations that we've been giving out to
9 industry and some things that we've discussed
10 at various meetings when using two or more
11 direct acting antivirals in a protocol, in a
12 research protocol?

13 Well, first, at this point, we're
14 not sure, and I don't think anyone is sure, if
15 direct acting antivirals alone without
16 interferon and ribavirin can yield permanent
17 SVRs. And we don't know how many direct
18 acting antivirals are needed.

19 One appears certainly not to be
20 enough. Two, probably not enough. Three?
21 Who knows? Four? I don't know. Ideally, we
22 would like to see combinations of direct

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1 acting antivirals with different mechanisms of
2 action. If not, there should be a rationale
3 for why the combination would be additive or
4 perhaps synergistic.

5 And some of the data recommended on
6 individual agents before combining them in
7 trials are as follows: cell culture
8 combination data, resistance and cross
9 resistance data, animal tox data on the
10 individual drugs. We're no longer, for the
11 most part, asking for combinations toxicology
12 studies to be done unless there's a particular
13 safety issue with the tox data from the
14 individual drugs.

15 We think that there should be some
16 human safety data, either as preliminary
17 monotherapy, the short, very short monotherapy
18 trials, or with standard of care, interferon,
19 ribavirin. We'd like to see enough
20 preliminary HCV activity to have a dose
21 rationale based on these preliminary trials.

22 We're really concerned about

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1 selecting a reasonably active dose for people
2 who are vulnerable, so they just don't waste
3 the drug needlessly, or perhaps the drug class
4 if there's cross resistance. And if drug-drug
5 interaction is expected based on in vitro
6 metabolism, drug-drug interaction studies may
7 need to be done first.

8 I think everybody in this room
9 knows about HCV viral kinetics that replicates
10 at an extremely high rate daily, and that what
11 we think is all single and double mutations,
12 those that can confer drug resistance
13 preexist. And under drug pressure, the
14 preexisting drug resistant strain becomes
15 dominant in approaching the original viral
16 steady state.

17 There has been some publications of
18 monotherapy studies for 14 days, with the
19 protease inhibitor. In this case, it's
20 telaprevir, and really the majority show
21 evidence of mutations developing in a very
22 short time, within 12 days.

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1 We also have to remember that
2 mutations, especially for some classes, are
3 shared among members of the class, and
4 sometimes all members of the class. And
5 there's evidence to suggest that resistance
6 variance selected during therapy may persist
7 long-term. And we have I guess seen at least
8 subsets of resistant virus in patients out to
9 three years, who have taken various new direct
10 acting antivirals.

11 So in the last couple minutes
12 before questions, I just wanted to go over
13 again what some of the issues are that we've
14 put out in the Federal Register that are for
15 public comment today.

16 So what types of patients with
17 chronic hepatitis C are most appropriate for
18 DAA expanded access programs, taking into
19 account disease stage, previous treatment, and
20 other disease characteristics, such as poor
21 prognostic factors?

22 Two, under what circumstances and

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1 in which populations would early access to a
2 single DAA be appropriate? Presumably, we're
3 thinking this would be used with interferon
4 and ribavirin. Again, under what
5 circumstances and in which populations would
6 early access to multiple DAAs be appropriate?

7 What potential adverse reactions
8 should be contemplated in formulating DAA and
9 multiple DAA treatment use protocols or other
10 intermediate sized protocols? How can
11 pharmaceutical companies, government,
12 academia, community physicians, and activists
13 collaborate to provide treatment use of
14 multiple new agents, with the goals of
15 maximizing response and reducing the emergence
16 of resistance or multi drug resistance, and
17 adverse drug reactions?

18 When developing DAAs for marketing,
19 because we always have to think about
20 marketing when we're thinking about expanded
21 access, what types of studies should be
22 conducted to best address unmet medical needs

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1 for patients with chronic hepatitis C,
2 including those with greatest risk of
3 progression of liver disease, those on
4 transplant waiting lists for example, and
5 those with lowest predicted response rates?

6 With that, I will -- we're going to
7 try to keep on time. And I went longer than I
8 expected, I think. I can take some clarifying
9 questions from the audience, if there are any.

10 And maybe if you could go to the microphone?

11 There's one right over there. And introduce
12 yourself, again, because we are transcribing
13 this. Thank you.

14 MS. LUPOLE: Yes, sir, Patricia
15 Lupole with HCVets, educational website. You
16 said that the three years -- on the issues for
17 the protease inhibitors, three years on the --
18 the resistance, the length of time that you're
19 seeing resistance in these drugs lasting.
20 There -- is that what I'm --

21 CHAIR MURRAY: There have been
22 reports of variants related to mutations

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1 associated with drug resistance in patients.
2 You can be detectable out to three years.
3 Very few patients.

4 MS. LUPOLE: Out to three years?

5 CHAIR MURRAY: Yes.

6 MS. LUPOLE: And this data is based
7 on?

8 CHAIR MURRAY: Reports presented at
9 meetings, yes.

10 MS. LUPOLE: Okay, I didn't realize
11 that there was any option there.

12 CHAIR MURRAY: It might not be the
13 major dominant species, but in a proportion of
14 patients, you can still see drug associated
15 resistance mutations.

16 MS. LUPOLE: Okay, thank you.

17 CHAIR MURRAY: Any more clarifying
18 questions on expanded access regulations, HIV
19 expanded access history, or the issues for
20 today before we begin with our presenters,
21 which I'm excited to hear? Okay, perfect
22 timing. Okay, we're ready to go. I'll go

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1 back there to introduce the next speaker.

2 All right, our first presenter is
3 Jules Levin, Executive Director of NATAP, and
4 Jules, thanks.

5 MR. LEVIN: So let me first -- I'm
6 pleased that the FDA is holding this hearing
7 today with prodding from other sources before
8 having this hearing, starting about a year
9 ago. It took us a year to get to this point,
10 but I think that it's good timing actually.

11 I think the timing of this hearing
12 is good considering where we are with drug
13 development right now. And I want -- so why
14 are we all here today? I think the reason
15 we're here today is as in HIV 12 years ago
16 approximately or so, people were dying and
17 needed access to therapy or they would've
18 died.

19 And you know, some observers in
20 this field think that the FDA had taken the
21 position that hep C was different, that it was
22 a lifetime disease, that it could take 30

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1 years to get sick and die, and only 20 percent
2 maybe do get sick and die. And so a lot of
3 observers felt that the FDA was taking a more
4 soft approach with hep C, not as serious as
5 HIV.

6 I'm one of those people, and so why
7 are we here today? We're here today because
8 that's not the case. Many people are facing
9 life and death situations right now, at risk
10 for dying before oral drugs become available.

11 And so I think that we need to address that,
12 and that's why we're here today, to do that.

13 So the title of my talk is a New
14 Regulatory Process. I'm going to propose a
15 new regulatory process, despite what Jeff
16 said. Maybe he said that because he saw my
17 slides, which I had to submit. I had to
18 submit the slides to the FDA. But I am going
19 to propose a new regulatory process, and I
20 call it early access, not expanded access, to
21 new oral HCV drugs for patients with advanced
22 liver disease.

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1 Let me say for the first time,
2 which I'll say several times during my talk,
3 I'm against expanded access for hep C. It's
4 more harmful to patients. It'll cause more
5 harm, and I'm going to propose a process that
6 I think would be much more helpful for
7 patients who are facing serious advanced
8 disease and death, and I think it's a better
9 process.

10 And I have a feeling that the
11 companies are all on board and are willing and
12 able and anxious to help out in this process.

13 I think the barrier here will be will the FDA
14 step up to the plate and facilitate us doing
15 this?

16 I think I already went through
17 this, but what I'm going to show, before I get
18 into my proposal, what I want to say is that a
19 lot of people, maybe not everyone in this
20 room, but a lot of people are under misnomer
21 that hep C takes 30 years to develop, and so
22 you can wait.

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1 Well, there was a publication that
2 came out. I think it was December
3 Gastroenterology by Gary Davis, showing a
4 model about where we are with people with
5 disease state now. And I'm going to talk
6 about that just briefly, just before I go into
7 my proposal.

8 The model reports that 25 percent
9 of people today with hepatitis C in this
10 country already have cirrhosis, and a
11 significant number have advanced to HCC and
12 decompensation. And that is because the so-
13 called baby boomers that everyone is talking
14 about have already aged. They're not -- they
15 weren't just infected yesterday. They've been
16 sitting with the disease for 30 years.

17 So the first slide here really just
18 shows the disproportionate effect of African-
19 Americans, and you can see the relative risk
20 of being hepatitis C positive is double for
21 African-Americans.

22 I very strongly believe that

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1 hepatitis C in this country is a disease of
2 African-Americans, and it's -- at first blush,
3 you may not understand what I say that, but I
4 don't have the time to really go into that,
5 but that is really very much the case if you
6 talk about this and think about it, and I'll
7 be glad to talk to anyone about it.

8 Nonetheless, you can see the risk
9 for African-Americans with hep C is double
10 here. It's not 2.5-3 million people with
11 hepatitis C in this country. This was
12 presented at AASLD a few years ago by Brian
13 Edlin at -- at Cornell. And those numbers
14 that come out of our CDC don't include
15 incarcerated, homeless, and other people where
16 the numbers increase probably up to about 5
17 million.

18 So the Gary Davis paper, let me try
19 and highlight some of the points here, as you
20 can look through my slide. The proportion of
21 chronic hepatitis C people with cirrhosis is
22 projected to reach 25 percent in 2010 and 45

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1 percent in 2030.

2 And he estimates hepatic
3 decompensation and liver cancer will continue
4 to increase for the next 10 or 13 years, but
5 I'm going to show you some data on what he
6 projects the numbers are right now for people
7 with decompensation and cirrhosis and liver
8 cancer.

9 So in 1989, cirrhosis accounted for
10 five percent of cases, 10 percent in 1998, 20
11 percent in 2006. And the proportion with
12 cirrhosis is projected to reach 25 percent in
13 2010, 37 percent in 2020.

14 So our understanding of where
15 people are at in the stage of disease, they're
16 much more advanced. There are a lot of people
17 who will probably die between now and the
18 launch of the two protease inhibitors in 2011,
19 and may die before we can have two orals on
20 the market.

21 So this is -- these are a couple of
22 graphs from his publication in

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1 Gastroenterology, and you can see -- I don't
2 know if you can see the years there where we
3 are, 2010. And I labeled the lines,
4 cirrhotics and chronic, and you can see 2010
5 the numbers of cirrhotics are peaking. And I
6 didn't label this one, so let me point it out.

7 You can see cirrhotics, the cirrhotics is
8 this line right here. And you can see where
9 we're heading with cirrhotics.

10 And here is his graph on
11 decompensated cirrhotics and -- and HCC, and
12 you can see 2010, where the graphs are taking
13 us. So this is where we are today. It's a
14 model. It's his projection, but it's the best
15 we have, and it's probably true, or I wouldn't
16 be saying it.

17 So I just want to get to my
18 regulatory process now, and there are three
19 points. So I'm proposing that access begin in
20 Phase II, and -- okay. So the proposal for a
21 new regulatory process has several points.
22 The first one is access should be provided

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1 during Phase II.

2 Expanded access in HIV, as Jeff
3 outlines, has traditionally been provided
4 during Phased 3 studies, to not interfere with
5 studies. But I -- as I said, I think expanded
6 access will do more harm to patients with hep
7 c.

8 What I concerned about? I'm
9 concerned about safety and drug resistance.
10 Now we don't fully understand drug resistance
11 in hep C. We don't know if it's going to
12 persist. We don't know if it will cause
13 cross-resistance.

14 So I think we have to presume the
15 worst until anyone in the companies proves
16 otherwise. And the onus is on the companies
17 to prove that resistance will not occur, will
18 not persist, and there will not be cross
19 existence.

20 In the meantime, we have to
21 presume, and I'm in agreement with the FDA on
22 this, that resistance is a very big concern.

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1 And we know that we're still paying for drug
2 resistance and expanded access that occurred
3 in HIV for years. People are still to this
4 day going on serial monotherapy in HIV.
5 People are still failing raltegravir because
6 they didn't have enough protection around it
7 when it came out last year.

8 So I'm proposing -- I do not
9 support expanded access in hep C. I propose
10 that we provide access through studies,
11 targeted, small studies, in Phase II, where we
12 can control who gets in the studies so that
13 not just anyone can say, "I want access."

14 There will be monitoring, and the
15 proper patient populations will be selected
16 who should be in this study, so that patients
17 who can wait should wait. And so there's
18 several things that we need to do this, and
19 there's several things that we're going to
20 need from the FDA.

21 So in order to do this study in
22 Phase II, the FDA will have to adequately, in

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1 advance tell the companies what safety data
2 they need so they can do the studies for that
3 safety data, so that they can then do that
4 study in Phase II. And of course, they'll
5 probably need PK data to look at dosing for
6 patients, for patients with hepatic or renal
7 impairment because dosing may have to be
8 different. And I'm sure there are other kinds
9 of safety studies that will have to be
10 identified.

11 So I also believe that in order for
12 the companies to do this, the FDA will have to
13 provide some incentive for them to do this.
14 That could be in the form of accelerated
15 approval. As we do in HIV, there's an outline
16 for accelerated approval with a smaller
17 submission in terms of safety and activity
18 data that goes to the FDA.

19 It could be that in hepatitis C, or
20 it could be other -- and I would ask the other
21 speakers here to suggest ideas of incentives
22 that the FDA could give them if they feel

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1 willing to do that today, that would help
2 support the companies doing this.

3 The other thing that concerns me is
4 so why are the companies producing these
5 drugs? Of course they want to make money, but
6 this is all for patients. We want these drugs
7 to come to market as quickly as possible for
8 patients, and there are a lot of researchers
9 who work in the companies who are treating
10 physicians who care about patients. And I
11 think they would like to do these studies if
12 the FDA would allow them to do it and set up a
13 framework for them to do it.

14 But we're all concerned about
15 toxicities. We don't want patients to get
16 toxicities, and what would happen if a patient
17 goes on three oral drugs in a Phase II or
18 Phase III study, in an early fashion because
19 they needed the therapy. And a toxicity came
20 up, and we didn't know if it was because the
21 patient was advanced, or if it was related to
22 one of the drugs.

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1 Well, we need to be very careful
2 about that because if the FDA is not flexible
3 on this issue, that could create a problem
4 with drug development and getting those drugs
5 to market in a timely fashion. And that will
6 not work for anybody here, for the patients.
7 And we're all in the same boat here. It's not
8 the companies and the patients. It's the
9 patients and the companies together.

10 We all want these drugs on the
11 market. So I suggest to the FDA that the FDA
12 must be flexible on this and be very careful
13 about labeling. We do not want an undue
14 toxicity mentioned in that label. I don't
15 want a black box warning.

16 It could be something like in the
17 label it says, "We saw a toxicity in this
18 study, and we're not sure if it was related to
19 the advanced disease of the patient." So it
20 has to be done very softly, but we need
21 flexibility from the FDA to be able to do
22 that.

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1 So the last consideration here is
2 the patient populations that would -- we would
3 consider doing in these studies. And I really
4 don't feel that I want to spend much time on
5 that because I think that it'd be better
6 served for people with more experience to talk
7 about which patient populations. We could do
8 that at a later time, but I would encourage
9 some of the people presenting here today, and
10 I think they will be outlining specifically
11 which patient populations could be -- could be
12 subject to these studies.

13 I will say that right now there are
14 people with late stage disease who are
15 cirrhotics, who probably are at risk for dying
16 before 2011, where we expect the two protease
17 inhibitors to hit the market. They're in
18 Phase III now.

19 And what provision are we making
20 now for them to prevent them from dying? So I
21 would suggest to Merck with boceprevir and to
22 Vertex with telaprevir to consider doing a

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1 study now for those patients who may not make
2 it to 2011. And I would suggest to the FDA
3 that they try and work with us to try and make
4 that happen, but not seven months from now.
5 Maybe sooner, as soon as possible.

6 So, you know, I don't want to take
7 up too much time. I think I've said most of
8 this. I don't need to summarize it. I just
9 said it. I want to mention drug resistance.
10 I think this is really crucial.

11 We do not want to set up a
12 situation, and that's why I'm against expanded
13 access, but it's not just that. The companies
14 and the FDA must help us set up a situation
15 where we can be prepared at launch, where we
16 can try and avoid patients getting resistance,
17 and then cross resistance within the class.

18 I would ask the speakers to comment
19 on FDA incentives, safety data that will be
20 needed to do early access in Phase II, study
21 design, size of studies, inclusion, exclusion
22 criteria, patient populations that could and

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1 should be studied, and other barriers that the
2 companies or researchers who are going to be
3 speaking feel need to be addressed or that are
4 issues, like, as Jeff alluded to, drug supply.

5 How can we have drug supply to do
6 this in Phase II? So I think that's -- I had
7 one more slide, I think, but I don't remember
8 what was on it. So I'll just forget it. I
9 think I've said enough. Thank you very much.

10 CHAIR MURRAY: Any questions from
11 the Panel? Jules?

12 DR. O'REAR: I have two questions
13 for you, Jules. How does disease progression
14 correlate with viral genotype? And are the
15 proportions of HCV genotypes in African-
16 Americans the same as in the general
17 population?

18 MR. LEVIN: Well, no. African-
19 Americans are predominately genotype 1.
20 Eighty to 90 percent here in the US, and that
21 creates an issue. In terms of genotype
22 correlating with disease progression, you

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1 know, I really -- off the top of my head, I
2 don't think there is a correlation. But maybe
3 somebody else has other information they could
4 comment on that.

5 But I think you bring up a very
6 important issue, and I didn't really mention
7 it, and it's not really the subject so much
8 for this discussion, but what about African-
9 Americans and Latinos in the US, and Puerto
10 Rico? I think the companies and the FDA need
11 to show special considerations for studying
12 these populations appropriately to get the
13 data we need at launch.

14 I think this is on the plate of the
15 companies, but I would like to see some
16 special attention for this.

17 CHAIR MURRAY: Linda.

18 DR. LEWIS: Jules, I'm interested
19 in what you call a new regulatory process, but
20 when I sort of look at the different steps, it
21 seems that this could fit in with the newer
22 expanded access regulations in sort of the

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1 intermediate size study population. But I
2 guess my question about that is how would you
3 get sort of distribution of the drug
4 availability if you're in a study-type
5 population?

6 How would you get it to the people
7 who might be somewhere like my hometown, where
8 there really isn't anybody who could do a
9 formal study, but might be willing to put one
10 patient on an investigational agent? Do you
11 have sort of an idea of how that might work
12 out in the real world?

13 MR. LEVIN: What town are you from?

14 DR. LEWIS: Panama City, Florida,
15 the redneck riviera.

16 DR. LEVIN: Well, thank you for
17 your comment by saying that you think it might
18 fit within the current regulations because
19 that encourages me that the FDA may be on the
20 same place with us here on this. So, that's a
21 hopeful point.

22 To answer your question, you know,

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1 I haven't been able to think that through.
2 It's a good point, and I don't know off the
3 top of my head what the answer is. Perhaps
4 more heads will come together after this
5 meeting, or at some point, to talk about that.

6 We only can do the best we can, and
7 if we can -- I think that what we're about to
8 maybe launch after today might change the
9 whole world of hep C drug development. And I
10 think that a proposal like this, this kind of
11 doing it in Phase II with safety data and so
12 forth, might have application in other
13 diseases as well.

14 So, I'd like people to think about
15 that too, other life-threatening diseases like
16 cancer, maybe change the whole paradigm. But
17 I can't think of, off the top of my head, a
18 way to answer. But there might be -- I'm sure
19 where there's a will, there's a way, to answer
20 that question too.

21 DR. LEWIS: Thank you.

22 MR. MOORE: Thanks, Jules. With

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1 that, we have our next presentation. It's two
2 people, right? Well, we have Dr. Mayers and
3 Dr. De Gruttola.

4 DR. MAYERS: Thank you. I want to
5 thank the Agency for the opportunity to
6 present today. Dr. De Gruttola and I are
7 going to talk about mechanisms to accelerate
8 the development of combination direct-acting
9 drugs, and optimize them for treatment of
10 hepatitis C infection.

11 Where are we today? Currently, we
12 have pegylated interferon and ribavirin, which
13 will produce and cure in about 50 percent of
14 genotype 1 infected patients, which means that
15 we have half the patient population treated
16 that has very few options available to them
17 today.

18 Additionally, over half of the HCV-
19 infected patients cannot receive treatment
20 with pegylated interferon or ribavirin because
21 of the restrictions of the label, and their
22 clinical status, so that many of our patients

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1 can't be treated today.

2 And because of the profile of
3 pegylated interferon and ribavirin, we
4 currently have no active surveillance of
5 hepatitis C in the United States. So, the
6 majority of hepatitis C infected patients do
7 not know they are infected at this time.

8 Where are we in the clinic, with
9 early online development? It's clear that
10 with our current ongoing DAA studies,
11 treatment naive patients current single agent
12 DAA's, combined with peg and ribavirin are
13 giving significant improvements in SVR, and
14 also are potentially allowing the shortening
15 of treatment intervals with response guided
16 therapy.

17 It's also clear in the partial
18 responder relapse populations, where you got a
19 significant kick from the peg and riba, that
20 these monotherapy additions are also getting
21 good SVR rates, and are going to significantly
22 improve patient management.

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1 I think there is concern where we
2 move into null responders where we're not
3 seeing much benefit of the peg and riba, and
4 we're getting response rates in the 50 to 60
5 percent rate, and there's potential for
6 significant levels of resistance, and this
7 functional monotherapy population is a
8 population of concern.

9 What do we know from HIV? We know
10 that combinations of drugs with different
11 mechanisms of action, and non-overlapping
12 resistance patterns, give us our best anti-
13 viral responses, as Jeff said earlier. It's
14 clear that we need to completely suppress the
15 virus through these regimens, or else drug
16 resistance will emerge.

17 And so, we need to get complete
18 viral suppression in order to get a durable
19 effect for these drugs. It's also clear that
20 in HIV, we know that when you get over about
21 three logs of activity, you can durably
22 suppress patients for lifelong with that

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1 therapy, and it takes that much activity to
2 shut the virus down.

3 For hepatitis C, we don't know what
4 that number is, but we believe it's going to
5 be somewhat higher, and potentially as high as
6 eight logs of activity may be required to
7 completely shut the virus down. Additionally,
8 drugs have to have a good safety and
9 tolerability profile when you put them in
10 combination for patients to be able to take
11 them long enough to get a durable response and
12 a cure.

13 This is some in vitro data that
14 we've generated, but it's similar data that's
15 been seen by a number of companies. And
16 basically what this shows is that when you
17 combine two direct-acting antiviral drugs
18 together, you typically add activity to
19 moderate synergy. When you combine three
20 antiviral drugs with different mechanisms of
21 action to test to -- for example a PI, a non-
22 nuc, and a nuc, or a PI an NS5A and a nuc, you

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1 get very significant synergy, in addition to
2 the potency and the resistance coverage.

3 So, we believe that the path
4 forward that's probably most likely to be
5 successful will be to combine three different
6 agents with three different mechanisms of
7 action to try and get a durable suppression
8 without peg and riba.

9 What are some of the benefits of
10 potentially trying to accelerate the
11 development of combination antiviral drugs?
12 What's clear is that, as we've shown, there
13 are populations of patients for peg and riba
14 has little or no efficacy, or is
15 contraindicated who have no treatment options
16 at this point in time.

17 Additionally, accelerating the
18 development of these drugs will broaden the
19 number of patients who can be treated, but we
20 believe this will also, as it was seen in HIV,
21 lead to efforts to screen the broad population
22 to detect the HCV infected patients so we can

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1 treat and cure them, so that a more effective
2 and safe combination regimen will lead to a
3 broader surveillance of the population, and to
4 finding the undetected HCV infected patients.

5 What are some of the pitfalls of
6 going to combination therapy early and
7 aggressively? Clearly, we're going to have a
8 smaller safety database for each of the agents
9 that we put into these combinations. When you
10 start combining three drugs together early in
11 development, you run the risk that when you
12 have a new safety finding, you won't know
13 which drug to attribute that safety finding
14 to.

15 I think one of the concerns that
16 we're going to try and address in the strategy
17 we're recommending is suboptimal regimens can
18 produce drug resistance, and as has been
19 stated, this drug resistance can persist and
20 take classes away.

21 So, I think it's critical as we
22 explore these combinations, that we find

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1 combinations that are fully suppressive in a
2 rapid fashion before we extend them out to
3 longer duration, and -- and larger numbers of
4 patients. And finally, this whole strategy
5 assumes we can get rid of peg and riba, and
6 get SVR in these patients. And at this point,
7 as was stated, this is an assumption.

8 I think the early development of
9 the drugs is a fairly standardized pathway
10 that we have, which is basically you do three
11 to five day monotherapy studies to show
12 antiviral activity, followed by 14 to 28 day
13 studies with peg and riba to -- to do your
14 dose selection to go into Phase IIB.

15 The thing that we think we should
16 add very rapidly into these is informed like
17 study designs, in which you go for 14 to 28
18 days, combine two and then three drugs
19 together, and try and get a 90 to 95 percent
20 PCR negativity rate without resistance and a
21 clean safety profile, and use 28-day studies
22 as a screening strategy to pick out optimized

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1 regimens to then take into Phase IIB.

2 So, the goals of these studies?
3 For the three-day studies, you want to see
4 viral load changes. Anything beyond three
5 days, PCR negativity has got to be the goal of
6 these studies. You need to know safety
7 tolerability. We need to work out PK/PD, and
8 we need to know about drug resistance, and we
9 need to screen for this to detect whether
10 we're getting complete suppression of the
11 virus.

12 One issue that I think needs to be
13 thought through is how soon do we start the
14 peg and riba after we do these short-term
15 studies? And there has been a desire to sort
16 of go seven to 14 days after the study to get
17 safety data that was clean before you start
18 the peg and riba.

19 I would argue that we really need
20 to start the peg and riba the last day of the
21 single drug or combination therapy. This
22 benefit is that the viral load reduction we

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1 get from the direct-acting drugs will be
2 potentially given to that patient when they
3 start their peg and riba, and also the peg and
4 riba will then potentially suppress the
5 emergence of drug-resistant virus that we know
6 can come up with as short as four days of
7 treatment with PI's and non-nucs.

8 The cost of this is pure safety
9 data is going to be three to five days when
10 you run the study because you lose the safety
11 day when you go to peg and riba. And we're
12 going to not be able to detect drug resistance
13 in the clinic until a later stage of drug
14 development, but I would argue that's actually
15 a significant benefit to patients.

16 Once you get through these studies,
17 it's a fairly clear, straightforward pathway
18 that we're all following right now, which is
19 that we go in treatment-naive patients with
20 drug added to peg and riba. We can go
21 treatment experienced patients with drug added
22 to peg and riba.

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1 I think this is fairly
2 straightforward and is being followed. The
3 null responders are a population when I think
4 we need to think carefully because single drug
5 add-ons to peg and riba in nulls is
6 essentially monotherapy, and we may get
7 benefit for some patients in these studies,
8 but it's going to be at a cost to the patients
9 who don't get benefit from the study.

10 And so, I think this is the
11 population where you need to accelerate
12 developmental combinations of at least two
13 classes of drugs very rapidly to get a benefit
14 for this patient population.

15 There are clearly patient
16 populations where we can go today with triple
17 combination therapy if we have the triple
18 combination without peg and riba. There are
19 peg contraindicated patients, peg intolerant
20 patients, which is 50 percent of our patient
21 population. There are peg riba null
22 responders, which is 50 percent of our

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1 treatment experienced population, and there
2 are patients who have genetic or demographic
3 markers to indicate a very poor response to
4 peg and ribavirin, such as potentially the IL
5 28 promoter gene.

6 What would it take to go into Phase
7 IIB in these selective populations? I would
8 argue that one month studies of combinations
9 that show us that we have a very high PCR
10 negative rate, we do not have drug resistance,
11 and have a clean safety profile is enough
12 information to take a triple combination in
13 parallel with the peg and riba studies that
14 would be ongoing in the classical pathway,
15 into these selected populations in an
16 aggressive way now.

17 One of the interesting things about
18 these studies is we can actually do triple
19 placebos for the first time in a long time,
20 because there is no acceptable treatment for
21 these patients. So, we can actually give them
22 three active drugs versus three placebo drugs

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1 for the treatment course of the study.

2 When the study is over, we can then
3 look at all the patients who got placebo and
4 they will not have gotten PCR negative. And
5 so, they will be considered as failures on an
6 ITT, and then can be rolled over to triple
7 therapy. So, this means that every patient
8 who participates in the combination study of
9 this type could be allowed triple therapy as
10 the benefit of having participated in these
11 studies.

12 One thing I think I'd like to point
13 out is right now, there's a number of studies
14 that are going on about ribavirin. I'm not
15 sure of the total regulatory background behind
16 this, but ribavirin has been required for SVR
17 in this disease. We know from Phase II
18 studies with NM283 and telaprevir that if we
19 do not include ribavirin in the regimen, we
20 get great end of treatment results, and
21 horrible SVR results.

22 And so, I would argue that we need

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1 to factorialize ribavirin into these ongoing
2 studies until we can prove that you can get a
3 good SVR rate with combination direct-acting
4 antivirals without the riba. And this is, I
5 think, an important issue that we need to
6 think through.

7 Finally, how do we go to pivotal
8 studies? I would argue that in the selective
9 population, peg and riba controls are not
10 reasonable, but we do know what the historical
11 response rates are, and we could reach an
12 agreement on what an acceptable benefit above
13 the historical response rate would be that
14 would allow you to progress into pivotal
15 studies in that population.

16 Alternatively, if your triple
17 combination is highly effective, gives you an
18 SVR rate that is comparable to the SVR rate in
19 treatment-naive patients on peg riba in
20 standard of care, I would argue that a
21 definitive Phase IIB that shows this should
22 allow us to take these into broad pivotals

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1 across the whole HCV population of naive,
2 treatment experienced, with the triple
3 combination running against the best standard
4 of care available at that time.

5 I'll now turn the talk over to Dr.
6 De Gruttola.

7 DR. DE GRUTTOLA: Thanks, Doug, and
8 to the Agency for inviting me to speak. As
9 Doug mentioned, the Phase IIA studies are
10 intended to choose combinations of agents, and
11 as everyone has mentioned, there are a large
12 number of potential combinations that need to
13 be investigated.

14 So, factorial designs may be one
15 useful approach. This slide illustrates a
16 factorial design in which there is comparison
17 of two drugs, A versus B, illustrated in the
18 columns, and a comparison of pegylated
19 interferon with some therapy C, maybe a drug
20 or combination. The advantage of factorial
21 designs is that you can use all of the
22 patient's information to answer the two

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1 questions, A versus B, C versus peg, and a
2 further advantage is an opportunity to
3 investigate interactions to address the
4 question of whether the relative benefit of A
5 versus B depends on whether a patient receives
6 peg or C.

7 In this design, all arms would get
8 ribavirin. A question for this type of design
9 is whether there is an interest in the
10 interactions in which case study may need to
11 be powered for interactions, which implies a
12 larger study.

13 Another issue is depending on the
14 type of interaction, the presence of
15 interaction can make more difficult the
16 interpretation of the main effects of
17 comparing, for example, A versus B.

18 This slide illustrates the same
19 type of design that's used to address a dose
20 question, whether high or low dose of drug A
21 is better, and similarly whether high or low
22 dose of drug B is better. Here, the bolded

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1 letters refer to the high, and the unbolded to
2 the low dose.

3 In this design, once again, all
4 arms would get riba, and perhaps there would
5 be a further randomization to take or -- or
6 not take peg interferon.

7 Notice the same kind of design
8 could be used to look at treatment duration
9 combinations. There may be two questions
10 about treatment duration. One, the duration
11 on triple or quadruple therapy, and the
12 second, the length of the study overall. So,
13 this type of design could be used to
14 investigate the treatment duration of
15 combinations as well.

16 As Doug mentioned, for patients who
17 can't benefit from peg riba, a design might be
18 drugs A, B and C versus placebo, and this
19 design would allow all patients to contribute
20 to a randomized portion of the drug. But as
21 Doug mentioned, all placebo patients rolled
22 over to ABC, then all patients would

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1 contribute safety data as well about this
2 combination.

3 There's a great deal of interest in
4 response guided therapy, and if a question
5 arises that if patients become PCR negative at
6 four weeks, and if you're comparing two drugs,
7 A versus B, how much more treatment with A and
8 B should they receive after they have attained
9 the PCR negativity? And following
10 discontinuation of A versus B, how much more
11 PEG and riba?

12 Similarly, if PCR negativity
13 requires 12 weeks, should these further
14 treatment durations be longer? One of the
15 concerns about using response guided therapy
16 is interpreting results. Supposing we're
17 doing a study of A versus B, plus peg and
18 riba. If there's subsequent modification to
19 treatment based on PCR status at week 4, the
20 RGT complicates analyses.

21 For example, if A has more patients
22 than B that are PCR negative at week 4, and

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1 therefore A has on average shorter treatment
2 durations, if at the end of the study there is
3 no advantage of A versus B, or maybe even a
4 disadvantage, we can't tell whether that was
5 because A was an inferior or equivalent drug,
6 or whether the problem arose because patients
7 have shorter duration of treatment on arm A.

8 Those two issues, the efficacy of
9 arm A, and the duration of therapy, are now
10 confounded. Of course, if A is better both
11 for PCR negativity at week 4, and for SVR,
12 then there's no problem in interpretation.
13 But the conclusion is we can't directly
14 interpret comparison of cure rates if arm B
15 had a different proportion of patients who are
16 PCR negative at week 4, than did arm A, unless
17 the drug that's better for PCR negativity is
18 also better for SVR.

19 And it may be that use of factorial
20 designs with regard to duration could help
21 with this issue. Thank you.

22 CHAIR MURRAY: Thanks. Any

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1 clarifying questions?

2 DR. STRUBLE: I do have a question
3 about your factorial designs. You proposed
4 that those studies would be about 28-day
5 trials to choose a correct dose or duration.
6 Have you worked through what the sample size
7 calculations would look like for those types
8 of trials that you were proposing?

9 DR. DE GRUTTOLA: I have not, and
10 the -- the only comment I would make about
11 that is that it depends on whether the studies
12 would be powered for main effect or powered
13 for interaction.

14 If they were powered for main
15 effects, then the sample sizes would be about
16 the same as if you just had a two arm study.
17 If you're powering them for interactions
18 because you believe that the interactions may
19 be important, then they would need to be
20 considerably larger.

21 CHAIR MURRAY: Doug, you had
22 mentioned whether historical controls could be

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1 valid for making specified populations. What
2 were you thinking of specifically?

3 DR. MAYERS: I think what I was
4 addressing was for patients who are null
5 responders, or for patients who are peg --
6 well, intolerant and contraindicated, their
7 response rate is zero. So, that's not
8 particularly hard. For the nulls, you may
9 well have to say, "Okay, we know when we reach
10 peg and riba, the historical rate is X, and
11 so, we would negotiate with the Agency that we
12 would have a clinically significant
13 improvement over that that was statistically
14 valid, based against a historical control."

15 Because I don't think it's
16 reasonable to re-treat a null responder with
17 peg and riba alone.

18 CHAIR MURRAY: Thanks. Any other
19 questions?

20 Patrick.

21 DR. HARRINGTON: I have another
22 question about the 28-day duration trial. Why

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1 not continue those patients for longer,
2 because presumably four weeks of treatment may
3 not provide any benefit? Maybe you can use
4 the data at four weeks to design their next
5 trial, but what's stopping you from just
6 continuing treatment longer with SVR as the
7 ultimate goal?

8 DR. MAYERS: I think it depends on
9 how much data you have with each of the drugs.

10 I think you can do it earlier for 28 days to
11 try and pick an effective regimen. You may be
12 doing that in parallel with getting three
13 month's data with peg and riba with the drugs.

14 So, the issue is how much data do
15 you have to convince yourself that that triple
16 has safety and efficacy worthy of going into a
17 restricted population? But you're clearly
18 right; you could do 28 days to do a selection
19 criteria, meet with the Agency, let the
20 patients continue onward to get more data,
21 while you then go to a larger sample size for
22 a Phase IIB.

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1 CHAIR MURRAY: Anymore clarifying
2 questions from the Panel? If not, we'll move
3 on.

4 PARTICIPANT: Would you ever
5 restrict your Phase IIB to an IL 28B
6 population --

7 CHAIR MURRAY: No, I'm sorry, we
8 can't take questions. If you have a
9 clarifying question, write it on a card, and
10 we can -- we can get that question back later.

11 Sorry, we're just under time constraints, and
12 the -- the quirky limits of our meeting here.

13 All right, so, our next presenter
14 is Lynda Dee. And so, Lynda?

15 MS. DEE: Thanks. Good morning.
16 I'm so glad to be here. I'm an old AIDS
17 activist, and I was diagnosed with HCV about
18 three years ago. So, I'm obviously very
19 interested in this.

20 I'd really like to thank the Agency
21 for having this hearing. In the past, it has
22 taken us much longer to get them to convene

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1 hearings like this. So, we're encouraged by
2 that. I'm also very encouraged by the number
3 of companies that are here today. So,
4 obviously this is a priority to you as well as
5 it is to us.

6 So, quickly, I won't have to talk
7 as much as I thought about the FDA regs
8 because Jeff did a great job of that. But I'd
9 like to discuss staging inclusion criteria,
10 and possible patient populations in the
11 administrative characteristics or features of
12 EAPs, especially how they relate to
13 underserved people.

14 So, Jeff talked about the expanded
15 access regs that were promulgated last summer,
16 and really, I think the only thing that I
17 would want to supplement that with, and I
18 think he did touch on this, is the fact that
19 there are risk benefits sort of, of a scheme
20 that may be in individual patients that are
21 very sick, cancer patients maybe. Phase I
22 might be the appropriate point in time for

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1 this. Might be not unreasonable.

2 For an intermediate sized group,
3 which I think is the newest part of the regs,
4 and the most interesting part, maybe we're
5 talking about either concurrent with, or after
6 Phase II. Once a dose has been established,
7 once we have more sufficient safety and
8 efficacy data, and obviously in these cases,
9 sufficient drug-drug interaction data.

10 We're actually working with the
11 Agency and a number of companies in this
12 regard in the HIV arena, for multi-drug
13 resistant HIV patients. So, we have heard
14 from the Agency that combination EAPs, that
15 they're not opposed to combination EAPs. They
16 have said it again today. They have put it in
17 writing in the bleeding disorders petition.

18 So, I don't think that there's any
19 question that we can proceed in that manner
20 without any trouble from them.

21 Obviously, the larger access
22 programs, the 1,000-patient programs that

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1 we're used to in HIV, no, that didn't work.
2 All right, so we can do this in two ways, I
3 think. We can use the intermediate sized
4 populations and gradually increase them once
5 we have more data, similar to what we've done
6 in the HIV arena, actually with Doug Mayers in
7 -- with the protease inhibitor when he was
8 living in that world.

9 We did what was called an open
10 label safety study, where we went from --
11 expanded the population from 50 CD4s to 100 to
12 200, once we had more data.

13 So, there's no reason, I don't
14 think, that we can't use this new intermediate
15 category for 20 to 100 patients, which the
16 regs say, and I'm encouraged to hear Jeff say
17 today, that that 100 number is not set in
18 stone. And then gradually increase that so
19 that we don't have to start all over again
20 with a new protocol. So, I think that would
21 probably save time. Or, we could start with
22 the traditionally larger EAP, like we have in

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1 the HIV arena.

2 Now, obviously, there are a number
3 of tensions for industry regarding EAPs.
4 First is their clinical trials. We all want
5 the clinical trials to accrue, to be finished
6 successfully. Obviously, that's the way we're
7 going to get the most data, the best
8 information for the most people.

9 I think that most people in the HCV
10 community would agree, if you're eligible for
11 a trial, you shouldn't be eligible for
12 expanded access. That being said, there's
13 always exceptions to every rule.

14 In the HIV community, we have a
15 rule that we follow that, if you might be
16 eligible for a clinical trial, and are
17 otherwise eligible for the expanded access
18 program, if you live 50 miles away from the
19 trial site, you would still be eligible for
20 the expanded access drug because you can't get
21 to the site. So, why should you be penalized
22 just because you live in the Panama City,

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1 whatever riviera. How did you say that,
2 Linda? I love that. It was funny.

3 Anyway, so, we don't want to crash
4 the trials, and we haven't done that in HIV.
5 There's no reason we should do that in HCV.
6 The other important area of tension is
7 patients in urgent need.

8 Now, you know, this is probably the
9 biggest difference or -- I don't want to say
10 the biggest difference, but the most
11 complicating factor in HCV, and something that
12 really distinguishes it from HIV, which is a
13 much easier, harder disease to -- to hopefully
14 someday cure or treat, but much harder, much
15 more complicated to design trials and to
16 design an EAP program.

17 Nevertheless, we're still talking
18 about patients in urgent need in both
19 categories. So, we know there are drugs apply
20 issues. We know that the new regs say that
21 companies/sponsors can charge. We have never
22 done that in HIV. We hope you won't do it in

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1 the HCV arena, although we would get your --
2 somebody would get the data of how much it
3 costs finally do your work. That might be a
4 big reason that you would not want to charge.

5 But anyway, I digress.

6 So, the other -- the good news for
7 this is you might be giving the drug away for
8 free, and you might have drug supply issues,
9 but this is a very good way to legally have
10 patients getting used to your drugs before
11 they're marketed, and prescribers getting used
12 to your drugs before they're marketed. It has
13 been a very good marketing tool, if I can say
14 that, in the HIV arena, and it shouldn't be
15 any different in the HCV arena.

16 So, some of the possible inclusion
17 criteria might be a staging -- I went one too
18 far. There we go. Why won't it go back?
19 Well, can you tell me why this won't go back?

20 Oh, I remember what they were. So, we'll
21 just forget about why that flew by.

22 Initial staging criteria might be

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1 people -- pre- and post-liver transplant
2 patients, well-monitored, compensated
3 cirrhosis patients, and well-monitored
4 patients might be feasible. Now, here's
5 another tension in that the sicker the
6 patient, the more adverse events that might
7 occur, and of course that has to be included
8 in the NDA, and that's always risky for
9 sponsors.

10 The other two categories would be -
11 - there it is. No, it keeps clicking and I'm
12 not even moving it. Anyway, must be my
13 energy, right?

14 So, the other category would be
15 compensated cirrhosis patients might be
16 measured by metavir three or four fibrosis;
17 that probably is a category that is the least
18 controversial for expanded access patients,
19 although I think most community people
20 wouldn't give up the pre- and post- transplant
21 patients, and the well-monitored decompensated
22 patients.

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1 I think it's not unreasonable to
2 start with that staging process, and to use
3 the -- the metavir 3, 4 patients. Why is this
4 moving? Can you make this stay still? All
5 right, if I stand away, I think it stands
6 still.

7 Okay, so after that staging, the
8 slide you didn't see. We might look at
9 patients' response to the standard of care.
10 So, if they have a poor response, or if
11 they're intolerant to the standard of care,
12 that may be a possible inclusion criteria.
13 And a poor response might be a treatment
14 failure, including null responders, partial
15 responders, rebounders.

16 Dave Thomas thought including no
17 EVR at 12 weeks on the standard of care was
18 also important. So, first, we would look at
19 the staging, and then we would look at their
20 patient standard of care sort of profile.

21 Once we do that, after we've staged
22 patients, after -- this is again to determine

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1 if they have an urgent need, and we see that
2 the standard of care isn't working for them, I
3 believe we should take all comers:
4 monoinfected patients, co-infected patients,
5 patients with bleeding disorders, renal
6 insufficiency patients, just to name a few.

7 And we might need more interaction
8 data for co-infected patients that are on
9 other drugs; maybe more PK data for renal
10 patients. The point is, though, that none of
11 these patients should be excluded because they
12 have either other conditions or complications.

13 There's a possible EAP design, not
14 the only design. Great help in this from Mark
15 Sulkowski, who we see back there. Our friend
16 hiding his little face. Thank you.

17 Anyway, genotype 1 or 4 patients we
18 discussed earlier today, often at the higher
19 risk. Compensated cirrhosis patients, again
20 metavir 3 or 4 stage fibrosis patients might
21 be a good way to define that. And again,
22 previous treatment failures: either null

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1 responders, partial responders, rebound
2 patients, no EVR on standard of care, or
3 standard of care intolerance.

4 Now, the drugs that we might use,
5 and what Mark thought was an approved protease
6 inhibitor, but we all know telaprevir and
7 boceprevir are well on their way to approval,
8 plus an experimental polymerase, NS5A, or
9 cyclophilin inhibitor. There are a number of
10 these drugs, a lot of DAAs, that might be
11 ready past Phase II, or in Phase II at this
12 point.

13 It would probably be more easy to
14 do this if we had an approved protease -- here
15 we go again. Stay still. But I don't see any
16 reason why we can't do these now with either
17 boceprevir or telaprevir before they're
18 approved. I believe their trials are well
19 underway. They're in Phase III, they're ready
20 to go. It's a perfect juncture for them to
21 initiate these programs.

22 In the HIV arena, it's been very

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1 important for activists to get companies
2 together to talk about how they might work
3 together to do PK studies, interaction
4 studies, use each other's compounds so that we
5 can get to these combination studies much
6 quicker.

7 I was very encouraged just this
8 morning to hear one company say, "Yes, I'll
9 talk to you next week." So, we've learned
10 that from HIV that that needs to be done. It
11 may even be easier in HCV because a lot of
12 companies have these multiple class compounds
13 in their portfolios.

14 So, all right, now, we've heard
15 about combination therapy. We know the
16 lessons learned from HIV. Functional
17 monotherapy sucks. Resistance blowing the
18 whole class of a drug? We cannot do this
19 again to people with HCV.

20 Activists like me, Jules, Tracy,
21 the bleeding disorder patients are not going
22 to let you do this again, and we're going to

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1 be talking to the FDA, talking to you. With
2 all the drugs that are in development, there
3 is no reason that we have to live through this
4 again.

5 Anyway, speaking about these
6 combination options, it's possible to use the
7 HRV model of one new drug, maybe either
8 telaprevir or boceprevir, and other
9 experimental drugs. And that would be the one
10 drug, being the main drug of the protocol,
11 with other drugs being allowed.

12 The other way to do this might be
13 the comp like we're doing in HIV with that
14 intermediate size group, like we're trying to
15 do with that. Starting the protocol including
16 two drugs from Jump Street: the informed
17 drugs, the polymerase inhibitor, and the
18 protease inhibitor.

19 They're being studied together.
20 There's no reason that they can't be used
21 together in an expanded access program. Now,
22 in the first bullet there, we might add the

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1 standard of care for that for people who are
2 treatment failures. In the second bullet, we
3 might use that with maybe a kinder, gentler
4 interferon product for people who are
5 intolerant to the standard of care. I mean
6 luckily we have a lot of things to mix and
7 match.

8 So, finally, I would really like to
9 talk about the administrative characteristics.

10 I was talking to somebody from one of the
11 companies, and he asked me, "Well, why don't
12 we just do studies of these drugs?"

13 Well, the primary purpose of
14 expanded access programs is access, not data.

15 Now, if we get more data, that's great. But
16 the purpose of these drugs is to give them --
17 get them to people before they die. I think
18 that that being said, what we've learned in
19 HIV is a lesson that we really need to
20 remember in the HCV arena, probably even more
21 so.

22 Limited data collection, minimal

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1 forms and labor, minimal administrative
2 burdens. And I'm talking about check the box
3 and fill in the blanks. We want not only
4 university-based settings, but health clinics,
5 community health centers and individual
6 doctor's offices to participate in this. And
7 if it's not easy, they're not going to do it.

8 They're all overworked and
9 underfunded. So, we really need to streamline
10 this stuff so that we can get them to work
11 with us, and do these EAPs. That would
12 include contributions from the sponsor for EA
13 staff. We know in HIV that most university-
14 based settings have refused in the recent past
15 to even do HIV expanded access programs
16 because they can't. They lose a fortune every
17 time they do.

18 So, the sponsors are going to need
19 to contribute to the staff it takes to conduct
20 these programs. National IRBs, when possible,
21 and when I say when possible, I mean many of
22 the university-based centers have to run this

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1 stuff through their IRBs anyway. But this
2 will never get done in doctor's offices and in
3 community clinics if there's not a national
4 IRB. They just don't have the capacity for
5 that.

6 Finally, I would like to mention
7 this, EAPs as they relate to underserved
8 people. I think Jules touched on this. There
9 are more underserved people in hepatitis than
10 -- than is -- I don't want to say more than
11 HIV. I don't know. I don't know what the
12 numbers are. There are plenty. They are
13 probably the majority of people touched by
14 HCV.

15 In HIV, we've given lip service to
16 doing EAPs in public health centers and
17 community clinics. We just haven't done a
18 very good job of making sure these programs
19 have gotten to the populations that are
20 underserved in those arenas.

21 So, I just want to really reiterate
22 that we need to do a better job of that in

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1 HCV, or with HCV EAPs, and that absolutely
2 means limited data collection, limited labor,
3 sponsor contributions, and national IRBs.

4 I'd like to thank the people that
5 helped me with this, and again, I'm really
6 encouraged that we're all working here
7 hopefully to get EAPs done. Maybe the FDA
8 can't force a company to do this, but a little
9 friendly persuasion of asking the sponsors,
10 "And what are your plans for expanded access
11 in your portfolio, in your development
12 process?"

13 It really goes a long way. So,
14 we're ready, willing and able to work with you
15 to do these programs, and we're going to be
16 making sure that they are part of your
17 development packages. So, thank you very
18 much.

19 CHAIR MURRAY: Thanks, Lynda. We
20 have a question from Deb and then Russ.

21 DR. BIRNKRANT: Thank you for your
22 comments. We appreciate them. We've been

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1 dealing with the situation of trying to make
2 trials available to the underserved
3 populations for a number of years. And when
4 we meet with them we bring that to their
5 attention.

6 Do you have any suggestions as to
7 how to engage that underserved population to
8 enroll in these trials?

9 MS. DEE: Well, you know, I have
10 actually two suggestions. One is I read
11 something about the -- from the START study
12 the other day about what those investigators
13 are doing to get the exact populations that
14 you're talking about, and they're offering
15 free testing at certain sites.

16 So, that might be a way for people
17 who can't afford to get tested who have -- who
18 don't have any other sort of place to
19 immediately go to. That seemed like a good
20 idea to reach out to those populations.

21 And you know, I -- I mean I'm glad
22 that you asked this because I think I'm going

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1 to give fair warning to the companies here
2 today that we're going to do just -- I for one
3 am going to do just what I did in HIV. And if
4 you don't have enough women and people of
5 color in Phase III, we're going to demand that
6 the Agency make you do it in Phase IV.

7 So, you can do it in Phase III, and
8 have it be part of your study, or you can pay
9 a lot of money for Phase IV studies to find
10 out the information in those populations.

11 So, I mean we've got a lot of smart
12 people in the room who can figure out how to
13 do all of this stuff. They certainly can
14 figure out how to reach out to underserved
15 populations. You get a doc who is busy; you
16 offer him a certain amount of dollars to
17 enroll a patient. He's going to take the
18 easiest patient that comes down the pike, and
19 not the harder patients.

20 So, somehow there's got to be a
21 carrot there to get to underserved
22 populations, especially the African-American

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1 community, where it's a scientifically proven
2 fact that they have -- their outcomes are
3 worse, and that things are different.

4 CHAIR MURRAY: Russ?

5 MR. FLEISCHER: I just have two
6 quick questions. On the intermediate sized
7 groups, the statement is, "Sufficient safety
8 data, sufficient efficacy data," on the
9 individual products. How much do you think we
10 should have before we start combining multiple
11 agents?

12 MS. DEE: Are you talking about the
13 intermediate sized group?

14 MR. FLEISCHER: Yes. I mean are
15 you talking about if you have three day
16 monotherapy data on both the individual
17 products, that's enough to put them together
18 in an EAP program, or do you need to have some
19 SVR data to know that they're actually
20 contributing to outcomes in individual
21 patients in combination with standard of care
22 before you put them together?

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1 How many patients for safety should
2 we have as a database before we start putting
3 two different classes together?

4 MS. DEE: Right. You know, I
5 thought about all that when I was doing this,
6 and I thought, "I'm never going to be able to
7 get to all that stuff." But I was very
8 interested in Doug's presentation about how to
9 look at all that, how to -- I think he
10 answered a lot of the questions that you're
11 talking about.

12 MR. FLEISCHER: Yes, he did. But I
13 want to hear the perspective of the community
14 too.

15 MS. DEE: Okay. All right, well, I
16 didn't disagree with anything that he said. I
17 thought everything he presented was a good
18 idea.

19 MR. FLEISCHER: Okay.

20 MS. DEE: I think it'd obviously a
21 shorter time in HCV than it would be in HIV
22 for different monotherapy sort of things

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1 because of resistance. I think you have to
2 put them together. You have to have
3 interaction data.

4 I think you need to be in Phase II
5 so that you know what the dose is. I mean
6 that sort of --

7 MR. FLEISCHER: We might not know
8 the actual dose or the actual duration until
9 the end of Phase II.

10 MS. DEE: I think that you might
11 have to wait for that.

12 MR. FLEISCHER: Okay. Then my
13 other quick question is in the next slide, you
14 said patient eligibility, available to
15 patients in urgent need. Can you give us some
16 examples of who you think would be an urgent
17 need --

18 MS. DEE: Well, that's the slide
19 that didn't come up. And I would say pre and
20 post transplant patients, patients with
21 decompensated cirrhosis. I mean I think you
22 could probably still do a trial or give them

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1 EAP access if they were well monitored, if
2 they weren't really -- I mean if they were
3 early stage decompensated. And of course the
4 compensated patients.

5 And again, if industry -- they
6 might -- they might not want to do
7 decompensated patients. They might not want
8 to do pre- and post-liver transplant
9 patients. But we may have to start with --
10 since they have to give us the drug, we may
11 have to start with compensated patients. Once
12 they feel more comfortable, expand the
13 criteria a little bit. Kind of do it
14 backwards as we did from HIV.

15 CHAIR MURRAY: All right, Linda?

16 DR. LEWIS: Just as a follow on to
17 that, in thinking about other populations who
18 might not do well with interferon, but might
19 have significant other adverse events or -- or
20 things that could be confused with adverse
21 events, where would you fit in into this kind
22 of program patients who have significant

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1 psychiatric disease, significant
2 cardiovascular disease, other sort of medical
3 reasons for not being good candidates for
4 interferon, but clearly who need some
5 treatment for their hepatitis C?

6 CHAIR MURRAY: Linda?

7 MS. DEE: I mean I don't think that
8 should make a difference. It doesn't make a
9 difference in HIV. I think that where -- when
10 I said all populations like that, I would mean
11 -- I would think all co-morbidities.

12 You may need more data if they're
13 on other drugs. You may need more PK data if
14 they might -- their bodies may deal with drugs
15 differently. But I don't think we should
16 discriminate against people just because
17 they're sick. I mean this is about people who
18 are sick.

19 CHAIR MURRAY: Okay, thanks, Lynda.

20 Thank you very much.

21 MS. DEE: Thank you.

22 CHAIR MURRAY: I think we're going

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1 to move onto break, because after break, we
2 have five presentations I think at lease. So,
3 we're going to being promptly again at 10:45.

4 Thanks everyone.

5 (Whereupon, the above-entitled
6 matter went off the record at 10:34 a.m., and
7 resumed at 10:47 p.m.)

8 CHAIR MURRAY: We're convening.
9 Tracy, we'll have you go up to the podium. I
10 apologize for the whole audience not being
11 here, but we have so many speakers. Panel and
12 -- okay, now our first presentation after the
13 break, Tracy Swan from Treatment Action Group.

14 MS. SWAN: Well, good morning,
15 everybody. I want to thank both the
16 organizers and the instigators of this
17 meeting. I'm very happy to be here. And my
18 talk is going to be in two sections this
19 morning. The first is my own remarks, and the
20 second are slides from my colleagues at the
21 European AIDS treatment group, who asked me to
22 present their responses to the specific

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1 questions because they were unable to be here.

2 So, first of all, why are we all
3 really here? I think we pretty much know
4 this, but the Davis Study that Jules cited
5 earlier predicts that more than 1 million
6 people will have hepatitis C associated
7 cirrhosis in ten years from now.

8 We already have more than 35
9 percent of the transplant list constituted of
10 people with hepatitis C. We know that
11 hepatitis C is a poor prognostic factor for
12 both pre- and post- transplant survival, and
13 we know that end stage liver disease from
14 hepatitis C is a leading cause of death, non-
15 AIDS related, among people with HIV in western
16 Europe and the United States, where
17 antiretroviral therapy is widely available.

18 And as of April 26th, there were
19 almost 16,000 people on the liver transplant
20 list, probably most of them with hepatitis C.

21 But what we also know is that SVR will reduce
22 liver related illness and death, and that we

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1 can cure hepatitis C. Not always and not for
2 everybody, but it is possible to do so.

3 So, I think it's really important
4 to think about how we move forward to help
5 people that can't wait for drug development as
6 it's currently configured.

7 So, the first question: who are the
8 patients? I thought FDA really captured this
9 perfectly in expanded access regulations in
10 the past. People with life-threatening or
11 serious conditions without other treatment
12 options, who may not be able to participate in
13 the trials because they have a different
14 disease or stage of disease than the one being
15 studied.

16 To me, it is just really, really
17 clear and simple. Of course there was a lot
18 of subpopulations involved here, but this is
19 the frame I thought that this really belongs
20 in.

21 And then question 2 and 3 about the
22 drugs, I see two distinct categories. There's

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1 a patient population for which a single DAA
2 may be sufficient. At present, there are two
3 groups, a low-risk very specific population,
4 who are most likely to cure their hepatitis C,
5 and least likely to acquire drug resistance.

6 The high risk population are people
7 that really can't wait, who have been through
8 treatment. They're at risk for treatment
9 failure, drug resistance and serious adverse
10 events.

11 You know, that's the way it is, and
12 we need to think about how to save people's
13 lives, and some people are going to have drug
14 resistance and adverse events, but they get a
15 chance at survival, and I think people really
16 deserve that.

17 The second category is when
18 multiple direct antivirals are required. Part
19 of the answer to this question depends on
20 whether or not they'll work without standard
21 of care. If they will not work without
22 standard of care, I think there are people at

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1 risk of acquiring drug resistance with a
2 single drug plus standard of care, and in
3 special circumstances when you can't use peg
4 interferon, ribavirin, or there's urgent need.

5 And transplant candidates and
6 recipients sort of fit this very well.
7 Particularly when these drugs can be combined
8 with low dose interferon or ribavirin. And if
9 the drugs will work without peg interferon and
10 ribavirin, everybody who really needs these,
11 but can't wait for or get into a trial is an
12 appropriate population.

13 And what I see in the future is
14 there's going to be a larger population that
15 may need a single drug once some of the drugs
16 are approved and on the market place because
17 they'll want to construct a regimen. They may
18 have resistance from participation in a
19 clinical trial or prior treatment, and it may
20 look sort of more like what the scenario for
21 HIV does, where people are selecting a single,
22 rather than combinations.

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1 And one thing I wanted to
2 highlight: the FDA has not said -- does not
3 prohibit the use of combination experimental
4 agents, but I think all of us need to put our
5 head together and say, "How can it be more
6 easily facilitated beyond not prohibited?"

7 So, what about meeting unmet needs?
8 What are the marketing studies? And I just
9 had a list of relevant drug-drug interaction
10 studies, including the other sponsors,
11 candidates, antiretrovirals, methadone,
12 buprenorphine, immunosuppressive drugs,
13 opportunistic infection prophylactics and
14 treatments for other co-morbid conditions that
15 are really common among the highest prevalence
16 population in the United States, which is
17 people over 50 years of age.

18 And study data on adverse events;
19 drug resistance barrier and mutations, early
20 viral kinetics, all of this from regular
21 trials will really apply to how we think of
22 doing this properly. But I can't really tell

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1 you, not having a crystal ball, exactly how
2 it's going to apply specifically in every
3 particular situation.

4 So, what about adverse reactions?
5 This is, I think, the most important point.
6 Say someone develops a drug in a low-risk
7 population. Say treatment-naive people with
8 mild to moderate fibrosis, and they allow
9 someone on a transplant list to get the drug
10 through an expanded access program.

11 If someone who is a high risk
12 patient has a serious adverse event, I don't
13 think that should be considered in the same
14 context as a lower risk trial population. And
15 if the drug was already approved, say, and
16 let's just use the two hepatitis C protease
17 inhibitors as an example.

18 Let's fast forward to 2011.
19 They're on the market. If they're adverse
20 events with the use of those drugs in a really
21 high risk population, I would be absolutely
22 shocked if they got pulled from the market for

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1 use in a broader population where they were
2 safe.

3 So, I think this is the way we
4 really need to take a step forward and look,
5 and say, "If there are adverse events, how do
6 we deal with them? How do we support access
7 to these drugs before approval in high risk
8 populations without endangering the approval
9 of the drugs so it becomes a win-win
10 situation?"

11 And I think there are possibly
12 different considerations for access programs
13 when the drugs are from a single sponsor,
14 versus drugs from more than one sponsor that
15 sometimes are not completely codified, and
16 they leave everyone with a vaguely
17 uncomfortable feeling that if something bad
18 happens, the burden of that will fall on them.

19 And I think obviously you can't be
20 rigid and overly specific with things like
21 this, but I think there does need to be a sort
22 of clearer direction about, well, if you bring

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1 this level of safety and toxicity data in and
2 there's a problem with your drug, and whether
3 it's your drug combined with another one of
4 your products or someone else's, there's a
5 clear frame to look at it so everybody knows
6 what's expected.

7 And so, I didn't have answers. I
8 had more questions. Sorry about that,
9 everybody. And you know what can regulators
10 do on the part of the sponsors that are here
11 to ensure -- to assure you that development of
12 promising drugs won't be compromised? And
13 what are sponsors willing to do?

14 Sometimes, I feel like this thing
15 has been two people in their cars about to
16 drag race. No one wants to step all the way
17 down on the gasket, but we're starting to
18 sputter along and get there, which I'm very
19 happy to see.

20 So, I think our colleagues from the
21 pharmaceutical industry really have to be
22 clear about an acceptable level of risk, and

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1 what you need from regulators, and what you're
2 willing to do. Will you make your own drugs
3 available? Are you going to provide your
4 drugs for use with drugs from another company?

5 And it's kind of time to let the
6 cat out of the bag here. Now, on the
7 regulatory side, what guidance can you offer
8 pharma for combining drugs across sponsors,
9 and consideration of serious adverse events in
10 EAPs, particularly in higher risk populations?

11 And then I just thought, "What's it
12 like to be a doctor that's running a clinical
13 trial?" Because I tend to think of things
14 from more of a patient perspective. But I
15 would hate to say, "Wow, there's this segment
16 of my patients I can really help, and I might
17 save their lives, but I'm going to have to let
18 the other ones get sicker and maybe die, or
19 risk waiting for a transplant because I don't
20 have a vehicle to offer them drugs that could
21 save their life."

22 And that would be a horrible

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1 position to be in. I'm really glad that there
2 are going to be physicians who can probably
3 give more specific examples, and speak more
4 eloquently than I can on this later in the
5 day.

6 And that concludes part 1 of my
7 presentation. Part 2, colleagues of ours from
8 the European AIDS Treatment Group were unable
9 to be here, but wanted to weigh in. So, I am
10 presenting their response to the questions,
11 separate from my own rather strident
12 presentation.

13 So, they have a specific list of
14 patients that they felt would be appropriate
15 for expanded access to DAA: people with
16 advanced disease, in-home standard of care is
17 not indicated. They were very specific that
18 although these programs should be available to
19 both treatment-naive and treatment-experienced
20 people, that prior non-responders should not
21 be exposed to a single agent only, because
22 their likely to only have drug resistance.

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1 They think both transplant
2 candidates and recipients are appropriate
3 populations; people with other co-morbidities,
4 people on opiate substitution programs, and
5 HIV genotypes 1 and 4, when drugs are
6 effective.

7 Clearly, if their drugs are
8 effective for people with other genotypes, who
9 are quickly going to become a rather neglected
10 population. Unless they too get better
11 treatment options, they should be included.

12 So, their idea of populations for
13 appropriate single DAA would be people with
14 compensated cirrhosis, both naive and
15 experienced, and people with the IL28B
16 polymorphism; multiple DAAs for previous non-
17 responders, people with cirrhosis, and whom
18 interferon use is contraindicated, and
19 transplant candidates and recipients.

20 And there are collaborative
21 suggestions for collaboration, extended use of
22 ILB polymorphism testing, and by involving

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1 activists and community members in designing a
2 framework to facilitate EAPs with multiple
3 direct-acting antiviral agents, and to
4 implement community support programs in tandem
5 with EAPs, which I think is an important
6 consideration that often gets overlooked.

7 Their advice was to perform PK
8 studies, and have the proper dose to avoid
9 overexposure, underexposure to investigation
10 on DAAs, particularly in co-infected people
11 because they're on so many other drugs.

12 Do drug-drug interaction studies
13 with a pretty explicit list, some of which I
14 had also mentioned, but they added drugs for
15 management of depression and other mild
16 psychological disorders. And they would like
17 to see some spaces for dialogue in
18 collaboration, as it has been successful with
19 HIV, and they mentioned specifically the form
20 for collaborative HIV -- sorry, I'm blanking
21 out on the last word there, but I think most
22 of you know what the form is. And if you

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1 don't, you won't know it if I remember the
2 last word. Sorry about that.

3 We really need to host a dialogue
4 where all the stakeholders can come together:
5 physicians, regulators, pharmaceutical
6 industry, patients, activists, advocates,
7 academics, etcetera, and really say, "How can
8 we make this work for both mono and co-
9 infected people?"

10 And last -- sorry about the small
11 font -- they think that marketing studies
12 should sort of follow what was said in
13 question 1: that they should be inclusive.
14 They should be specific about the group of
15 patients and the circumstances, like really
16 well define what is non-response? What is no
17 response?

18 These words have become sort of a
19 moving target. It's really alarming now that
20 null responders are non-responders -- and it
21 gets very confusing. I think a certain level
22 of precision and clarity needs to be restored

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1 and maintained in the field about this.
2 Clearly, they do too.

3 And they'd like to see
4 circumstances from intensive multi-drug
5 therapy to studies with more prolonged periods
6 of exposure, and intensification, which they
7 mean as multi-drug, followed by
8 simplification, which would probably be
9 standard of care, or maybe two oral drugs,
10 depending on how it's going to work. No one
11 is sure yet. And interferon and ribavirin
12 free regimens, and at least two oral DAA
13 regiments.

14 I thank you very much, everyone.

15 CHAIR MURRAY: Thanks, Tracy.
16 Panelists, questions for Tracy? Okay, if not,
17 I think we can go onto Dr. Duff from
18 Genentech.

19 DR. DUFF: Good morning, everybody.

20 My name is Frank Duff. I'm the Head of
21 Clinical Development Virology at Genentech,
22 and I'm really happy to be here. It's great

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1 to not only have the opportunity to share our
2 thinking on early access to investigational
3 agents in hepatitis C, but as Jeff mentioned
4 earlier, to listen and learn. Because I think
5 everybody coming together in this day has
6 really allowed us to pool our collective
7 wisdom, and hopefully be able to move forward
8 with what are some quite complex matters.

9 So, with that, I'll dive in. Over
10 the next 12 to 15 minutes, keeping an eye on
11 the time, I'll be sharing our company
12 philosophy, and also our history and our
13 experience with early and expanded access.

14 In terms of the specific topic at
15 hand, I'd like to establish a context for
16 early access in hepatitis C. As has been
17 mentioned earlier, I think there are a lot of
18 learnings from our HIV experience, some
19 similarities, but also some differences that
20 are important to consider. Also, a number of
21 organizing principles that have helped us
22 internally as we have thought through this

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1 matter.

2 I think there needs to be some
3 discussion around the enabling of this
4 process, specifically moving hep C direct
5 acting antivirals into the EAP setting,
6 specifically related to early development
7 activities that in our view must occur, so
8 that we can safely move into early and
9 expanded access, some reflections on
10 collaboration among stakeholders, and finally
11 some regulatory aspects and questions that
12 will hopefully facilitate this process.

13 I'll start with the Roche-Genentech
14 philosophy regarding early access to
15 investigational agents. We believe that this
16 should be considered when clear, unmet medical
17 need exists, and reasonable benefit to risk
18 information is available. And I understand
19 that reasonable and sufficient are somewhat
20 soft terms, and they need to be because it
21 really will depend on the specific
22 circumstances of the agents at hand.

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1 In our view, access through
2 clinical studies or sponsor-run access
3 programs is preferred, particularly in the
4 high risk and complex setting that we're
5 talking about today, because it allows us to
6 define inclusion criteria and also more
7 systematically collect data that will
8 safeguard patient safety.

9 It has also been mentioned that
10 formal development activities may initially
11 limit the scope of early access programs.
12 Drug availability constraints are obvious.
13 Also human resource constraints within
14 companies, and perhaps it won't be
15 appreciated, but even those are finite in
16 pharma.

17 But also importantly, the fact that
18 plan development programs should not be
19 compromised. We recognize that getting a
20 clear and compelling positive risk benefit
21 that allows for the approval of an agent
22 really has the advantage of benefitting many,

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1 and that should never be compromised as we
2 focus on the urgent unmet medical needs in the
3 near term.

4 And also very important for us, as
5 a global company, we must consider fairness on
6 a global level because expanded access that
7 occurs in one jurisdiction really has to occur
8 in all the jurisdictions where an
9 investigational agent is being developed.

10 I'm not going to go through the
11 details of this slide, but I just wanted to
12 illustrate our history, which has been quite
13 extensive, in early and expanded access
14 programs to help critically ill patients.

15 You'll see that for almost 20
16 years, the combined companies of Roche and
17 Genentech have been involved with a variety of
18 early and expanded access programs in
19 oncology, ophthalmology, hepatitis C, and HIV,
20 and we firmly expect to be continuing to be
21 involved in early access, moving forward with
22 new investigational compounds.

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1 In terms of establishing a context,
2 let's spend a little time reflecting on HIV,
3 and I won't move -- I'll move fairly quickly
4 because I think Jeff has summarized some of
5 these aspects quite well.

6 We all remember the HIV days, and
7 many of us who are now in hep C development
8 really cut our teeth in those dire days. And
9 of course, acute medical urgency was very,
10 very high, and the early expanded access
11 programs addressed imminence and considerable
12 morbidity and mortality.

13 The hep C situation is a little bit
14 different. The acute medical urgency is
15 there, but is variable. We appreciate that
16 there are high risk urgent patients in need of
17 intervention, but many will remain clinically
18 stable, while we await the approval of the hep
19 C antivirals. And by awaiting the approval,
20 what we're really doing is awaiting a
21 compelling assessment of risk benefit.

22 Safety considerations: this perhaps

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1 is a little bit of an over-simplification, but
2 in the HIV days, the risks for the
3 investigational agents were anticipated to be
4 broadly similar across the disease spectrum of
5 HIV.

6 In the hep C situation, we find
7 ourselves with an additional complexity, and
8 that is that many of the patients have
9 greatest medical need with advanced liver
10 disease are actively contraindicated, or
11 intolerant to critical components of current
12 standard of care. And this is an additional
13 complexity that we have to keep in mind.

14 Moreover, many of the agents that
15 are being developed for hepatitis C of course
16 are metabolized, and eliminated through the
17 liver. So this subject introduced additional
18 complexity that must be thought about in terms
19 of enabling studies to generate data to ensure
20 that we're being safe.

21 The antiviral drug resistance
22 question is a very important one, and Jeff

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1 highlighted some of the challenges and
2 unintended consequences that were associated
3 with the benefits of the early HIV days in
4 terms of prolonging life, and certainly
5 monotherapy did lead to resistance, but then
6 needed to be addressed in subsequent access
7 programs that were really developed around
8 creating a viable regimen.

9 The hepatitis C situation is still
10 a little bit unformed. I think it's clear
11 that resistance is a legitimate concern, and
12 we need to take it very seriously, and proceed
13 carefully. But the clinical implications in
14 this setting are not fully understood, and we
15 need to balance the potential resistance
16 benefits of EAP with wanting to avoid any
17 unintended safety consequences that may occur
18 by moving a little bit too fast in this
19 regard, without having the necessary clinical
20 data.

21 A few organizing principles: I
22 think it's been stated by many in different

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1 ways. It's important to balance the risk of
2 mortality due to the disease state with the
3 unestablished and unknown risks introduced by
4 the compound, and the treatment setting. In
5 our view, clinical trials should be considered
6 as the first option for access. So, if a
7 patient has the ability to access one of the
8 other clinical trials are our preferred
9 method. This is our perspective on a
10 hierarchy of clinical urgency.

11 We feel that the focus really needs
12 to be on those with advanced disease, first
13 and foremost, and at the top of this list
14 would be those with advanced fibrosis and
15 cirrhosis. We'll talk a little bit about the
16 need for compensated cirrhosis, given the need
17 to pair with SOC at least in the near term.

18 Next in the queue, if you will,
19 would be those with an increased risk of rapid
20 disease progression. Examples of this would
21 include the co-infected population, and those
22 who have had a liver transplant reinfected

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1 graft, and we know the natural history is
2 rapid disease progression.

3 Urgent but not as urgent in our
4 view are those with poor prognostic factors,
5 but less advanced disease. In other words,
6 those who are clinically stable, and may be
7 advised to wait until we have a really
8 compelling risk benefit ratio or confirmation,
9 if you will, for the investigational agents.

10 This is not to say that all of
11 these categories shouldn't be important
12 components of drug development programs, and
13 that was one of the questions that were posed.

14 Should we be emphasizing perhaps the top two
15 at the expense of the third in drug
16 development? And I would say no. We need to
17 really be focusing on all three.

18 But what we're talking about here
19 today is early access. We're talking about a
20 sense of urgency, and when we would move. So,
21 we believe that would be important to
22 distinguish. And as a result, we believe we

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1 should focus on those with advanced disease,
2 and higher risk of progression.

3 Our assessment of the situation is
4 that early access programs are likely to
5 involve triple and potentially quad therapy,
6 but with interferon and ribavirin, because
7 that's how these drugs are being developed,
8 and that's how the data is emerging as
9 positive. And therefore, they will be
10 suitable for those who are interferon and
11 ribavirin tolerant.

12 So, this reflects a subset, if you
13 will, of those most at need. But of course
14 broader access is anticipated after proof of
15 concept of interferon and ribavirin's pre-
16 strategies is obtained. And in our view,
17 proof of concept is not the very, very
18 compelling and exciting early viral load data
19 that we've generated, but really proof that we
20 can generate -- that we can maintain an SVR
21 when patients come off treatment.

22 This of course then presents a much

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1 broader option for interferon and ribavirin in
2 tolerant and contraindicated patients. So, as
3 a result of this, DAA combination clinical
4 studies are really on the critical path to get
5 to this state, which will allow much broader
6 access in our view. And we need to keep that
7 in mind.

8 One of the things that I think is
9 very tempting to do is to perhaps think about
10 EAP and drug development in an intertwined
11 manner, and our position is that early and
12 expanded access programs are not the place to
13 develop drugs. Drugs should be developed in
14 combination, programs should be developed in
15 the controlled settings that really allow us
16 to safeguard patient safety, and really
17 understand what we're doing with new and
18 investigational agents. So, we need to be a
19 little bit careful about the temptation that
20 this would be done in a less controlled
21 manner, through EAP.

22 It's also important to remember

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1 that there are characteristics of the
2 available classes that may favor early access
3 in certain subpopulations and clinical
4 settings. We know that the different agents
5 have different metabolic and elimination
6 pathways, hepatic or renal.

7 So, we may want to target some of
8 the emerging classes to specific
9 subpopulations. We also know that what is
10 emerging is that there are different
11 thresholds to the development of resistance,
12 and indeed different resistant profiles that
13 may need to be brought to bear as we think
14 through which drugs may go into which
15 settings.

16 Let's talk a little bit about what
17 I call the enabling studies for DAA
18 combinations. Clearly the specifics need to
19 be determined based on the characteristics of
20 the investigational compounds. I think that's
21 drug development 101.

22 Well, we believe it's really

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1 important to get in early with drug-drug
2 interaction studies for the appropriate target
3 populations, and these are just examples. I
4 think Tracy has given a more comprehensive
5 list of the things that we would anticipate
6 are going to be used quite frequently in the
7 populations that are eventually targeted for
8 EAP.

9 We also believe that Phase II
10 safety studies do need to be performed in the
11 target populations. As an example, advanced
12 liver disease, certainly the co-infected
13 population, and the OLT population. And we
14 also believe that we really need to be very
15 careful in carefully characterizing the
16 resistance profiles of the agents, so that we
17 really know what we're dealing with and what
18 the potential risks and clinical implications
19 may be, once we move into a less controlled
20 EAP setting.

21 There's a lot of discussion about
22 early access with multiple DAAs and tremendous

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1 excitement. And our thinking on this was I
2 think similar to what Jeff had summarized.
3 There's a strong rationale when certain
4 characteristics of the agents exist.

5 Obviously, evidence of added
6 adverse synergistic effects in vitro,
7 different toxicity profiles, different
8 metabolism profiles, and different resistance
9 profiles of various agents all help us
10 understand which combinations have most
11 promise.

12 So, it's really important for us to
13 consider drug-drug interaction studies for
14 suitable candidates, and we know that a lot of
15 that work is already underway, and there's
16 been actually quite a groundswell of that in
17 the last six to 12 months.

18 We believe that it's important to
19 conduct initial combination studies in lower
20 risk populations to generate the necessary PK
21 safety and efficacy data before moving into
22 higher risk settings. If favorable, we would

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1 also consider moving as quickly as possible
2 into pilot clinical trials for those with
3 advanced liver disease.

4 But I think the message is that we
5 really need to perform considerable what I
6 call EAP enabling work in a clinical trial
7 setting to safeguard patient safety before we
8 open the doors more widely, given the
9 constraints and indeed the reality of our
10 inability to collect that level of data in an
11 expanded access setting.

12 How can we all work together? I
13 think a very attractive model has already been
14 alluded to by several multi stakeholder forums
15 run by independent third parties. The forum
16 has been discussed, and I think that's a great
17 example of how this could work for all the
18 reasons that I've stated here.

19 I think inter-company
20 collaborations need to increase. I think
21 we're starting to see movement there. Tracy
22 described it. I think I would say that the

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1 gas on the pedal not only relates to the
2 agency and sponsors, but sponsors together.
3 The willingness is happening.

4 It clearly increases the pool of
5 candidates that have the characteristics that
6 I've discussed. It also has to be
7 acknowledged that it introduces the potential
8 for some delay in clinical trial conduct, but
9 it's our responsibility and a shared one to
10 address these logistical complexities, and the
11 agency can help guide us here as well.

12 And of course community
13 representation is key because these are key
14 stakeholders, and can advise us on the
15 practicalities of EAP design, and indeed serve
16 as a critical conduit of information between
17 sponsors and the community.

18 A few regulatory considerations
19 before I close. I think to just restate that
20 we believe EAP should only be initiated once a
21 reasonable likelihood of positive risk benefit
22 can be assumed. We have a strong preference

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1 for the sponsor to submit EAP protocols to an
2 existing IND, and for investigators to do so,
3 largely related to the desire to
4 systematically safeguard patient safety.

5 We acknowledge that the
6 interpretation of safety signals from early
7 access programs is a challenge, especially
8 when we're combining multiple investigational
9 agents. One proposal and certainly there will
10 be several, is that safety reporting and
11 safety events from EAPs be clearly
12 distinguished in product labeling so that it
13 is apparent that these populations may be more
14 complex, and investigators or prescribers can
15 interpret it accordingly.

16 Also, we believe that EAPs should
17 really only be conducted up to the time of
18 drug approval for the population in question,
19 at which point authorization conditions will
20 apply.

21 So, to summarize, we do support
22 early access for selected patients with

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1 hepatitis C. We believe that priority should
2 be given to those with advanced disease, and
3 high risk of progression prior to DAA
4 approvals. We believe that early access
5 should be considered only after the efficacy
6 and safety have been reasonably well
7 established in clinical trials.

8 Again, I highlight because of the
9 need and importance of DAA combinations for
10 many of the patients in question, this is a
11 critical path activity that we all really need
12 to focus on. I think that's been nicely
13 highlighted by my colleagues from Idenix as
14 well.

15 Greater clarity on regulatory
16 implications of safety signals will really
17 help us all, and I think there's an
18 opportunity for a good dialogue with the
19 health authorities, and it will help to
20 relieve some of the anxiety that Tracy alluded
21 to in terms of what the implications of
22 unexpected safety signals may be on the

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1 primary registration program.

2 And I guess first and foremost, but
3 also bottom line, patient safety remains our
4 primary concern in this setting, and we want
5 to move with all speed, but also prudently, to
6 ensure that we do not do harm. So, thanks
7 very much.

8 CHAIR MURRAY: Thanks for your
9 comments and presentation, Frank. I have a
10 question for you.

11 DR. DUFF: Certainly.

12 CHAIR MURRAY: What kind of clarity
13 could FDA give sponsors or re-assurance about
14 safety signals? I mean what kind of things,
15 do you think, a sponsor would like to hear
16 regarding that?

17 DR. DUFF: So I think whether it's
18 real or imagined, there is a sense that moving
19 into high risk populations, particularly with
20 combinations early, generating a safety signal
21 will -- it may be an oversimplification, but
22 will scuttle the program, the primary

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1 registration program. Perhaps that may not be
2 a reasonable expectation. Maybe you can help
3 me understand whether that is indeed likely to
4 be the case.

5 Certainly, when we talk to
6 prospective partners about combining agents,
7 and even our partners with the informed
8 programs, there is a level of concern that one
9 may impact the other, and this could be
10 deleterious for the primary program.

11 CHAIR MURRAY: I don't know if
12 there's other questions from the Panel? Okay.

13 DR. HARRINGTON: In one of your
14 earlier slides, you were comparing HIV and
15 HCV, and sort of the clinical implications of
16 resistance, how they're not quite clear with
17 HCV. What's our gap in that knowledge? And
18 are there some additional things that we can
19 do to sort of fill those gaps, so that we can
20 better understand the clinical implications of
21 resistance?

22 DR. DUFF: I think a lot of the

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1 work is underway, and will probably emerge as
2 the primary registration program is complete,
3 as we understand the implications of having
4 investigational agents for longer durations in
5 the more traditional settings. I think that's
6 going to be helpful.

7 I think the whole concern around
8 functional monotherapy needs to be tested. I
9 think there's a strong theoretical belief that
10 particularly for null responders, re-treating
11 with triple therapy is an absolute zero, but
12 we know from data sets that indeed some
13 patients are responding.

14 So, I think it's a matter of taking
15 the natural course of allowing these primary
16 registration programs with careful resistance
17 monitoring to develop and assemble the
18 database that way, rather than some new
19 activity in my view.

20 DR. O'REAR: You listed a number of
21 expanded access programs. So, you have a
22 broad history, experience with these. Any of

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1 those cases where there are unexpected
2 consequences on your drug development program,
3 positive or negative, that might be useful
4 information for us?

5 DR. DUFF: To be fair, I'm not
6 totally familiar with the line and verse on
7 each and every program, particularly from the
8 Genentech experience. I'd have to get back to
9 you on that. But I mean all of these programs
10 have indeed progressed to approve products.
11 So, I would suggest that ultimately, they were
12 worked out. It's a fair point.

13 CHAIR MURRAY: I think we have to
14 move on. Sorry. All right, thank you. Our
15 next presentation will be from Dr. Charles
16 Howell from the University of Maryland School
17 of Medicine.

18 DR. HOWELL: Well, good morning.
19 First, I'd like to thank the FDA for
20 conducting this very timely hearing. My name
21 is Charles Howell, and I'm a Professor of
22 Medicine at the University of Maryland. But

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1 today, I appear on behalf of the American
2 Association for the Study of Liver Diseases,
3 or the AASLD.

4 Okay, so, the AASLD was founded in
5 1950, and is the leading organization for
6 scientists and healthcare professionals
7 committed to understanding, preventing and
8 curing liver diseases.

9 The Association has a number of
10 programs to address these goals, including
11 education, research, patient care, advocacy
12 and the development or contribution to public
13 policy in liver and biliary tract health and
14 disease.

15 So, as most of you in the audience
16 know that the results of Phase II trials, or
17 least of two HCV specific protease inhibitors
18 indicates, that a sustained virologic response
19 can be achieved in close to 70 percent of
20 individuals with hepatitis C genotype 1, the
21 most common genotype in the US.

22 This is a significant advance

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1 because as you know, in SVRs are associated
2 with a significant reduction in the
3 progression of liver disease, the development
4 of decompensated cirrhosis, as well as a
5 decrease in the incidence of a hepatocellular
6 carcinoma. Thus, the AASLD strongly endorses
7 the early access program, the principals for
8 access to direct acting antiviral agents for
9 chronic hepatitis C in patients with the
10 greatest need, those with serious and or
11 immediately life-threatening complications.

12 We specifically support controlled
13 clinical trials of direct acting antivirals in
14 selected populations that are covered by the
15 early access program. In general, this
16 includes groups, patients or groups, who have
17 a higher prevalence of HCV, who experienced
18 excessive morbidity and mortality from chronic
19 HCV infections, and for reasons that are not
20 completely clear, appear to have lower
21 response to standard of care therapy.

22 And lastly, these groups have been

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1 traditionally or historically under-
2 represented in the Phase II and III programs
3 for standard of care, and now currently for
4 the new direct acting antiviral agents. And
5 because of the potential impact of these
6 diseases in terms of decreasing morbidity and
7 mortality, we strongly embrace the accelerated
8 approval and translation of these advances in
9 HCV treatment for individual patients.

10 The potential benefits of these new
11 class of treatments and in the early access
12 program are fairly clear. Of course, we can
13 improve the care of patients, potentially
14 improve the care of patients, with unmet
15 needs. However, in addressing or in
16 developing these programs, we need to be
17 cognizant of the main risks that are involved.

18 First, because we will be studying
19 these medications or using them in populations
20 with multiple co-morbidities and more advanced
21 disease, there's the potential for more
22 frequent, severe and unanticipated side

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1 effects.

2 And not to be lost, and as has been
3 discussed by several of the preceding
4 presenters, there's also a significant risk
5 for the emergence of viral resistance to
6 individual agents, or to a whole class of
7 agents. Therefore, the AASLD believes that
8 certain conditions and criteria should be used
9 in assessing the -- in approval or
10 consideration of the requests for INDs in this
11 program.

12 And as indicated, I think most of
13 these are consistent with what's already been
14 promulgated in the Federal Register, and
15 presented earlier by Dr. Murray. But we
16 believe that these programs should be
17 supported by sound data on efficacy, safety
18 and HCV resistance, at least on the Phase II
19 programs.

20 It would be great, of course, even
21 greater, if the results were publically
22 available in the medical literature. And as

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1 indicated by several previous speakers, it's
2 imperative that the potential benefits of
3 these individual regimens must exceed the risk
4 in the individual patients or populations to
5 be studied, taking into consideration multiple
6 factors including the disease stage, and the
7 risk of serious disease or death in the
8 absence of therapy.

9 So, we also believe that the best
10 interests of patient care and medical science
11 will be served by the development, or by the
12 implementation of scientifically rigorous,
13 well-designed clinical trials in the
14 intermediate sized populations, and in larger
15 treatment IND groups relative or compared to
16 the individual IND or individual patient IND.

17 Not discussed by many of the
18 preceding speakers is the whole issue of
19 patient selection, but because of the issue,
20 the risk of drug resistance, it is important
21 that the patients selected for participation
22 in these studies have the -- have a high

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1 likelihood for high levels of protocol
2 adherence, and complies with the medications.

3 We also believe, as stated and
4 presented by others, that there needs to be
5 adequate funding for these INDs at all levels,
6 to ensure the highest quality of data
7 integrity and quality, particularly in the
8 larger sized studies.

9 A number of the activities are
10 listed here. They include the investigation -
11 - the efforts of the investigators or
12 clinicians and other personnel, and coverage
13 of all the areas, the full scope of activities
14 and responsibilities associated with
15 conducting at least clinical trials.

16 There must be an uninterrupted
17 supply of the antiviral drugs. I mean
18 obviously. It would be very crucial to
19 preventing the emergence or selection of drug
20 resistance. Also, of course resistance
21 monitoring during treatment is also I think an
22 essential ingredient in this, so we can learn

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1 among other things what to expect perhaps with
2 broader use in these populations.

3 So, what patients are most
4 appropriate for inclusion in the early access
5 program? Obviously, and as indicated by
6 others, it's the difficult to treat
7 populations, individuals who have a lower
8 likelihood of response to standard of care
9 therapy, and individuals who are at risk for
10 severe complications.

11 I think we would all agree that
12 patients with advanced liver fibrosis, metavir
13 F3, or Ishak stage 3 or greater are --
14 certainly should be considered as a top, or at
15 least as requiring priority in this program.
16 We also believe that there is a place for
17 patients with decompensated liver cirrhosis,
18 and then there are the other groups that are
19 listed here, the HCV/HIV co-infected, HCV
20 patients on liver transplant waiting lists,
21 with the goal of potentially stabilizing the
22 disease, and/or preventing HCV recurrence

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1 after transplantation.

2 Patients with recurrent HCV after
3 liver transplantation or HCV in other solid
4 organ transplant recipients should also be
5 considered. And lastly, patients with severe
6 extrahepatic manifestations of HCV infections
7 that have not been controlled with standard of
8 care therapy should also be considered.

9 Now, we didn't really talk about
10 the types of regimens that should be
11 considered, but we do identify certain groups
12 or classes of patients that we believe are
13 appropriate for dual or multiple direct acting
14 antiviral agents in the early access program.

15 This includes the patients with advanced
16 liver fibrosis who failed treatment with a
17 direct acting antiviral plus standard of care
18 in a Phase II or III program, for example.

19 They also include the different
20 groups of patients who are intolerant of
21 interferon and ribavirin, or for whom these
22 agents are contraindicated, and I won't go

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1 through the details, but you can see those
2 listed here on this slide.

3 Concerning monotherapy or single
4 therapy, I think -- I'm not sure if I
5 understood completely the -- kind of the
6 question in the Federal Register, but because
7 -- and there are different terminology being
8 used. There's functional monotherapy, et
9 cetera. But we're talking about monotherapy
10 as a single agent alone.

11 We do not feel that that is
12 appropriate and recommended at this time
13 because as indicated and shown by all of the
14 studies to date that there's rapid emergence
15 in selection of resistant HCV variants, maybe
16 with one exception. And again, the data is
17 fairly short in terms of -- in terms of follow
18 up.

19 This would require, though -- if it
20 is to be considered in the future, it would
21 require prior documentation of the lack of
22 resistance with longer term therapy. We also

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1 note that the development or the use of
2 monotherapy is contrary to the emergent
3 treatment paradigm, or multiple agents with
4 different mechanisms of action.

5 However, it could be considered, we
6 believe, as I indicated in the earlier slide,
7 that combinations of direct acting agents
8 could be considered in patients who are
9 intolerant to interferon and ribavirin.

10 Now, just in the -- the Register
11 also solicited comments and testimony
12 regarding patients, other patients with unmet
13 needs, many of whom or some of whom may be
14 eligible for clinical trials, but for various
15 reasons are under represented.

16 And specifically, we refer in this
17 group, in this presentation, to African-
18 Americans, non-Hispanic African-Americans, and
19 Hispanics. As many of you know, there's a
20 large, emerging and growing literature
21 documenting the disparities in health and
22 status in healthcare among patients in

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1 African-Americans and Hispanics compared to
2 Caucasians or whites in the US.

3 There's a high HCV prevalence,
4 particularly in the African-American
5 populations. Both African-Americans and
6 Hispanics experience excessive morbidity and
7 mortality from HCV, particularly high
8 incidence in mortality from primary
9 hepatocellular carcinoma, and higher rates of
10 HCV-related mortality.

11 We also recognize that there's a
12 lower probability of sustained response for
13 hepatitis C genotype 1, 19 to 28 percent in
14 African-Americans, and 34 percent in
15 Hispanics, as documented by Dr. Rodriguez-
16 Torres, who will be presenting later. These
17 populations unfortunately are under-
18 represented in the Phase II program for
19 telaprevir and boceprevir.

20 So, we believe that probably the
21 most pressing need in this population is
22 controlled clinical trials to determine the

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1 efficacy of these agents, of a direct-acting
2 agent, plus standard of care as is being
3 conducted in the Phase II programs at the
4 current time.

5 Finally, in conclusion, the AASLD
6 supports the goals of the FDA early access
7 program to direct acting antivirals for
8 populations that have been excluded, or have
9 been under-represented in clinical trials.

10 We recommend scientifically
11 rigorous and well designed controlled clinical
12 trials as a best approach to realizing the
13 objectives of the program in furthering
14 medical science and patient care. And we
15 stand ready to collaborate with all of the
16 stakeholders in the area to maximize efficacy,
17 and decrease and minimize resistance. Thank
18 you.

19 CHAIR MURRAY: Thanks for your
20 remarks on behalf of AASLD. Any questions
21 from the Panel? Linda?

22 DR. BIRNKRANT: Thank you for your

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1 presentation. I have a question about the
2 patients most appropriate for early access to
3 DAAs. There are a number of patient
4 populations there. I would imagine for a
5 company, and perhaps for a clinical trials
6 network, it may be difficult to conduct
7 separate trials in each of those patient
8 populations.

9 So, do you have a suggestion as to
10 how to address the needs of all of these
11 patients? Do you foresee that we could
12 possibly extrapolate from one advanced
13 population to another?

14 DR. HOWELL: Yes. I think that the
15 -- therefore, I think that's the basis of our
16 recommendation in studying this in
17 intermediate sized populations or larger,
18 because one can then focus on a population,
19 for instance, on a specific group.

20 So, you can focus on patients with
21 compensated liver cirrhosis, for instance, and
22 study different regimens, for instance, I

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1 think that as opposed to multiple small groups
2 of individual patients.

3 So, I think clearly there's an
4 unmet need in many of these groups. I mean a
5 natural -- I think certainly if it's not
6 already done, should be coming soon would be
7 studies in the HCV/HIV co-infected population,
8 for instance.

9 We need controlled clinical trial
10 data. We need to study adequate numbers of
11 patients so we can take, even in this program,
12 early access program, that we can learn and
13 gain valuable information about the
14 usefulness, the utility and all the ins and
15 outs of these treatments in the populations.

16 So, I think that there are many
17 different groups, all deserving of access, and
18 all deserving of study. Whether one -- I mean
19 I suspect different companies may pursue this
20 in different populations, at least from a
21 clinical trial, or from maybe post marketing
22 studies for instance. And the early access

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1 program, of course, would hopefully complement
2 that.

3 DR. LEWIS: Okay, a couple of
4 people before you have mentioned the
5 possibility of an accelerated approval process
6 for hepatitis C products, and it just -- now
7 you're going to get the question because I've
8 heard it two or three times.

9 We've always used SVR as our
10 endpoint for approval of hepatitis C products,
11 and kind of by definition that makes it a
12 little bit more difficult to have an
13 accelerated approval process. That's already
14 a surrogate endpoint, and we don't really have
15 another one validated yet.

16 Do you have a proposal for how we
17 might actually approach the idea of an
18 accelerated approval for these products,
19 particularly for genotype 1, where treatment
20 may required longer periods, even for these
21 agents?

22 DR. HOWELL: Well, first of all, I

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1 think -- I believe that SVR still would be --
2 is the main study endpoint because at least
3 based on what we know so far, it is the only
4 endpoint, at least so far, that appears to be
5 associated with significant clinical benefit
6 in terms of the natural course of the disease,
7 et cetera.

8 And so, I think that -- I don't
9 think that we could -- I think at the current
10 time, that's the current standard. I think in
11 some of these future regimens, for instance in
12 some of the multiple DAAs for instance,
13 perhaps in individuals who have not -- or who
14 are unlikely to achieve a sustained response,
15 it might be important to look at other
16 endpoints, particularly histologic endpoints,
17 to determine whether at least for instance
18 complete suppression of virus would be
19 associated with improvements, and
20 histological.

21 Of course, those are longer
22 studies, but it may be important to let -- to

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1 determine that, because there may be a
2 situation, a paradigm, similar to chronic
3 hepatitis B, where complete suppression in the
4 absence of viral clearance is associated with
5 significant improvement in fibrosis, even
6 among some patients with advanced fibrosis and
7 cirrhosis.

8 So, I think that those are the big
9 endpoints as it relates to clinical --
10 clinical outcome. Of course, in studies with
11 cirrhotic patients, one has the ability to
12 assess issues of decompensation and
13 complications of that sort. So, those are
14 also potential endpoints.

15 CHAIR MURRAY: Thank you very much.

16 I think we will move onto our next presenter,
17 who is Patricia Lupole from HCVets.

18 MR. FISHER: Obviously, I'm not
19 Tricia. So, we're kind of breaking this down
20 a little bit. My name is Dennis Fisher, and
21 first off, I'd like to thank the Panel for
22 letting us speak today. I'd also like to

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1 thank the University of Virginia and Vertex
2 Pharmaceuticals for enrolling me in a Phase
3 III study for telaprevir.

4 And also, I'd like to thank
5 HCVets.com's educational website and forums.
6 Extremely good group. They've really helped,
7 I know, myself, as I went through the
8 treatments.

9 I was diagnosed with hepatitis C in
10 early 2008. I was enrolled in the study, and
11 my biopsy revealed stage 1 fibrosis, portal
12 expansion with stage 2 macro inflammatory
13 activity.

14 I had to stop the treatment, the
15 study drug, after 10 days. Ten days, I
16 received a rash, and with protocol for the
17 study, they had to remove me off the study.
18 But then I continued on with the 48-week
19 treatment with the interferon and ribavirin.

20 All right, let's see. Okay,
21 HCVets.com, we have over 1 million visitors
22 each year to the website. Our online

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1 treatment support forum has about 5,000
2 members, and through direct patient contact,
3 it is our observation and experiences that
4 there exist many different medical opinions
5 about HCV disease and its treatment protocol.

6 Concerns arise with a poorly
7 understood virus. And the effects caused by
8 the viral interactions with the drugs, and the
9 drug to drug interactions. Failing to
10 recognize these interactions results in life-
11 long side effects, despite achieving SVR. You
12 still have these side effects that can affect
13 the quality of your life.

14 And a lot of these are frequently
15 overlooked by the healthcare providers, and a
16 systematic review of the current computerized
17 systems show that 55 to 91.2 percent of drug
18 interaction alerts are ignored by physicians.
19 Probably because of alert fatigue.

20 Okay, education we feel plays a
21 very critical role in treatment success. It
22 is very important for -- to prepare the

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1 patients for what he or she is about to
2 experience when they go through treatment,
3 whether it be a study treatment or a standard
4 treatment. An example of this was during my
5 treatment, and I have up here two doctors and
6 two answers.

7 In the course of my treatment, I
8 was experiencing some memory loss, some
9 confusion, some other type of cognitive
10 issues, and when I questioned the doctors
11 about it, one doctor told me that basically,
12 well, the treatments, they're not causing
13 that. And another doctor that I talked to, he
14 actually showed me and brought me two studies
15 that showed that HCV can cause -- HCV can
16 cause cognitive dysfunctions, and the
17 treatment can cause these dysfunctions to be a
18 little bit worse than what they are.

19 And you have to excuse me a little
20 bit, as I go through this here.

21 Another thing we feel is very
22 important for treatment success is the -- that

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1 the patient understands what information is
2 needed, and how to access the patient's
3 current condition.

4 So, when a patient goes in for
5 evaluation, they really need to understand the
6 information that the provider needs in order
7 to get him the proper treatment that they
8 need. And a lot of general practitioners,
9 non-specialists, have not been -- do not -- I
10 won't say educated. Might not be the right
11 word. But don't have the knowledge to inform
12 individuals on what to expect.

13 Okay, treatment outcomes and
14 factors. This is kind of a short list of
15 factors responsible for the side effects of
16 both the HCV disease, and the treatment
17 protocols. And all of this affects the
18 outcome. A patient's pre-treatment health
19 plays a major role in success, and that is why
20 it is very, very important that your patient
21 understands what information you need to know,
22 and you need to know to assess the patient's

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1 current condition.

2 Now, I want to talk a little bit
3 about brain fog. I'm sure everybody has heard
4 that word. Brain fog is one of the number one
5 complaints of HCV patients.

6 Okay, cognitive impairments, brain
7 fog. One-third of people with HCV experience
8 some type of cognitive dysfunction at the
9 early onset of the disease progression. Sixty
10 to seventy percent will go on to develop
11 depression, and/or other mental health related
12 problems as the disease progresses.

13 There is limited research, but it
14 strongly suggests a large number of these
15 patients are at a high risk of irreversible
16 neuropsychological damage induced by
17 interferon. And this seems to be unrelated to
18 viral load, unrelated to genotype, and
19 unrelated to the disease progression.

20 Then we're going to talk about
21 insulin resistance, and I'm going to turn it
22 over to Tricia. Thank you.

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1 MR. LUPOLE: Hi, everyone. I just
2 wanted to point out on that last slide that
3 Dennis had up there the possible solution to
4 neuropsychological damage and the cognitive
5 function area may be performed in a cognitive
6 pattern recognition program before giving your
7 patients interferon or products that follow
8 that we're still not sure of their effects on
9 the disease. And if these patients fail this
10 treatment or this testing procedure, you may
11 consider alternate treatment.

12 On our forum, I can honestly tell
13 you that out of every 50 patients, 25 to 30
14 percent suffered a cognitive function prior to
15 treatment, and after treatment continue to
16 suffer, if not worse, which is devastating to
17 quality of life.

18 That is one of our major problems,
19 and the next major problem that we've
20 discovered among patient reporting is that
21 many patients have insulin resistance. I
22 forget how to move the slide thing. Sorry.

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1 All patients are at risk for
2 insulin resistance. Various studies and
3 clinical trials have shown that almost all HCV
4 patients are at high risk, and many of these
5 cases lead to diabetes. By identifying
6 insulin resistance, we can potentially
7 increase treatment success, and decrease
8 fibrosis progression on those who can't treat,
9 or those who choose not to treat. Yet many
10 doctors are not testing patients to see if
11 they have this deficiency.

12 Okay, myth breaker, most doctors
13 we've talked to, oh, well, you don't have
14 insulin resistance. You're not fat. Well,
15 that just simply is not true. You can have it
16 and still be very thin. Let's see.

17 Then I'm going to present some
18 charts here to show you some pretty startling
19 data. Okay, here we have insulin resistance
20 in early viral kinetics. This is a response
21 at 24 hours, four weeks and 12 weeks. The
22 higher the HOMA, the lower the drop in the

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1 viral load.

2 Hyper insulinemia makes interferon
3 ineffective. It also increases HCV
4 replication, viral replication. Okay, SVR
5 decreases in insulin resistant patients with
6 genotype 1. All right, this is what I was
7 getting at. Insulin resistance lowers the
8 SVR, and the higher the HOMA, the lower the
9 SVR.

10 Insulin resistance is associated
11 with having a higher viral load. I think my
12 slides got messed up here. We're going to go
13 on.

14 Associated with insulin resistance
15 and fibrosis progression, and as you can see
16 here, the HOMA, as the HOMA rises -- does this
17 still work? As the HOMA rises, the effects of
18 treatment and fibrosis are reduced. Okay,
19 okay, so -- okay.

20 This is -- did we go backwards?
21 I'm sorry. I apologize. I'd like to have had
22 a fast run through of this before we did this.

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1 Okay, this was on the viral load, and
2 associated with having a higher viral load
3 with the higher HOMA.

4 Okay, improving treatment outcomes
5 would be managing insulin resistance. The
6 physician can better predict treatment
7 outcomes as a result of this. Potential
8 increase for treatment success, and a decrease
9 in the fibrosis progression, which I think is
10 the ultimate goal here in being able to better
11 predict what the patient is going to need.

12 It is just critical that doctors
13 test for this, and most doctors just really
14 are not aware that this is even a factor with
15 interferon treatments.

16 Okay, what you see is what you get.

17 Another thing that we find most ineffective
18 in treatment is the pre-existing autoimmune
19 diseases. INF is problematic itself in over-
20 activating the immune system. And steroids
21 are used to treat autoimmune disease, but the
22 problem is steroids also increase viral load.

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1 So, if you have an autoimmune
2 disease, and you're trying to use steroids to
3 treat it, then you're really making the person
4 much more ill. There is no solution for this,
5 and there is no funding for research.

6 Okay, hepatic iron overload. Now,
7 I know in the past recent years, we've come to
8 a lot more knowledge about iron levels in the
9 body, but what we have found is a lot of
10 physicians will only run a serum iron, or
11 they'll just run the ferritin, or the
12 transferrin saturation. And individually,
13 these tests are not going to give you a good
14 prediction of iron load, which totally affects
15 SVR.

16 And used together, you're just
17 going to get a much more accurate picture
18 compared to the ultimate method, which would
19 be biopsy. Phlebotomy is used to treat iron
20 overload, and it's something that should be
21 tended to immediately. If you find whether
22 the patient is treating or not, these iron

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1 levels need to be adjusted and simple
2 phlebotomy can do this, and lower the toxic
3 levels within the liver, and hopefully
4 increase SVR as a result of the treatment.

5 Okay, the patients' concerns are
6 the drug interactions are common in current
7 protocols. We don't know if it's the drug,
8 and we don't know if it's the virus. They're
9 just -- the data is not separated. We have
10 concerns that we're going to now add more
11 drugs to this mix.

12 It's 48 percent are producing a
13 rash from the new drugs that are being added.
14 We're finding documentation that 37 to 40
15 percent are previous null responders, and the
16 cost of these drugs are running about \$50,000.

17 We question without getting pre-
18 treatment care to the patient, are we really
19 going to be effective at all adding any new
20 drugs to this? We recommend in our conclusion
21 better management of medicine recording
22 methods; the failure to recognize medication

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1 and viral interactions can result in serious
2 side effects.

3 Dennis Fisher is our poster child.

4 He is a brilliant computer data expert that
5 has had total and complete cognitive function
6 for years. And since treatment, and during
7 treatment, he had extremely rough time. We
8 nursed him through it.

9 He's been off the treatment quite a
10 while now, and still suffers from these
11 effects. He, along with many, many other
12 people that are members of our organization.

13 So, to better manage these, we'd
14 encourage everybody to know what the virus is
15 doing to start with to our bodies. Let's know
16 what the drugs we're adding is going to do at
17 that point, and then the further drugs that
18 are added, we'll have some idea of what's
19 causing what. And maybe through all these
20 combinations, we can come up with a
21 combination that's going to really treat the
22 patient without leaving them with devastating

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1 side effects that are going to last a
2 lifetime.

3 There is no other alternative to
4 that. And that's pretty much it. We're just
5 patients. We're just people. We're not
6 doctors and physicians, but we do deal with
7 everybody everyday, and these are the
8 complaints that we have, and we do know for a
9 fact when we get together and we talk, and we
10 go to our doctors and we present our findings,
11 and they listen, we're seeing higher levels of
12 SVR.

13 Patients are not suffering from
14 debilitating side effects, and I would ask the
15 FDA to please consider this when you're ready
16 to kind of rush these medicines through to
17 understand what the other ones are doing to
18 start with. And data collected more
19 accurately than what we're doing with the
20 system that you have in place I think will
21 pave the way for all of us. Thank you.

22 CHAIR MURRAY: Thanks Patricia and

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1 Dennis for reminding us of the number of
2 adverse events that patients experience when
3 on treatment for hepatitis C. I think we're
4 going to just move onto the last speaker, and
5 that is Dr. Albrecht, from Merck. And then
6 after that, we'll be having a lunch break.

7 DR. ALBRECHT: Good morning. I'm
8 Janice Albrecht. I'd like to thank the agency
9 for allowing us to share with you the types of
10 patients we think might be eligible for early
11 access.

12 I think this morning, our speakers
13 have covered the fact that we are all very
14 much aware that HCV is different than HIV.
15 Fortunately, we can cure patients, which I
16 think is a huge difference. And also, the
17 fact that we do have a window where patients
18 can wait to be treated.

19 We have new drugs coming. I think
20 some of them are very promising. I've been in
21 the area for a long time, and we've moved from
22 7 percent cure to maybe 40 or 50 percent cure

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1 now, and there's the possibility we're going
2 to 70 percent.

3 So, there is a window for those
4 patients. However, we do agree that there are
5 patients that do need early access, and I
6 think we have to think about these patients in
7 two ways.

8 There are those patients that can
9 potentially have success with one new agent
10 added onto standard of care, and there are
11 those patients that probably need more direct
12 antivirals than just simply one, or you'll end
13 up with functional monotherapy.

14 So, the add-on patients to the
15 current standard of care. We certainly feel
16 that patients with advanced liver disease,
17 certainly with bridging fibrosis, and those
18 with really compensated cirrhosis need to be
19 treated, and those are in the Phase III
20 studies. They're ongoing.

21 The HIV-HCV co-infected. Those
22 studies are started generally when we get

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1 enough Phase II data that we're comfortable
2 that we have a reasonably safe and effective
3 drug, and those studies are going on now.

4 I think the more difficult patients
5 are those that are going to need combination
6 with more than one direct antiviral. And I
7 think the really unmet need in this whole
8 hepatitis C area is that transplant
9 population. Lots of folks are waiting. Lots
10 of folks are not being transplanted, and they
11 really do need to have something that will
12 either prevent reinfection when they're
13 transplanted, or treat the infection that has
14 occurred after they're transplanted.

15 This can be a really difficult
16 population. I don't think anyone has really
17 mentioned it, but I think the renal transplant
18 patients are another very, very important
19 group. Those folks can't be transplanted
20 until they're clear of their virus. And if we
21 can clear the virus pre-transplant, that's
22 very important.

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1 I don't think we're going to do it
2 with peg interferon and one direct antiviral.

3 So, those are folks that we need to think
4 about, and how are we going to get at them?

5 So, obviously the fibrosis III and
6 IV patients, we really believe strongly that
7 these patients belong in Phase II, and they
8 belong in Phase III. So, we tried very hard
9 to get our hepatic function studies done early
10 so that we can get them into really our late
11 Phase II studies, and then put them in our
12 Phase III studies.

13 So, many of these patients are
14 going to do well with just simply two drug
15 therapy. Patients with decompensated disease
16 clearly we can't treat with the backbone we've
17 got now, and those patients are going to have
18 to go onto other kinds of drugs.

19 Co-infection. Drug interactions
20 are our biggest problem with these patients.
21 We have to do a lot of drug interaction
22 studies before we're willing to put these

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1 patients into a trial. So, we usually end up
2 doing it in late Phase II. We advocate that
3 these patients studies be started in late
4 Phase II, and certainly after you get late
5 Phase II going, you can start studying the
6 effects.

7 These transplant patients are very
8 challenging, as I mentioned, and I think we're
9 going to have to use direct antivirals in
10 multiple quantities to treat them. Certainly,
11 we advocate that liver transplant patients be
12 one of the first patients in which we might
13 consider early access. And we also, as I
14 mentioned, add onto the fact that we think
15 renal patients should be looked at.

16 So, this is an interesting
17 category: intolerant or non-responsive to
18 current standard of care. We don't talk much
19 about interferon intolerant patients, but our
20 last speaker I think really pointed out there
21 are many, many patients that simply will not
22 tolerate our current therapy.

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1 As we begin to develop better
2 directing antivirals, perhaps more than one
3 class, and can get rid of what I've always
4 called the ugly sister, ribavirin, with it's
5 anemia, and also interferon with its multiple
6 neurologic side effects, this population of
7 patients that we can treat is going to expand
8 exponentially.

9 So, I think as we begin to think
10 about perhaps early access, and we develop
11 enough safety and efficacy in this population,
12 this is going to be a very, very important
13 population to look at.

14 We don't talk very much about
15 ribavirin intolerance, but think about the
16 patients that we can't treat because of the
17 anemia. Patients that have poor renal
18 function can't be treated basically with
19 ribavirin, and we keep reducing the dose, and
20 we still find out that we have problems with
21 the patients.

22 So, that is a set of patients that

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1 could be treated. And also hemophiliacs. We
2 all know the story about ribavirin and the
3 hemophiliacs. So, this is another population
4 that when you really think about early access,
5 these are very small groups of patients that
6 we have good data that we might consider,
7 rather than hundred patient populations.

8 So, access to multi-drug therapies
9 are probably really needed in this, what we
10 might consider, truly unmet medical need.

11 So, what are the prerequisites? I
12 think everybody has covered it early this
13 morning, but we feel very strongly that you
14 need adequate safety data and efficacy data
15 before you start. You also need adequate drug
16 interaction studies before you start because
17 once we get into these populations, we're
18 finding with some of these new direct
19 antivirals there are significant drug
20 interactions that can occur.

21 So, I think rather than rushing in
22 and giving a patient drugs that we don't have

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1 a good handle on is not a very good idea. But
2 again, I think that once we develop the safety
3 data, we can certainly consider in some of
4 these small populations that they do need
5 treatment, and I think FDA is giving us ways
6 that we can make this drug available. Thank
7 you very much.

8 CHAIR MURRAY: Questions from the
9 panel? Yes?

10 DR. STRUBLE: I just want to ask
11 what your definition of adequate safety and
12 efficacy is before you start these expanded
13 access programs?

14 DR. ALBRECHT: Well, certainly, I
15 think that we need Phase II data, and I think
16 that some of the other speakers have pointed
17 out that we need good antiviral data. We need
18 good safety data. We need drug interaction.
19 And I think there was a question asked earlier
20 about endpoints.

21 I think in some of these drugs that
22 if we had, for example, week 12 antiviral data

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1 with good safety, we could think about it.
2 I'd prefer to see SVR data. I would be
3 willing to accept for making decisions around
4 protocol design week 12 data, for example.

5 I would be willing to accept for
6 SVR data SVR 12. I think that we've shown
7 with two- drug therapy that SVR 12 and 24 are
8 similar. So, for SVR, I'm happy with 12.

9 I do think you can make a lot of
10 treatment decisions based on these new drugs
11 because they're acting very similar with in-
12 treatment week 12 data. I think it's a good
13 surrogate for predicting what might happen.

14 DR. STRUBLE: And when we talk
15 about SVR 12 and SVR 24, are you talking about
16 the whole patient population that completed
17 your Phase II, or a portion of those patients?

18 DR. ALBRECHT: I think if you have
19 a reasonable proportion, and I'm not talking
20 20 patients. I'm probably talking 300.
21 Because in my mind, Phase II studies really
22 belong in the 300 to 500 range, rather than

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1 the 100 to 200 range. So, I think half of the
2 patients with a good interim analysis might
3 give us data that would let us go forward.

4 CHAIR MURRAY: In the pre-
5 transplant population, you said the goal was
6 to avoid SVR to avoid reinfection of graft.
7 Is there any role for anything less than that?

8 If somebody is going more imminently to liver
9 transplant, I mean could you see protocols
10 where you would give in and around for some
11 time after transplant, but not having an SVR
12 prior to transplant?

13 DR. ALBRECHT: With transplant time
14 being so variable, you never know for sure how
15 long you're going to get the drug. If we have
16 drugs that we believed were safe post-
17 transplant, and we had the interaction studies
18 we need with the transplant drugs, I'd be
19 comfortable giving the drug pre-transplant for
20 as long as you could, and then continuing the
21 drug post-transplant if we believe -- if we
22 have a combination with a high resistance

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1 backbone in it, for example, like a
2 nucleoside.

3 Continuing it after the transplant
4 just to be sure that maybe you can re-
5 eradicate the virus; there's possibly a way
6 that you could continue to treat the
7 transplant patient post-transplant, just like
8 you treat another patient, if your drugs are
9 tolerable. So, I would be perfectly
10 comfortable continuing it after transplant.

11 CHAIR MURRAY: Thank you. Okay,
12 so, right now we have a lunch break, but we
13 have a lot of speakers this afternoon. So,
14 we'll be beginning at 1:00 with Dr. Rodriguez-
15 Torres. And so, back here at 1:00. Thanks
16 everyone.

17 (Whereupon, the above-entitled
18 matter went off the record at 12:10 a.m.)

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

20 1:10 p.m.

21 CHAIR MURRAY: Take your seats.
22 It's ten after 1:00. We're starting a little

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1 bit late, but we might have some squishy time
2 later in the afternoon. So, we are going to
3 begin with our first after lunch break
4 presentation. That's with Dr. Maribel
5 Rodriguez-Torres, Chief Medical Officer.

6 DR. RODRIGUEZ-TORRES: Good
7 afternoon. I hope you are not too sleepy
8 after lunch. First of all thank you very much
9 FDA for this opportunity. I am Dr. Maribel
10 Rodriguez-Torres from San Juan, Puerto Rico.
11 Most of you know me. I am a treater of
12 hepatitis C patients and co-infected patients
13 with HIV/hepatitis C and I am also a very
14 active researcher with the new Nobel
15 therapies. Actually I have worked with most
16 everybody, most of everybody here.

17 Today I want to talk in particular
18 about three populations and I am going to skip
19 a few slides. Some of my colleagues have
20 already talked about, in particular Dr.
21 Charles Howell talked a little bit about
22 African Americans. I'm going to try to

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1 comment on some of the questions that FDA has
2 put forward.

3 First, one program, one question,
4 or the first important question was which
5 populations could be or should be the targets
6 for early access with these medications. And
7 certainly I see that most of the speakers
8 during the morning agreed that actually we
9 should restrict this to genotype patients with
10 advanced liver disease, naive or experienced.

11 The point that I want to make this afternoon
12 is that given that we have also to emphasize
13 populations that have significant problems,
14 specifically Latinos and African Americans
15 that are present not only the majority of the
16 cases of chronic hepatitis C in the United
17 States but also have very poor standard of
18 care efficacy. In the case of Latinos we have
19 an additional problem that I want to talk a
20 little bit about it.

21 They do indeed have a rapid
22 progression to cirrhosis and both populations,

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1 African Americans and Latinos have been very
2 under-represented in clinical trials and some
3 of our prior speakers have pointed that they
4 have significant socio-economical barriers to
5 access to therapy. The other important
6 population is the HIV co-infected patients and
7 this has been talked about a little bit in the
8 morning. They have not only rapid progression
9 to cirrhosis but also a poor response to a
10 standard of care.

11 Why the emphasis on Latinos? It is
12 not because I'm a Latino, but it helps. But
13 certainly Latinos is the largest minority in
14 the United States and people don't seem to get
15 it. We need to accept this. I'm not talking
16 here about the Arizona Latinos. These are
17 legal American citizens.

18 (Laughter).

19 These are legal American citizens
20 and in 2002 there were more than 37,000,000
21 and expected to be 18 percent of the total
22 population by the year 2025. It is

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1 interesting that Jules presented some slides
2 this morning from the manuscript of Davis and
3 he showed the big problem with the African
4 Americans but if you see that slide you can
5 see Mexican Americans separate that other
6 Hispanics. If you join those groups the
7 problem of Hispanic is as bad as in African
8 Americans. So, this disease in the United
9 States is the disease of the African Americans
10 and the Latinos.

11 Why emphasis on Latino? Rapid
12 progression to cirrhosis and we publish
13 regarding this, a few years ago we showed that
14 in my cohort in Puerto Rico 50 percent of our
15 Latino population was cirrhotic, 40-42 years
16 after diagnosis. This is higher than any
17 population every reported but what was very
18 troublesome was that the mean age of my
19 cirrhotic patients is 57 years old. So we are
20 talking cirrhotic younger people. And that is
21 troublesome. These people are becoming
22 infected very earlier in their lives,

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1 certainly because of their Phase of IV drug
2 use.

3 Then Charles Howell commented on
4 these. Last year we published the only study
5 that has been done in Latino-whites, comparing
6 to whites of Caucasian/Whites, Caucasian
7 patients this was done in 50 sites among the
8 United States and we demonstrated that Latino-
9 wise had an SVR of 34 percent compared to
10 Caucasians of 49 percent. This study
11 demonstrated that ethnicity only to be a
12 Latino was a predictor of non-response and
13 this is important to understand.

14 Why emphasis in the co-infected
15 population? We are not going to go much along
16 this because of this population. We all know
17 they have rapid progression. What is
18 troublesome and worrisome is that the fourth
19 bullet there that all the benefits that we
20 have gained obliterating opportunistic disease
21 in this population. We are losing already and
22 we will lose to HCV-related liver disease and

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1 death and morbidity.

2 This is extraordinarily worse in
3 co-infected patients, non-detectable viral
4 load CD4s of more than 800 die of liver
5 disease. Treatment of co-infected patients is
6 going to be very complex because we are going
7 to have a lot of drug-drug interaction
8 problems. We are going to have antiretroviral
9 therapy toxicity and we don't know at the
10 moment how much hepatic toxicity we are going
11 to have of these new drugs.

12 Okay. Another question, who should
13 have access to single drug DAA in the early
14 access program? We understand, we believe the
15 naive and experienced patients in particularly
16 relapsers, breakthrough relapsers with
17 advanced fibrosis, and well-compensated
18 cirrhosis could be excellent candidates. Of
19 course we would like to see FDA to say we need
20 to have a specific, significant representation
21 of African Americans and Latinos.

22 We understand that all co-infected

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1 patients should be candidates for early access
2 with one drug. And non-responders that have
3 cirrhosis either detection of additional
4 antiviral to be available is more than two
5 years, may be also candidates.

6 Which should not be considered for
7 a single drug in an early access program?
8 Null, partial non-responders without cirrhosis
9 should wait for combinations with two or three
10 or more other drugs. Certainly and we thought
11 some of the colleagues agreed this morning,
12 the compensated cirrhotic patients are not the
13 patient population for an early access
14 program.

15 They should be treated only in
16 clinical trials because certainly this is a
17 very difficult population that require
18 expertise, could result in monotherapy with
19 the older drug without or suboptimal ribavirin
20 or interferon. Many proposals have been
21 discussed in the morning and I think that we
22 all are saying the same with different names

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1 and different construction. But I think that
2 the point is we are agreeing on the following.

3 The protocols of early access have to be
4 detailed, clear, defined inclusion/exclusion
5 criteria, good documentation and has to be
6 enforceable. They have to enforce and provide
7 for frequent PCR monitoring and rules to stop
8 the other drugs in case of breakthrough or
9 resistance.

10 They would require close monitoring,
11 more like a clinical trial. So if we say
12 clinical trials instead of early access
13 programs, that is the same. The third bullet
14 here is important. I don't think even now you
15 see interferon and ribavirin. I don't think
16 that every physician out there is prepared to
17 treat these patients. And the patient that
18 talked this morning actually made my case.

19 Treatment with these drugs is going
20 to be more complex. You cannot give this to
21 the family physician or the general physician
22 out there that doesn't know anything about

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1 this. You will have to give this to
2 GI/hepatologists or physicians under their
3 supervision. And more important than
4 anything, I am extremely concerned about drug-
5 drug interactions. I am concerned even if the
6 drugs go in to the market. I'm more concerned
7 in these early access programs. No early
8 access should be allowed without significant
9 information on DDIs.

10 I'm not going to go over this but
11 these drugs have the high potential to be very
12 toxic, very problematic. They are as toxic in
13 theory as any antiretroviral drug and we have
14 to be sure that we understand this before
15 these drugs go out and I don't care if FDA has
16 to put 100 black boxes. I don't have a
17 problem with that. I think that is good if
18 that is what is needed for physicians to
19 understand the severity of the situation.

20 In the case of the co-infected
21 population, somebody mentioned this, this
22 morning, I lost track of who he was. This can

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1 not be done with all the drugs. There has to
2 be some, you have to prioritize with drugs you
3 are really going to test with different
4 antivirals. You have to understand the
5 metabolism on the drug and more important you
6 need to assess the frequency of use. As I say
7 here on this slide, it will be completely
8 useless to have 50 drug interaction studies
9 for drugs that are not used in real life. So
10 the selection has to be prioritized on terms
11 of the frequency of the use of the drugs.

12 Multiple drug antivirals -- I think
13 that the colleagues have discussed this ad
14 nauseum, but certainly this is the future. We
15 would like to see 3/4 drugs that we can give
16 to the patients, certainly those combinations
17 are expected to be more efficacious and reduce
18 the rates of resistance.

19 Certainly patients with advanced
20 liver disease including the compensated
21 cirrhotics may be treated with two and
22 ribavirin without interferon, non-responders,

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1 nulls and partials, co-infected patients with
2 controlled drug interactions and certainly
3 going back to the patient discussion this
4 morning, Latinos, African Americans, patients
5 with metabolic syndrome that really have a
6 higher possibility of failure with available
7 therapies.

8 The agency asked for clinical trial
9 design ideas and actually the stuff that I put
10 there like 30 slides I decreased that to about
11 16. But in general, Latinos and African
12 Americans they have a fantastic opportunity
13 that with this older drugs we can bypass the
14 genetic and metabolic causes of nonresponse
15 that caused them to respond so poorly to
16 therapy. So I would like to see trials for
17 those populations including metabolic syndrome
18 patients designed not only on one single drug
19 but with two drugs with and without peg or
20 ribavirin for those specific population. In
21 patients with advanced fibrosis and cirrhosis
22 certainly they use multiple drugs is extremely

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1 effective. I would like to see trials with
2 and without peg and ribavirin in those
3 populations. Even in patients with
4 compensated cirrhosis I would like to see
5 studies that are tailored to the response and
6 function improvement and maybe add on
7 interferon is required. The same for new, non
8 responders combination as they go. The co-
9 infected population is interesting. We need
10 to do everything, anything good, anything we
11 do in this population is better than what we
12 have now. Actually I think that to use
13 another drug with peg or a drug, a single drug
14 with peg or ribavirin just to or peg or
15 ribavirin just to see if we get the same core
16 efficacy would be an advantage, would be an
17 improvement if we can decrease the duration of
18 therapy or decrease their perseverance. But
19 of course we all agree that to prevent
20 resistance, the combination is true. We know,
21 you know that the trials have been started in
22 configurations that are not in ARTs. But the

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1 clue here is not the population. Is the
2 population that isn't ARTs. So those are the
3 studies that we need to do further. I have
4 only two slides and one is I have to give
5 something to the sponsors. And this is
6 important for me. I think that you as a
7 sponsor pharmaceutical industry is going to be
8 required to do much more work to assure the
9 safety and best use of this drugs. You are
10 going to be doing more studies with this
11 drugs. So I think that is fair that in special
12 awareness of that situation that you are
13 treating the matter of public health, the
14 regulatory agencies should provide incentives.
15 Incentives through the pharmaceutical industry
16 in order to encourage these.

17 And finally just final thoughts.
18 We have to remember that chronic hepatitis C
19 is mainly a disease of minorities and the
20 underprivileged and I love the slide that you
21 presented about the groups that have the
22 disease and the prevalence in the patients.

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1 This is a very underprivileged in general
2 population. We know that the economic and
3 human cost of this aging chronic hepatitis C
4 population will be enormous if we don't use
5 the hope of these therapies for those that are
6 more affected. This morning the FDA director
7 said that we have done a very bad job of
8 working with prevention of hepatitis C and
9 controlling the death from hepatitis C because
10 we have not attended the most affected
11 population. So I hope that we can all have a
12 productive collaboration and move forward the
13 process of development of these therapies and
14 prevent the death of our patients. Thank you.

15 (Applause.)

16 CHAIR MURRAY: That's fine, thank
17 you. Any questions from the panel? All right
18 Jules?

19 DR. O'REAR: On the last one of
20 populations that you identified. Do any of
21 those have an unusually high rate of
22 progression in terms of disease? And the

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1 additional question is what types are found in
2 the Latino population?

3 DR. RODRIGUEZ-TORRES: The Latinos
4 have the same distribution of genotypes as the
5 rest of the population in the United States.
6 So five to 30 percent will have genotype 1 and
7 will have genotype 2s and 3s in the rest. But
8 the genotype is not the cause of the
9 progression. Actually we examined a few years
10 ago the differences between co-infected
11 patients and monoinfected Latino patients in
12 our cohort and we could see the difference of
13 more progression in the co-infected cohort.
14 However, when we examined the monoinfected
15 population along gender and this is published,
16 we saw that the difference was in women
17 mostly. Women that are monoinfected have less
18 progression. But when we examined males they
19 have better similar progression as co-infected
20 males. We found that alcohol ingestion in
21 that study was a factor. But in the Latino
22 study that we did last year, we examined

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1 everything, all the variables possible and
2 ethnicity was the most important predictive
3 fact.

4 DR. O'REAR: And what about the
5 sub-population?

6 DR. RODRIGUEZ-TORRES: Well, okay.
7 There is not much of that under progression of
8 all the populations. But in the Latino trial
9 we showed that there was no difference along
10 the different countries.

11 CHAIR MURRAY: Any more questions?

12 All right. If you have a question and you
13 want to write it on the card, we can maybe
14 address that at the end of the session. Thank
15 you. So we are going to take our next two
16 speakers. We have Mark Antell and Paul
17 Brayshaw from an organization called People
18 with Bleeding Disorders and HCV.

19 MR. ANTELL: Thank you, good
20 afternoon. As you see, we have posted a call
21 for urgency for people with bleeding disorders
22 and chronic hepatitis C. We need rapid access

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1 to these DAA drugs. I think that the key word
2 there is urgency. It has to do with getting
3 it done and getting it done quickly. We would
4 like to start off with a thanks to FDA,
5 actually I should introduce myself. I am Mark
6 Antell. I am one of the principals of this
7 citizen petition asking that FDA provide a
8 path to access for these promising new drugs
9 beyond that which is currently allowed by
10 clinical trials. This meeting is something
11 of a response to that citizen petition in part
12 and we would like to thank FDA. We
13 additionally see a lot that's positive in the
14 response of the FDA and in the whole structure
15 of this meeting. There is a general
16 recognition that there is a lack of treatment
17 options, good treatment options for a lot of
18 people with chronic hepatitis C. There is
19 some recognition that maybe some of the
20 guidance on two pharmaceutical firms who were
21 promising new drugs could see some revision.
22 We've seen that there was some very positive

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1 suggestions in the response from FDA to the
2 petition about things that ought to change,
3 multiple drug combinations are encouraged.
4 There seems to be a willingness to maybe back
5 off from requiring that drug combinations
6 shouldn't be even considered until everything
7 had cleared IIB which has been a terrible
8 stopping point until this point. Maybe we are
9 going to back off from that. That's a
10 wonderful thing. And we are also pleased that
11 FDA is asking for some input from the
12 stakeholders. We like the format of this
13 meeting. Right, I've got to advance it.

14 Personal perspective, that's what
15 I'll talk about. People with bleeding
16 disorders are dying, getting sick and dying.
17 There is some AIDS involved. There is not all
18 that much people dying from hemorrhage. What
19 they are dying from is chronic hepatitis C.
20 That is true. That is anecdotal. I don't
21 know that I've seen it published but I've
22 talked to patients, I've talked to primary

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1 treaters and that's what people are dying of.

2 You could do the same thing if you went to
3 the treatment centers and there is no one that
4 will deny that. We also saw back before we
5 put in this petition, we saw few successes in
6 terms of treatment with SSC. We saw a lot of
7 failures and not infrequently with failure we
8 saw rapid deterioration. We saw some of our
9 brothers rapidly become ill shortly after they
10 finished an unsuccessful SSC treatment. I
11 don't know if it is all that well correlated.

12 Maybe in those days nobody understood that
13 SSC could be deadly for people with
14 decompensated liver but it can and it maybe is
15 not all that good for people that are on the
16 edge of decompensated liver.

17 We also saw the trials and still
18 see that trials are unavailable for many
19 people with hemophilia, probably most co-
20 infection, other morbidities, well advanced
21 liver disease. We can't get into those
22 trials. And historically again this comes

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1 before we submitted this petition. We saw
2 reports of therapies. It has got to be four
3 years ago that probably many of you remember a
4 report from Vertex saying this is really
5 working, VX950 and we want to run this with
6 some other drugs and nothing has happened. We
7 will cover in our presentation something about
8 the size and the status of our cohort. We
9 will throw in a topic that had not been
10 mentioned to this point that liver biopsy is
11 required in a lot of these protocols and yet
12 it is a particularly troublesome requirement
13 for us. There is, we will talk a little bit
14 about the expectation, the combination
15 therapy. I guess everybody has the same hope
16 that the combination DAA therapy is going to
17 work. I will talk a little bit about how the
18 guidance can be improved. I guess that FDA
19 has asked a series of questions about what
20 needs to be done. We have some suggestions
21 about that and I guess the fundamental thing
22 that we've talked about and Paul will, my

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1 partner in this effort, will talk about is the
2 whole idea of accepting additional risks when
3 there is a high need.

4 Finally, I just want to mention we
5 don't have a conflict of interest. I'll
6 conclude with just a couple of addenda that
7 maybe hadn't been in this document that we are
8 an endangered community. You've asked us
9 questions. You, FDA have asked us questions
10 about how you can speed our access to DAAs
11 ethically without damaging good regulatory
12 practice and consistent with healthy business
13 models for new drug development. We will
14 provide recommendations but we are open to
15 other approaches. The only thing that we are
16 utterly certain about is our urgent need. I
17 will now turn this over to Paul Brayshaw who
18 is president of the Hemophilia Federation of
19 America.

20 (Applause.)

21 MR. BRAYSHAW: Thanks Mark and
22 thanks to the FDA. My name is Paul Brayshaw.

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1 I am one of the citizen petitioners and we
2 represent a group of people with bleeding
3 disorders and chronic hepatitis C. We
4 submitted the petition basically to give some
5 sense of what we are dealing with. We
6 represent members from the Hemophilia
7 Federation of America and we also have support
8 from other national organizations, the
9 National Hemophilia Foundation and several
10 local hemophilia foundations. We recognize
11 the lack of good treatment options for
12 substantial numbers of people and we are
13 hoping that we can find a way to do something
14 about this.

15 So for people with bleeding
16 disorders and chronic hepatitis C we need some
17 rapid access to these promising therapies.
18 Standards of care are not the option because
19 of advanced diseases, advanced disease,
20 progressive disease or a low likelihood of
21 success as well its contraindicated for many.

22 If you have any sense of the history of the

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1 bleeding disorders community, it goes back a
2 long way to our dependence on blood and blood
3 products. Fortunately today we can depend on
4 recombinant products but I'll just say that I
5 spent several years over at the Parklawn
6 building as a federal employee making payments
7 to people who contracted HIV through the blood
8 supply. They were compassionate payments but
9 it was a tragedy that could have been averted.

10 So what we are trying to do here is basically
11 respond to some of those historical issues
12 that we've had to face. It is something that
13 seems to be an ongoing process and this just
14 adds one more hurdle to overcome.

15 So I guess in the other part about
16 the bleeding disorders community that might be
17 considered as part of a blueprint would be how
18 the bleeding disorders community accessed HIV
19 medications early on when a lot of people were
20 dying from the effects of that virus.

21 So at this point we did a quick
22 study on UDC data. This is the universal data

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1 collection. It is information that is
2 provided to the UDC. They collect information
3 on people who are affected and we found that
4 about 6,000 to 7,000 people in the Hemophilia
5 community are positively infected with hep C
6 and of those nearly the entire cohort of
7 people over 35 also have hepatitis C and HIV.

8 So the clinical trials are unavailable. Mark
9 mentioned that with co-infection or advanced
10 disease we are poor candidates. But also as a
11 result of liver biopsy, we have, it is a
12 complicated procedure and it is very costly
13 for people who are affected because of
14 hospitalization and the need to treat with
15 this anti-hemophilic clotting factor. But we
16 do see that there is a potential cure and we
17 are hopeful for that. We are hoping that you
18 can recognize some of our needs as a
19 population that is vulnerable to the impact of
20 this illness.

21 So Mark slightly mentioned but we
22 thought it was a high risk for high need type

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1 parallel track. Where a default philosophy
2 would be to heal people who are affected. It
3 would be limited to situations where the need
4 is great, where the risk of drug failure is
5 substantial and the probability of success
6 potentially significant. This is justified by
7 a great need and a real possibility of
8 success. And any alternative track might
9 include enhanced patient warnings, some hold
10 harmless provisions for liability and analysis
11 of adverse events. But data would be a
12 secondary purpose of this pathway not a
13 replacement for the current access track.

14 So within the citizen petition we
15 requested the FDA modify guidance and I guess
16 that is at some point, it seems that is the
17 point we are at now. So we applaud the FDA
18 regarding that and hope that can be an
19 expedited process and one that is highly
20 publicized and available for comment as soon
21 as possible. As we said here the parallel
22 track would be focused on healing. It would

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1 encourage early testing of various combination
2 as well as combinations without standard of
3 care and it would encourage the companies to
4 collaborate. But the idea is to expedite this
5 process and set some goals that would be
6 tenable in the very near future, hopefully in
7 2010. We would hope that the access to those
8 medications might come before the completion
9 of Phase II trials.

10 So we also tried to respond to some
11 of the questions here and I think a lot of
12 people have done just that throughout the
13 morning. So people with bleeding disorders,
14 we basically just copied the question verbatim
15 but the response, the most important piece is
16 the response that we've come forward with and
17 that involves this parallel track, a high risk
18 for high need. Candidates might include those
19 who are highly threatened by advanced disease
20 or people who are unlikely to benefit from
21 standard care. These are also people that
22 standard care is contraindicated. So, they

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1 would be ineligible for any traditional
2 clinical trial.

3 The circumstances that we've
4 suggested would be something that doesn't
5 involve single agent therapy because it
6 doesn't seem to work for us and it goes
7 against our experiences, anecdotal
8 experiences, science and ethics as well. So
9 those are things we would like to be involved
10 in your consideration.

11 Multiple DAAs, we suggest this be
12 balanced against the likelihood of progression
13 without new treatment options, recognizing
14 that therapy failure may be high but the need
15 is also very high.

16 How can pharmaceutical companies,
17 government, academia, and community physicians
18 not just collaborate? Again, we go back to
19 the treatment paradigm established for HIV
20 using multiple different agents and small
21 studies that would be beneficial to look at
22 two different, two or more investigational

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1 agents.

2 Potential adverse reactions.
3 Certainly some cases of advanced liver disease
4 will progress to decompensation or even
5 towards an acute decompensation during the
6 course of therapy. But for drug combinations
7 that show a high activity we would hope it
8 would be recognized and acceptable, reduced
9 levels of adverse events versus expectations
10 without therapy.

11 So how can all the stakeholders
12 provide for the treatment? Well we would
13 suggest through the guidance to clarify the
14 regulatory fabric that encourages
15 pharmaceutical companies to offer access and
16 we recognize also that there are some issues
17 with compassionate access but that, especially
18 in regard to negative results and we would
19 hope that companies and stakeholders would
20 recognize the alternative by not doing
21 anything. Those results could be the same or
22 worse. We do need protections in that regard

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1 but not at the cost of life itself.

2 And finally in the course of
3 developing the DAAs for marketing, the types
4 of studies that might best address these needs
5 would be expanded access delinked from the
6 expectation of providing rigorous high quality
7 data. These types of studies will be helpful
8 in identifying the most powerful effects and
9 side effects and hopefully give us some chance
10 to carry on and lead a long life, long healthy
11 life. So that's it. Thank you.

12 (Applause.)

13 CHAIR MURRAY: And thank you. Any
14 questions? Okay. With that then I guess we
15 will move on to Dr. Sylvestre, Assistant
16 Clinical Professor of Medicine at the
17 University of California San Francisco.

18 DR. SYLVESTRE: I appreciate you
19 guys putting together this thing which I guess
20 essentially allowed me to come 2,800 miles to
21 vent. I am a doctor and I treat hepatitis C
22 and I am an addiction specialist. My clinic

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1 is known for its work in the community to
2 develop algorithms to help the marginalized
3 patients in the world with hepatitis C and my
4 first vent would be, how come this podium is
5 put toward them? I am here to talk to you.
6 We've gotten through this, almost this whole
7 day without talking about the main issue which
8 is hepatitis C is driven by injection drug
9 use. We haven't talked about drug users. It
10 is nothing about the color of your skin that
11 gives you hepatitis C. Yes, it affects the
12 natural history but we are hiding our heads in
13 the sand if we don't confront this issue about
14 drug use and hepatitis C. Now I work in
15 settings like this. This is a syringe
16 exchange in Oakland, California. This is
17 where my patients get their medical care. And
18 I do everything I can for prevention. But in
19 order to prevent hepatitis C with the viral
20 loads being that high and with the virus
21 having such durability, you ain't going to get
22 there. It is needles and syringes and cottons

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1 and cookers and rinse water. Good studies
2 have shown that this is extending the duration
3 of time it takes to get hepatitis C but it is
4 not preventing hepatitis C. And until we
5 start getting these drugs into these kinds of
6 patients we are not going to get anywhere with
7 this epidemic. This is where we do our
8 studies. This is where my clinical
9 coordinators consenting a patient out in the
10 cold and the rain in a tent. I will start
11 with this. We talk about 54 to 56 percent
12 SVR. Let's get real. Who are these patients
13 in those studies? I have never had a patient
14 accepted into a clinical study. They are
15 routinely rejected from these studies of
16 hepatitis C because they have mental illness
17 because they have history of drug use.
18 Sometimes because get this, they are on the
19 most effective treatment for heroin use which
20 is methodone. And that is changing but you
21 know even I do studies like this. And we
22 parade this around and say isn't this

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1 wonderful. I got an IND for buprenorphine
2 before it was approved. This is a drug that
3 stabilizes heroin use. We stabilized street
4 recruited heroin users and then transitioned
5 them to hepatitis C treatment while they were
6 on buprenorphine and, hurray hurray, despite
7 all of the negative prognostic factors we saw
8 a 40 percent SVR rate. Isn't that marvelous?

9 Well, not really. Because if you go back and
10 look at the real SVR, when you take that group
11 of patients who actually showed up in those
12 tents to sign up in our studies and trickled
13 them down to the ones that initiated
14 buprenorphine, that started hepatitis C
15 treatment, that completed hepatitis C
16 treatment, the SVR is 8 percent. And we
17 didn't enroll every single person with
18 hepatitis C in that syringe exchange program.

19 So when you look at these SVR rates that you
20 parade around, you remember we are not looking
21 at 55 percent SVRs. It is probably 1/10 of
22 that. We are in desperate need of developing

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1 new paradigms for hepatitis C treatment and I
2 look to you to develop leadership strategies
3 so we can help eliminate this disease. We are
4 not doing that right now. This data can go on
5 and on. This is a study of HIV co-infection
6 clinic where .7 percent of 300 patients were
7 likely to be treated. This is the real world.

8 Here is another hep C treatment in an urban
9 clinic, again, 29 percent were considered
10 eligible. That doesn't say 29 percent were
11 treated. That is only 29 percent who were
12 considered eligible for things like
13 psychiatric disorders. Things that happen
14 when you have hepatitis C. So you know why is
15 -- all of sudden why should we even care?
16 Well you know again these patients are driving
17 the epidemic. My patients are driving your
18 epidemic. And we are not doing anything about
19 that right now. We are doing a little piece
20 out trying to prevent it but we need to get
21 treatment into these people and they are not
22 eligible for care. Interferon is a double

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1 drug. I use it all the time. I love it. I
2 love curing patients with hepatitis C but
3 almost none of my patients, 3,500 screened in
4 my little clinic, we calculated it was six
5 percent of the people in the Bay Area that
6 we've actually screened for hepatitis C and we
7 have treated only a small fraction because
8 they can't be treated because they are not
9 eligible for interferon treatment and the side
10 effects you don't see. I cover them from
11 front to back. We provide integrated care,
12 psychiatric care, all the way through medical
13 care and God knows psychosocial whatever they
14 need. And you are not seeing what I see. I
15 mean a homeless woman blind with this disease
16 I had never heard of. And then when you are
17 homeless and female and blind you don't do
18 very well and she killed herself. We've seen
19 pulmonary hypertension. We see rashes that
20 nobody can explain. It goes on and on and on.
21 This is interferon. It is wonderful but it
22 is hateful and it is not the future of

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1 hepatitis C. Liver transplantation. Right.
2 I have had one patient in all these years get
3 a liver transplantation. You are not eligible
4 for liver transplantation. So let's not even
5 assume that's going to happen for the majority
6 of the people with hepatitis C. Good thing I
7 took my jacket off. Again, so what. So why
8 do we care? These people gave it to
9 themselves. Well you know we are all paying
10 for this. We are all paying for their
11 hepatitis C or paying for their end stage
12 liver disease. It is costing us a lot of
13 money. We need to care about this because we
14 can shut down this epidemic if we try. It is
15 not going to be easy. I agree with all these
16 speakers, all these wonderful talks about
17 concerns about drug interactions et cetera, et
18 cetera, but we can do this if we try. And so
19 first we have single agent early access.
20 Well, you know, that's marvelous. We have
21 some people that did fairly well on interferon
22 who didn't quite clear but there is problems

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1 with this and that's interferon is still the
2 backbone, that still excludes the majority of
3 patients who have hepatitis C. You know we
4 will see better outcomes but it is at a cost.

5 There are more side effects. Most of you who
6 have been following the telaprevir data. That
7 rash is a big deal. There is a lot of rashes
8 on interferon. This is going to be a big
9 problem here. We are adding more problems as
10 we improve efficacy. And it is interferon.
11 No one is going to qualify. It is the same
12 problem. Nobody is going to qualify for these
13 treatments if they didn't qualify before and
14 then I would raise a very important issue.
15 Quite frankly if I start treating active drug
16 users who are not particularly adherent then
17 they might be developing resistance in
18 themselves and guess what. You are going to
19 pass it on. So let's confront this issue
20 right now and say we need to be very carefully
21 developing strategies for monitoring adherence
22 for assuring adherence and then looking at

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1 resistance as it might come out.

2 The other thing I would like to
3 just vent about even though it is not quite on
4 topic here is how come we are not including
5 subsets of relevant patients in the Phase III
6 registration trials? You could a priori have
7 a co-infection arm and a drug addiction arm
8 and say okay we will allow you to do that but
9 we won't, we will allow you not to put those
10 statistical analyses in as part of your
11 ultimate SVR, as part of your final
12 statistical analysis because they are subsets
13 that you need to study because that's who hep
14 C represents. Not your pie in the sky four
15 percent that actually qualify. But this is
16 what it is really going to look like and that
17 way we can look at safety early on, we can
18 look at efficacy early on and start to
19 strategize our programs down the road. And in
20 that please, please, please we have to be very
21 carefully monitoring adherence and resistance
22 you know with MEMS caps and things like that,

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1 not just like did you take all your pills this
2 week? You know what kind of answers you are
3 going to get. It is kind of like what are you
4 side effects? We need to be more rigorous in
5 monitoring this. I would also like to suggest
6 that you guys strongly suggest PK studies with
7 methadone/buprenorphine because these are two
8 of the approved and effective treatments for
9 heroin users. They are not the only drug
10 injectors but they represent about a million
11 people in the United States.

12 And then I get to triple agent
13 therapy which is the future and there are all
14 the issues that have already been brought up
15 and I agree with them 100 percent. But it is
16 the future of hepatitis C treatment, I hope.
17 Certainly interferon does not look to me to be
18 the Holy Grail in the sky in 50 years. It is
19 going to have a potential huge impact on
20 access to care. Interferon is excluding the
21 majority of the people who have hepatitis C.
22 It has a huge impact on the development of

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1 viral resistance unfortunately. We have to be
2 very careful in the way we structure these
3 studies and monitor what's going on with
4 adherence and resistance. It has potentially
5 huge safety issues. Let's face it. But it is
6 the future of hepatitis C and this is what I
7 would encourage you to try to move this
8 industry toward because I think there is a
9 financial disincentive to eliminating
10 interferon. Quite frankly the paranoid me
11 says you know you had a couple of companies
12 who are selling a lot of interferon and
13 ribavirin bundled together and maybe since
14 they are making a lot of money they don't want
15 to move forward as quickly as I would like
16 them to move forward. My husband works for a
17 pharmaceutical company. So I'm not anti-
18 pharmaceutical but that makes sense to me. It
19 is going to be territorial squabbles that you
20 might be able to help guide. That was a nice
21 word. I was hoping that you know you might
22 require companies that are initiating a Phase

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1 III approval study to make their agent
2 available for PK studies with other agents
3 perhaps through an NIH mechanism. There are
4 people doing good PK studies. If they had
5 access to this and that, they would probably
6 be very excited to look at different agents
7 together before they are approved to see what
8 kind of interactions you might see. And
9 again, I'm over and over again carefully
10 monitoring for adherence and resistance and
11 again PK with methadone/buprenorphine and any
12 other agents that seem to be effective for
13 persons who are being treated for addictions.

14 I put a cartoon at the end. That is what I
15 usually do. Maybe zero tolerance is setting
16 the bar too high. And with that not having
17 vented too badly I end.

18 CHAIR MURRAY: Thank you for your
19 great presentation. I have a question but I
20 wanted to see if anyone else has a question
21 first. You have mentioned and the last
22 speakers I thought of this as well, a possible

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1 idea instead of maybe -- and expand -- a
2 separate expanded access program maybe adding
3 on to existing trials a cohort of patients and
4 that you would somewhat set them aside from
5 the regular statistical analysis, maybe they
6 wouldn't get randomized, it would just be a
7 cohort. And then you said -- you know, you
8 could do -- two separate analyses but then at
9 the end of the day if it were approved would
10 you or would you not want something in the --
11 wouldn't you want that information in the
12 label if you knew that your cohort did worse
13 or better or however, wouldn't you still want
14 that information?

15 DR. SYLVESTRE: I would absolutely
16 want that information you know because let's
17 say it doesn't work in co-infected patients.
18 Oh, yes, I want that information, and I want
19 it now. That's the thing. The more
20 information you can get me now, the better,
21 and this is one way of getting the information
22 now, for good or for bad.

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1 CHAIR MURRAY: But they could
2 still have their analysis of their other
3 population?

4 DR. SYLVESTRE: I would give them
5 that.

6 CHAIR MURRAY: Any other
7 clarifying questions?

8 DR. SYLVESTRE: Thanks, guys, for
9 having us.

10 CHAIR MURRAY: Thank you.

11 (Applause.)

12 CHAIR MURRAY: I think we are
13 going to have another presentation because we
14 have time and -- before doing a break. So we
15 will do one more presentation, have a break,
16 and then I think we will do the last two
17 presentations and just move on to people who
18 didn't pre-register or signed up via a card to
19 make some final comments. We will do that all
20 in one block. So the next presenter is Dr.
21 Apelian from GlobeImmune.

22 DR. APELIAN: Well, while we are

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1 getting set up, I would like to thank the FDA
2 for having this forum. I think it is a really
3 important time to be looking at expanded
4 access and early access. My name is David
5 Apelian. I am the Chief Medical Officer at
6 GlobeImmune. We are a clinical development
7 stage therapeutic vaccine company based just
8 outside of Boulder, Colorado. My purpose for
9 coming here today is to raise the awareness on
10 a couple of issues that might be a little
11 outside the mainstream of this particular
12 meeting. Number one, I would like to draw
13 some attention to what's been mentioned a
14 couple of times today, the IL-28B genotyping
15 story that has recently emerged last year, and
16 it really has become a very exciting and
17 compelling way of looking at hepatitis C
18 patients. As you are all well aware for many
19 years we've been looking at the genotype of
20 hepatitis C virus and that's been a very
21 powerful tool in tailoring and customizing our
22 approach to treating patients. Now we finally

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1 have a marker of the patient that's helping us
2 understand which patients are more likely to
3 respond to therapy. And I really think that
4 kudos go to the Duke team and the Schering
5 team for collaborating on this and really
6 delivering, I think, one of the biggest
7 breakthroughs in understanding hepatitis C in
8 the last 15 or so years.

9 My second purpose for being here is
10 to try to broaden the awareness of other
11 therapies outside of the DAA class. I
12 recognize the need to focus on the direct
13 acting antivirals in this particular meeting.

14 But in looking ahead at early access and
15 expanded access, I'd like to broaden the
16 horizons a little bit and share with you the
17 fact that there are going to be some other
18 types of therapies out there. We develop
19 therapeutic vaccines. I think today's meeting
20 is timed interestingly with the approval of
21 Provenge yesterday to treat prostate cancer.
22 That's the first approval of a therapeutic

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1 vaccine in cancer. We believe strongly that
2 we will see further approvals for similar type
3 agents in cancer but we also believe strongly
4 that we'll see similar types of approaches
5 being used in chronic viral infections as
6 well.

7 So just to let you know that this
8 isn't totally pie in the sky, we are
9 developing a platform which can target various
10 disease antigens. In the case of hepatitis C
11 we are targeting NS3 and core. And we use
12 saccharomyces-based therapeutic platform,
13 therapeutic vaccine platform that we call
14 Tarmogens. There are some distinct
15 differences between this approach to the
16 direct acting antivirals. Number one, we
17 don't suppress the virus. What this vaccine
18 is designed to do is to increase the T cell
19 response the patient generates to improve the
20 clearance of infected cells from the liver and
21 other sanctuaries in the body.

22 Secondly, this has a completely

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1 different mechanism. So we don't see and
2 don't expect or don't predict the same kinds
3 of rapid pathways to resistance that you see
4 with the small targeted molecule approaches.
5 And secondly, this being a vaccine has a very
6 different PK/PD profile, so you can imagine
7 how combination of this approach with other
8 direct acting antivirals could be very
9 attractive and very useful.

10 We are reporting out, in fact just
11 two weeks ago we reported data at the EASL
12 meetings of our triple therapy Phase two study
13 combining GI5005, our therapeutic vaccine with
14 Pegasys and ribavirin compared to standard of
15 care alone. My intention is not to present
16 our data today but we did see SBR advantages
17 in terms of the treatment effects observed not
18 only across all IL-28B genotype patients but
19 also in the most difficult to treat patients.

20 In fact some of the biggest treatment effects
21 that we saw were in the T allele containing
22 subgroups, so we find that to be a very

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1 interesting trend that we intend to look at
2 further.

3 We believe that there is going to
4 be a need for a multiple class agents in the
5 treatment of hepatitis C. I would readily
6 acknowledge that the direct acting antivirals
7 will play a very important role in the future
8 of how we treat this disease. But it is hard
9 to ignore the fact that interferon probably
10 does, interferon plus ribavirin probably does
11 other things than simply suppress the virus.
12 There is some data from kinetic modeling that
13 it perhaps also influences the reinfection of
14 neighboring healthy cells in the liver and
15 potentially in other sanctuary sites in the
16 body. We think the completely unmet part of
17 how we treat patients right now is improving
18 the patient's ability to clear the virus, the
19 infected cells from the liver and infected
20 cells perhaps elsewhere in the body. So this
21 is really the big gap in how, as clinicians,
22 we are trying to treat this disease. This is

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1 where therapeutic vaccines and active immune
2 therapies can be very important.

3 We are convinced that the immune
4 response to the patient matters in this
5 disease. If you simply look at the natural
6 history of chronic hepatitis C, 20 percent of
7 the patients that get exposed to the virus
8 actually cure themselves without therapy
9 whatsoever. And when people have looked at
10 what makes those patients different than the
11 unfortunate 80 percent is the fact that these
12 patients have a much stronger T cell response
13 specific to the hep C virus.

14 Not only is that response stronger,
15 but it's broader and recognizes more different
16 epitopes of the hepatitis C virus than a
17 chronic patient. We also know, and this is
18 clear from hep B as well as hep C therapy, it
19 takes many months of consolidative therapy
20 even after the patient is PCR negative in the
21 serum to get that patient to an SBR.

22 Kinetic modeling has also shown

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1 that there is likely a strong relationship to
2 hepatic clearance to get those patients to a
3 meaningful remission status. So simply
4 becoming PCR negative in the blood is not
5 sufficient to assume a patient is going to
6 have a long term response or an SVR. I think
7 the IL-28B story really is resonant now
8 because it has shown not only a prediction and
9 I'll get a little background on that. Not
10 only predicts which patients will respond to
11 interferon based therapy, but a study that
12 came out of Hopkins within a few weeks
13 probably of the Duke manuscript showed that it
14 predicted spontaneous clearance of the virus
15 as well without therapy. So this really
16 points to a fundamental difference in these
17 different types of patients. So an IL-28B C/C
18 patient appears to be quite different
19 fundamentally from an IL-28B T/T patient for
20 example.

21 This was, as I mentioned, the
22 recent breakthrough late last year, but

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1 already it's really gotten a lot of attention.

2 At the EASL meeting I would say this was
3 probably one of the hottest new stories that
4 got attention. As I mentioned the fact that
5 this predicts not only spontaneous clearance
6 of the virus but response to interferon really
7 points to the fact that this is reflecting a
8 fundamental aspect that is different in these
9 different types of patients.

10 And as some background, just to
11 show you, and this is based on the Duke
12 manuscript that was recently published. About
13 a third of the patients will have the
14 favorable genotype, the IL-28B C/C genotype.
15 That is shown in orange here. About half will
16 have a moderate risk genotype, and about 1/6
17 of the patients will have the poorly
18 responsive genotype, the T/T, shown here in
19 green. If you look at the SVR difference of
20 these groups, you can see the striking
21 difference. Almost 80 percent SVR in the C/C
22 group, under 40 percent in the C/T group and

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1 less than 30 percent in the T/T group. This
2 was even a highly compliant population, 80,
3 80, 80 analysis that came out of this
4 manuscript. So you can see the profound
5 difference in SVR that is predicted by the IL-
6 28B.

7 Furthermore, if you look at African
8 Americans and the rate that they have a T/T,
9 the bad genotype, it is profoundly higher than
10 that seen in the general population. It is
11 three times higher. There is 37 percent T/T
12 genotype in the African American group
13 compared to 12 percent in Europeans and about
14 15 percent overall. So when you look at the
15 data from the Duke manuscript, it actually
16 shows that the T/T genotype predicts about 2/3
17 of the poor responsiveness in African
18 Americans. So here is an important clue,
19 something that has baffled us for years.

20 Why do African Americans respond
21 more poorly to interferon based therapy? Well
22 here is a huge piece of that story right here.

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1 There has been other important associations,
2 and I would venture that there likely will be
3 more in the near future. But when people have
4 looked at the T/T subgroup of IL-28, it has
5 been shown now to predict progression of acute
6 exposure to chronic disease. It has also been
7 shown in the Duke manuscript, as I mentioned
8 before, to predict response to interferon
9 therapy.

10 There has also been recent
11 associations of the T/T genotype to poor
12 response in HIV co-infected patients. I would
13 venture to say that in the coming years we
14 will likely see relationships of the T/T
15 genotype to other long term outcomes such as
16 progression to cirrhosis and to hepatocellular
17 carcinoma. And right now we don't know how
18 the direct acting antiviral group will perform
19 in an IL-28B T/T or even C/T group. I'm sure
20 we'll see data of that sort in the next year
21 or two with the big programs maturing, but
22 right now this is still a big question mark.

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1 We don't know what kind of impact the direct
2 acting antivirals will have in this space.

3 So in conclusion I think it is
4 important that we consider this as an
5 important factor in looking at unmet
6 population needs and underserved populations
7 in planning early access and expanded access.

8 IL-28B, I think, will continue to become an
9 important and increasingly important part of
10 this story. And I think we really need to
11 keep in mind how we need to look at other
12 types of therapies. Not just the direct
13 acting antivirals but other modalities that
14 might have a different influence in patients
15 of high risk IL-28B T/T subgroups, and I think
16 I added a few comments after hearing today's
17 session which was really informative.

18 I think we also need to be really
19 careful as we define either surrogate
20 endpoints that are earlier than SVR or if we
21 use historical comparators for future studies
22 that we need to understand the influence of

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1 IL-28B genotyping. It would be a tragedy to
2 have so-called positive studies really be
3 positive because of an underlying imbalance or
4 less than representative IL-28B profile. So I
5 think we need to keep this in mind as we get
6 more aggressive, especially in the early
7 access and expanded access programs. Thank
8 you very much for your time.

9 (Applause.)

10 CHAIR MURRAY: Questions?

11 DR. O'REAR: So for hepatitis B
12 virus, resistance to some of the RTIs can
13 impact T cell epitopes. Would you care to
14 comment on possible resistance to the DAAs in
15 your therapy?

16 DR. APELIAN: Well one of the
17 things that I didn't get into great detail
18 about was our approach actually targets
19 multiple epitopes so large stretches of the
20 hep C antigens. So what that does is it
21 changes the resistance story a bit because now
22 you have multiple ways of targeting the virus.

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1 So this is quite different than the small
2 molecule approach where a single mutation of
3 the virus can actually evade pressure and we
4 see this in the hep B antivirals and the hep C
5 antivirals.

6 So by using big pieces of foreign
7 antigens in a vaccine approach you can then
8 have multiple epitopes being targeted by the
9 patient's immune system and it dramatically
10 decreases the risk of a single or even double
11 hit in the virus being capable of evading that
12 kind of pressure. So there could be
13 influences on how a vaccine works so that is
14 something in the future that could be a very
15 important area of inquiry but certainly
16 wouldn't provide a simplistic single or poly-
17 hit escape mechanism to the virus the way a
18 small molecule approach would.

19 DR. STRUBLE: Can you comment or be
20 more specific on the IL-28B genotype and how
21 that would play a factor in expanded access?
22 Going back to Lynda Dee's presentation about

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1 how you would stage and prioritize patients.
2 So how would you integrate that in
3 prioritizing for those programs?

4 DR. APELIAN: I think one example
5 of that is if you look at the African American
6 community and for years we've wondered why
7 they don't respond well to therapy. Well if
8 the T/T genotype explains up to 2/3 of that
9 poor responsiveness you can certainly think of
10 in terms of addressing an underserved
11 community and the community at high risk of
12 treatment failure as a way of focusing on
13 early access program and really focusing on
14 centers that service that community looking at
15 the IL-28B genotyping as a requirement to make
16 sure you are stratifying or even enriching the
17 study specifically for T/T patients. This is
18 one example of how you could use that
19 information to really improve how we target
20 not only poorly responsive populations but
21 underserved populations.

22 CHAIR MURRAY: Okay. I think we

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1 are going to take a break now until about 2:30
2 and then when we come back we will have two
3 scheduled presenters and then we will go into
4 an open format.

5 (Whereupon the above-entitled
6 matter went off the record at 2:14 p.m. and
7 resumed at 2:31 p.m.)

8 CHAIR MURRAY: We're going to get
9 started here in just a minute but before we
10 move on to our last two scheduled
11 speakers/presenters, I am going to go back and
12 ask some questions of clarification. So we
13 have a clarification question for Dr. De
14 Gruttola. So it says given that the IL-28B
15 C/C genotype has been shown to be a strong
16 predictor of positive response with treatments
17 of interferon under what conditions might you
18 restrict a Phase IIB trial to IL-28B C/C
19 patients only or would you ever restrict Phase
20 IIB trial to IL-28B patients?

21 DR. DE GRUTTOLA: I think its really
22 more a medical question. I think that the

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1 issue on the -- the most important issue of
2 course is what is the medical question. Is it
3 a treatment comparison for the whole
4 population or a treatment comparison within
5 subgroups? Obviously there is always interest
6 in finding out what subgroups might have
7 better or worse response or comparative
8 response than would another. So I think the
9 issue in doing design is the question of: Are
10 different groups such as defined by the IL-28
11 so different that you really want separate
12 studies for them or would you want to do one
13 study with a stratification factor?

14 And if you do the latter do you
15 want the study to be powered so that you can
16 get, detect a subgroup effects and basically
17 be able to determine if there are any
18 interactions between the stratification factor
19 and the treatment comparison you are looking
20 at. And is the goal ultimately to try to
21 combine across those groups or are they seen
22 as being medically so different you don't

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1 know. So that's not, I don't have a specific
2 answer but I think its very dependent on,
3 driven by the medical issues.

4 CHAIR MURRAY: Thank you. Then we
5 had a question for Dr. Rodriguez-Torres but I
6 don't know if she is here still. But if any
7 of the other presenters know this but it has
8 to deal with African Americans and Latinos, is
9 the poor response rate also true for genotype
10 Type 2 and 3 as it was for genotype 1? Yes,
11 great. All right. So we are going to move on
12 to the two scheduled presenters and then we
13 will have public time and we have at least one
14 person in the back for that. And so Dr.
15 Heath-Chiozzi from Bristol-Myers.

16 DR. HEATH-CHIOZZI: Good afternoon.
17 My name is Margo Heath-Chiozzi and on behalf
18 of Bristol-Myers Squibb I would like to thank
19 the FDA and specifically today's meeting
20 organizers for asking us to share our thoughts
21 and hear from the other presenters on this
22 important topic. I would also like to thank

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1 the people who've chosen to say for the last
2 two presentations because you will note that
3 much of what you are going to hear has already
4 been said and so I really appreciate your
5 patience in sitting through yet another set of
6 comments.

7 Bristol-Myers recognizes chronic
8 hepatitis C as a major cause of morbidity and
9 mortality in the U.S. and globally. As noted
10 by the other speakers, we strongly agree that
11 collaborative research is urgently needed to
12 address the unmet medical needs of this
13 medical disease. I skipped this slide because
14 other previous speakers have done a much
15 better job at presenting the complexity of the
16 patient's needs for this disease.

17 Bristol-Myers is committed to
18 improving therapy for chronic hepatitis C with
19 the goal of improved cure rates. We see three
20 main opportunities for advancing therapy.
21 First we believe that research efforts can and
22 will increase the percentage of patients that

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1 are eligible for therapy. We see that
2 happening by decreasing the adverse events and
3 leading to better tolerated therapies, few
4 discontinuations and addressing the emergents
5 of resistance by really delivering effective
6 therapies and we feel strongly that the
7 effective therapies also need to be studied to
8 optimize durations to provide cures with as
9 short a duration of therapy as possible. So I
10 think relative to the comments that were made
11 by the previous speakers where we really would
12 like to see emphasis also placed is on
13 research that clearly states how to optimize
14 minimal durations of therapy, again all with
15 the stated goal of improving cure.

16 As others have noted, there really
17 is a disappointing current response to
18 therapy. So our goal in improving cure,
19 again, is to improve efficacy, safety and
20 minimize the duration. We've chosen to pursue
21 a comprehensive research agenda to optimize
22 our chances of actually delivering against our

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1 stated goal. So as we've publically stated,
2 we've already partnered with ZymoGenetics to
3 study their novel interferon, lambda
4 interferon in combination with one or more
5 small molecules. In addition we are pursuing
6 clinical investigations of peg interferon
7 alpha with ribavirin again with one or more
8 small molecules. And in addition we've
9 already begun our pilot studies of small
10 molecule combinations.

11 Bristol-Myers is keenly aware of
12 the propensity of viruses to mutate to
13 resistant forms when exposed to targeted to
14 antiviral therapy. We've deliberately
15 prepared to study combinations of agents
16 against multiple targets to minimize the risk
17 of resistance development. In partnership
18 with the FDA and other global health
19 authorities, we've commenced pilot
20 investigations combining agents against the
21 multiple targets that we are studying again
22 both with and without alpha interferon and

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1 ribavirin.

2 We also have extensive experience
3 in providing investigational agents by
4 expanded access, specifically in patients with
5 life threatening diseases, with a lot of
6 experience in HIV and cancer. This slide
7 shows the internal considerations that we
8 review for determining if sufficient data is
9 available to support appropriate expanded use
10 in life threatening situations. Just to
11 highlight a couple of the bullets. We do
12 believe that expanded access programs really
13 should target patients who cannot participate
14 in controlled clinical trials and as noted by
15 the other speakers, that's not just by trial
16 design but also trial access.

17 We believe that you have to have
18 sufficient understanding of the efficacy
19 profile to have a meaningful, expectation of
20 providing clinically meaningful benefit as
21 well as have sufficient safety understanding
22 to note that patients would not be exposed to

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1 unreasonable risks. And we believe that it
2 should also be considered whether there is
3 anything unique about the patient that would
4 lead them to have a different benefit risk
5 expectation. And again here I think other
6 speakers have spoken eloquently to the
7 limitations of what these molecules look like
8 in combination with alpha interferon and we
9 hope that the progression of better tolerated
10 interferons may broaden the ability of
11 patients to build regimens that really will be
12 successful for individual patient situations.

13 hepatitis C illness spans a wide
14 range of clinical settings. So we think it is
15 important to clearly state the goal of therapy
16 as you are going forward. With our expanded
17 access principals we believe that
18 investigational agents currently should best
19 be presented in clinical trials whenever
20 possible.

21 Investigational agents are being
22 administered in more advance patient

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1 populations and we think that just describing
2 that experience precisely in focus clinical
3 trials with detailed patient population
4 descriptions is going to be very important
5 going forward. We believe that the DAA
6 combination studies do need to take into
7 consideration the risk of overlapping
8 resistance as well as the risk of overlapping
9 toxicity issues and we support the concept the
10 cross company collaborations need to be
11 encouraged to optimize the study regimens that
12 are provided in the clinical trials.

13 Again noting the complex clinical
14 situations that have been mentioned by other
15 speakers. We think that it is important to
16 note the goal of the therapy. And so we think
17 that the way to envision going forward in
18 expanded access you really should look at
19 patient populations where your goal of therapy
20 remains cure.

21 And we hold that the patients with
22 decompensated HCV illness should still fall

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1 into a range where you target cure. And so
2 even though they've not responded or relapsed
3 or been intolerant to their previous regimens,
4 we think that in that segment you need to have
5 a vision of an optimized regimen hoping for
6 cure rather than just progressive viral
7 declines without an optimization strategy
8 focused on cure.

9 In addition, we do see liver
10 disease, the peri-liver transplant setting as
11 unique. And that's the place where we think
12 that targeted studies of these combinations of
13 agents may most appropriately be used to think
14 of what peri-transplant use and what post-
15 transplant use will lead to clearance and
16 eradication of the virus. So it may not be a
17 classic SVR kind of endpoint. It may be
18 something that is more a study of the duration
19 of therapy post transplant and when can you
20 stop and still have protected the transplanted
21 organ.

22 At this time we feel there is

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1 insufficient data to support current expanded
2 access use. We think that the early data that
3 is very exciting doesn't really give you
4 sufficient information to know whether you are
5 going to be able to deliver sustained SVRs and
6 there's really only very limited to drug data
7 that's already in the public sector.

8 So, we believe that the small proof
9 of concept studies that have yet to
10 demonstrate SVRs are really insufficient to
11 move beyond a controlled clinical trial
12 setting and that that's the information that
13 we believe would be most important in moving
14 then to a non-trial access setting. And the
15 individual patient considerations, companies
16 should talk but I think that even in your
17 paradigm of intermediate patient populations
18 still some understanding of SVR would be a
19 gate that we would like to see prior to moving
20 to that paradigm.

21 I would like to spend a couple of
22 minutes just noting ways that we think that

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1 the FDA can help accelerate the pace of HCV
2 drug development. First we would like to
3 encourage the support the FDA's
4 Pharmacometrics ongoing activities in building
5 a robust dynamic HCV Disease Model. We think
6 that they are in a unique position to take the
7 clinical data that's being generated by all of
8 the companies that's emerging so rapidly and
9 build a model where we can partner our
10 epidemiologic expertise with theirs to define
11 patient populations that are at greatest risk
12 of rapid progression for disease.

13 We think that the FDA across the
14 board as well as other global health
15 authorities can give us much more clarity
16 around the individual patient populations and
17 as other speakers have spoken, the importance
18 of staying on top of the emerging science,
19 especially things like how to think through
20 the IL-28 polymorphisms and co-infection and
21 drug interaction issues, et cetera, can be a
22 place that you are in a unique leadership

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1 position.

2 I also would like to note that
3 pediatrics hasn't been mentioned to this point
4 in the day but is very important in terms of
5 knowing what is going to warrant therapy, at
6 what age groups for pediatric patients. I
7 think a consistent global acceptance of what
8 are the treatment paradigms for children would
9 be something that would be of great benefit to
10 all of the companies and anyone that is trying
11 to optimize therapy for this disease.

12 As we dialogue about our
13 development programs we have lots of
14 discussions about the rationale behind the
15 combinations but its not just the rationale
16 for the combinations but also the dose
17 selection within the combinations and as
18 previously noted, resistance issues. We think
19 FDA can provide a lot of collaborative
20 information on how we partner the
21 investigational agents but then also what are
22 the rational comparator regimens? In addition

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1 how do we really get at that question of the
2 duration of therapy and are we moving to a
3 place that response guided therapy is going to
4 be the most important way of determining
5 really the appropriate duration for different
6 patient segments?

7 As noted, endpoints that are
8 earlier SVR, that are useful not just for
9 development decision making but also for
10 regulatory decision making, we think is going
11 to be an evolving issue in development. And
12 we want to reiterate that we think that liver
13 transplant is the situation where controlled,
14 early controlled investigations where we get
15 data to possibly ask simple questions around
16 duration if nothing else is an important place
17 that we think the FDA could partner with us.

18 In summary, Bristol-Myers is
19 committed to partnering with global health
20 authorities to advance the treatment of HCV
21 leading to improved cures in the U.S. and
22 globally. We believe this is going to be best

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1 advance through well designed controlled
2 clinical trials. The combination therapies
3 will expand the patient populations that are
4 eligible for shorter more effective regimens.

5 We will continue our long tradition of
6 partnership with other companies and health
7 authorities to deliver optimal therapies for
8 patients with this serious disease. Thank you.

9 (Applause.)

10 DR. BIRNKRANT: Thank you very much
11 for those comments. You mentioned cross
12 company collaboration. How do you envision
13 that working?

14 DR. HEATH-CHIOZZI: Well I think
15 that we've already partnered with ZymoGenetics
16 because we felt strongly that novel
17 interferons would be very valuable in
18 optimizing what could be delivered with small
19 molecules. We are open to discussing other
20 company's molecules and we think the pilot
21 studies first followed by, you know drug
22 interaction studies, followed by the pilot

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1 studies in appropriate patient populations and
2 determine how the regimens actually perform.

3 DR. BIRNKRANT: I mean that's a
4 big step though even pilot studies amongst
5 various companies. How do you propose to move
6 forward to attempt to look at drug
7 interactions with the other company's
8 molecules?

9 DR. HEATH-CHIOZZI: I think we
10 have done drug interactions with other
11 antiretrovirals for years in cross
12 company/cross IND experiments. So I think
13 getting to the drug interaction stage has been
14 something that most of the companies in the
15 room, we've always done.

16 So then I think getting to the
17 pilot activity study Phase is where more
18 guidance partnering with you about the
19 appropriate patient selections and what
20 duration of therapy based on which doses and
21 in which patient populations would be the
22 questions that we will be coming to talk to

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1 you together about. I think we are on the
2 horizon of how this is going to move forward.

3 So I think we are going to follow much the
4 same path that we have previously taken.

5 CHAIR MURRAY: I have a question
6 about HIV co-infected studies. And BMS has a
7 lot of experience in developing HIV drugs and
8 you know that sometimes for an HIV drug to
9 market you might have 20 drug-drug interaction
10 studies. So I guess my question is from
11 industry perspective, when is it feasible even
12 from an investment perspective of considering
13 doing that many drug-drug interaction studies?
14 What Phase do you really feel like it is
15 feasible to do that?

16 DR. HEATH-CHIOZZI: Was it
17 Maribel? One of the previous speakers made
18 the really important comment that you do the
19 drug interactions that are most pertinent to a
20 broad use of antivirals. I think that the
21 Phase two time frame where you are really
22 trying to understand the correct dose in broad

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1 patient populations is where you have to do
2 informative drug interaction studies that may
3 help you understand at the sick level possibly
4 not at the precise medication level.

5 So I think that Kim's got a lot of
6 experience in helping with how you can
7 understand the metabolic profile of your drug
8 in combination with the metabolic profile of
9 other drugs and it's things like where does
10 the ritonavir study fit because if you've got
11 a 3A4 drug that's just part of the landscape.

12 So I think we really do believe they need to
13 be early and that you tailor the panel of what
14 you do to make sure you understand what you
15 are doing.

16 DR. STRUBLE: Expanding upon that,
17 do you think it's feasible to have those
18 important drug interactions like with other
19 protease inhibitors at the time of so you have
20 some SVR at the end of Phase IIB so you can
21 start a co-infected study?

22 DR. HEATH-CHIOZZI: I think that

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1 you can look at the map of the programs and
2 determine where your SVR data is going to be
3 coming from, some early experiments and try to
4 build up to be informed, to have as broad a
5 patient population eligible for studies as you
6 build your program.

7 DR. STRUBLE: But I think that
8 kind of feedback from you and other companies
9 -- because a lot of us on the panel have no or
10 very minimal clinical trial operational
11 experience and we know that we would like to
12 see data at this point to do it but what it
13 takes to get that information and as you
14 educate us, then we can help too, help
15 prioritize further also.

16 DR. HEATH-CHIOZZI: I think that
17 as we do a few we'll start, it is a function
18 of the investigational molecule as well as the
19 patient you are going after. But I think
20 after we've done a few, we'll have a better
21 understanding of what were the studies that
22 mattered the most based on the profile of the

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1 molecules we are putting together.

2 DR. O'REAR: So you mentioned
3 duration and certainly shortening the length
4 of treatment could be important to some of the
5 groups we are concerned about here today. Do
6 you have any data or what sort of targets do
7 you think are reasonable lengths of time that
8 we can shorten duration? Do you know of any
9 examples of -- what is the shortest time you
10 see an SVR?

11 DR. HEATH-CHIOZZI: Well I think
12 the colleagues in Vertex that are coming
13 behind, actually have more direct experience
14 than we have at this point. But I think
15 they've done very interesting studies where
16 it's, what's the duration of the direct acting
17 antiviral and then what additional duration of
18 standard of care have they added on.

19 I think that that paradigm of
20 having different durations of components of
21 the treatment, while it adds complexity as
22 long as it optimizes your opportunities for

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1 SVR or something that we really think need to
2 be understood. And that's where the response
3 guided therapy paradigm of depending on where
4 you are at four and twelve weeks informing
5 where you go from here is something that we
6 think is worthy of really trying to
7 understand. And it may be that different
8 patient populations will clearly need
9 different durations of therapy.

10 DR. LEWIS: Okay so it took until
11 this time in the afternoon for anyone to
12 mention pediatrics. As a pediatrician I'm
13 glad somebody at least did. And as you
14 pointed out there really has not been in the
15 treating community any uniformity of decisions
16 about how to manage pediatric patients with
17 hepatitis C. At what point in this schema of
18 looking at direct acting agents would you be
19 willing to expand that to a pediatric age
20 group and how would you fit that into your
21 clinical trials program?

22 DR. HEATH-CHIOZZI: We've started

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1 the discussion but as you know we've not found
2 any consensus opinion as to what really would
3 be the appropriate approach. And so even our
4 programs that are in early Phase two moving
5 into later Phase two, we are having the
6 discussion of what to do. But we don't have a
7 vision right now of how to do it. And so I
8 think that's where having some convened expert
9 opinions try to get a clearer view about when
10 is the appropriate time to intervene and to
11 what stated goal is important. Because we do
12 believe it should be part of the panel of
13 studies as early as you've got sufficient
14 understanding of your molecules to know what
15 kind of a benefit risk you would expect. But
16 sine there is such ambiguity about which
17 patient population we really ought to be going
18 after, we don't have a worked out synthesis of
19 what we ought to be doing.

20 DR. LEWIS: Right. I think a lot of
21 the problems with the current state of
22 treatment is because the current state of

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1 treatment is so bad for pediatric patients.
2 Interferons are not very well tolerated by
3 adults but children really have some
4 additional problems with tolerating them
5 including growth retardation and you know, all
6 of the neurocognitive things that interfere
7 with learning and development. So you know,
8 it is possible I suppose that moving to non-
9 interferon based regiments could have an even
10 greater impact on bringing some uniformity.
11 But anyway, I am interested in anyone's ideas
12 about how to proceed in that population.

13 CHAIR MURRAY: Any other questions
14 from our side? Okay.

15 DR. HEATH-CHIOZZI: Thank you.

16 CHAIR MURRAY: All right, thank
17 you very much. And now Dr. Kauffman from
18 Vertex Pharmaceuticals.

19 DR. KAUFFMAN: Thanks very much.
20 I'm very happy to be here today. My name is
21 Bob Kauffman. I am Chief Medical Officer at
22 Vertex Pharmaceuticals and I'm happy to be

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1 here to give Vertex's view on early and
2 expanded access for HCV. One of the perils of
3 going last on the program is everything and
4 many things have already been said so I'll ask
5 your forbearance if some of what I say is
6 redundant to some of the other speakers. I
7 think what distinguishes me from everyone else
8 is I'm not planning to use slides. So you
9 will just have to hear, so you will just have
10 to listen to me.

11 Clearly we were struck by the
12 questions that were being asked by the FDA in
13 the Federal Register notice and I would just
14 say this is a very promising time for those in
15 the HCV community with the advancement of
16 multiple direct acting antiviral agents into
17 late stage clinical trials as has been amply
18 illustrated today with a number of
19 pharmaceutical companies that are here talking
20 about this issue.

21 Vertex has been a leader in the
22 development of these new agents as a result of

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1 our longstanding, more than ten year
2 commitment to improving treatment for
3 hepatitis C. As you've heard today and it
4 goes without saying hepatitis C is a major
5 public health problem in the United States and
6 around the world. It is the leading cause of
7 liver cancer in the United States and the
8 leading indication for liver transplantation.
9 And frankly as you've heard already, as time
10 progresses and patients age, the risk of
11 progressive liver disease, cirrhosis and its
12 complications obviously increases. The large
13 population of patients who were infected back
14 in the 60s and 70s through infected blood
15 supplies are now 30 years or so into their
16 disease and really had quite high risk of
17 adverse outcomes and I think that always has
18 to be in the back of our minds as driving
19 treatment and trying to get better treatments
20 for these patients.

21 To date we've enrolled more than
22 3,000 patients in clinical trials in

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1 telaprevir. These trials have included
2 patients that traditionally have been
3 difficult to treat successfully such as null
4 responders and other nonresponders to the
5 current treatment. Patients of African
6 American and Hispanic background or those with
7 cirrhosis and patients that are co-infected
8 with HIV and HCV.

9 It is our clear view that making
10 promising drugs like telaprevir available to
11 the broadest group of appropriate patients in
12 the safest and most effective way is best
13 accomplished through rapid advancement through
14 clinical trials, completing a regulatory
15 submission and working with the FDA to ensure
16 a timely review and regulatory decision. On
17 the other hand we also acknowledge that there
18 are subsets of patients with more immediate
19 and serious needs. With those patients in
20 mind I am obviously going to continue with my
21 remarks today. Vertex is certainly to working
22 with FDA and to other stakeholders to evaluate

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1 the possibility of expended access program for
2 telaprevir with some cautions that I will
3 expand on later and I think many of those
4 cautions have already been discussed by other
5 speakers.

6 Before I do that though I would
7 like to briefly convey our view of
8 investigational drug development in hepatitis
9 C. Successful treatment with achievement of a
10 sustained viral response which is understood
11 to represent a viral cure remains the most
12 important goal for all patients with hepatitis
13 C, no matter their underlying disease state or
14 degree of fibrosis. Successful treatment has
15 been shown in numerous studies to improve
16 long-term outcomes including a reduction in
17 the risk of hepatocellular carcinoma and
18 hepatic decompensation.

19 Today as you are aware, the
20 currently approved treatments really have
21 limited efficacy and substantial morbidity
22 with 48 weeks of treatment necessary for

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1 genotype one and achievement of SVR in about
2 40 to 45 percent of patients. At the same
3 time Phase II clinical trial data with
4 individual direct acting antiviral agents
5 added on to the current therapy have
6 demonstrated the potential for the new agents
7 to both increase SVR rates and to reduce the
8 duration of treatment for many patients. And
9 obviously we hope all of this will be borne
10 out as the Phase III study start to read out
11 in the near future.

12 Most clinical development programs
13 for direct acting agents have initially
14 focused on adding one new agent onto the
15 current standard treatment and treatment naive
16 patients with compensated liver disease. This
17 strategy is straightforward in the sense that
18 this represents the largest potential patient
19 population and is considered the safest if you
20 will enabling more effective recognition of
21 side effects and leaving open the possibility
22 of rescue treatment for patients who don't

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1 respond.

2 For these reasons it is considered
3 the most appropriate approach for the early
4 stages of development. And in addition
5 patients who have not achieved SVR with prior
6 treatment have also been studied again, people
7 with compensated liver disease. And we
8 certainly expect and recognize that the
9 initial applications for marketing approval
10 for these first agents, are expected to be for
11 those two groups of patients with compensated
12 liver disease, treatment naive and treatment
13 failure patients with one direct acting agent
14 added onto pegylated interferon and ribavirin.

15 However, within the spectrum of chronic
16 hepatitis C several subsets of patients stand
17 out who may have a more urgent need of more
18 effective treatment and you've heard a lot
19 about that already today.

20 In patients both previously
21 untreated and those who failed prior therapy,
22 these include patients with advanced fibrosis

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1 and cirrhosis, particularly those with
2 incipient hepatic decompensation. Patients
3 who are approaching transplant including those
4 with hepatocellular carcinoma in whom
5 recurrence of hepatitis C post transplant is
6 almost universal unless the virus can be
7 eradicated prior to transplantation. Patients
8 with post transplant recurrence of hepatitis C
9 who may experience accelerated disease
10 progression and HIV HCV co-infected patients
11 in whom progressive liver disease is now among
12 the most common causes of death. Those in
13 more urgent need of treatment also include the
14 following categories of patients and these are
15 based primarily on the progression of liver
16 disease rather than other factors.

17 These would include African
18 American and Hispanic patients who have a
19 lower response to the current therapy.
20 Patients with hemophilia, both mono and co-
21 infected. Many of who have advanced liver
22 disease and a lower response to current

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1 therapy. And patients who are considered
2 intolerant of or unable to be treated with
3 pegylated interferon and ribavirin due to
4 immunologic, psychiatric or other
5 contraindications.

6 I would just add here there's been
7 a lot of discussion about those patients here.

8 I have to say that when you scrape beneath
9 the surface and try to actually identify who
10 those people are, it is a rather heterogeneous
11 group and part of the driver in the Vertex
12 development program has been to shorten the
13 duration of treatment as you've heard from
14 other speakers.

15 One of the reasons for that is that
16 we believe that many patients who cannot
17 tolerate 48 weeks of interferon and ribavirin,
18 could tolerate a shorter treatment duration.
19 They could be nursed through it. There is
20 much better opportunity for supervising
21 therapy if it is only, for example, 12 weeks
22 or 24 weeks long as opposed to 48 weeks. We

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1 think that will open up treatment to many
2 patients who currently for many reasons cannot
3 really tolerate one year of therapy. And it
4 is these subsets of patients who may
5 potentially gain the most benefit from early
6 access to new treatments.

7 Vertex believes that a potential
8 treatment of these patients through an early
9 access program must be approached with care,
10 bearing in mind the potential risk to the
11 patients such as, for example, failure of
12 treatment, not achieving an SVR or the risk of
13 unanticipated safety issues not observed in
14 the more prevalent populations or risks
15 related to adverse or unanticipated drug
16 interactions.

17 Frankly there may be risks to the
18 development program itself as you've heard
19 today concerns in which a promising therapy
20 for thousands of patients could be derailed by
21 significant safety events that may be
22 population-specific, particularly if they

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1 occur before a solid body of safety data for
2 the compound has been obtained. And it could
3 be that in the setting of a large database
4 certain events that might be expected in those
5 populations might not have quite so
6 significant an outcome and that's something
7 that I think the sponsors and regulatory
8 agencies would need to discuss beforehand.

9 There are certainly examples from
10 the past where premature expended access has
11 frustrated the goal and the maximum benefit
12 brought about by earliest and widest
13 availability through marketing approval.
14 Vertex believes that the most appropriate way
15 to move forward to address the specific needs
16 of the subsets of hepatitis C patients is to
17 conduct careful clinical trials to uncover
18 problems that may occur and to develop data
19 that can support understanding of the
20 potential benefits and risks that might then
21 allow you to go forward into an expanded
22 access program.

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1 With telaprevir, Vertex is
2 currently conducting a pilot study in HIV HCV
3 co-infected patients to evaluate safety,
4 antiviral activity and drug interactions so as
5 to avoid compromising treatment of HIV or HCV
6 for these patients. And again I'll add the
7 question came up when these drug interactions
8 studies are done and we did many studies
9 during the Phase II program so that once we
10 had SVR data in a more mainstream population
11 if you will with the drug interaction data, we
12 would then be able to go into patients that
13 are at higher risk. We had in mind even early
14 in the program that co-infection was one of
15 those situations where we really wanted to be
16 ready to explore telaprevir in that population
17 and so we did conduct those studies at a
18 fairly early stage in the program.

19 In addition Vertex is currently
20 evaluating drug-drug interactions of
21 telaprevir and immunosuppressive agents as a
22 first step in approaching the treatment of

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1 post transplant patients. And we've also
2 examined the pharmacokinetics of telaprevir in
3 patients with decompensated liver disease as
4 an initial step in approaching this population
5 group as well as the group of patients who are
6 pre-transplant where viral clearance prior to
7 transplantation may have value in preventing
8 post transplant recurrence. We believe trials
9 like these are needed to safely proceed into
10 these more difficult to treat populations and
11 to provide guidance to physicians on the
12 appropriate use of such drugs should they
13 reach the market.

14 As these data become available
15 these may also be the populations for which we
16 could consider expanded access but within a
17 treatment protocol or treatment IND so that we
18 have the opportunity for adequate data
19 collection. And again one of the comments
20 earlier about expanded access, it would be
21 very difficult to run an expanded access
22 program and at the same time a real clinical

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1 trial program because obviously enrollment in
2 either one of them could be compromised.
3 Therefore our general view is we would opt for
4 the clinical trial approach because obtaining
5 reliable data as early as possible is
6 ultimately the best way to get drugs into the
7 hands of patients who really need them.

8 As a practical matter, any
9 requirement for pegylated interferon and
10 ribavirin in the treatment regimen will
11 continue to constrain use of the new agents in
12 many of the populations most in need. It is
13 notable that even before the first of the new
14 direct acting agents has been approved, new
15 studies have begun in which two
16 investigational direct acting agents are being
17 combined either with or without pegylated
18 interferon and ribavirin. Eliminating the
19 need for these agents could result in safer,
20 shorter and more effective treatment for a
21 much larger group of patients including the
22 difficult populations I've already mentioned.

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1 As is evident in the listings on
2 clinicaltrials.gov the FDA has been open to
3 such trials with proper safeguards. And
4 several studies are now underway in the U.S.
5 to evaluate various combinations of protease,
6 polymerase and NS5A inhibitors both with and
7 without pegylated interferon and ribavirin.

8 There is substantial sensitivity
9 among both the sponsors and the regulatory
10 agencies to the issue of viral resistance. As
11 a result where the use of two directing agents
12 is proposed without peg and ribavirin,
13 sponsors will need to advance carefully and
14 with careful deliberation beyond initial short
15 term studies and expanded access as has been
16 noted before will not be appropriate until
17 longer term data have been obtained.

18 These longer term data will also
19 include information on the natural history and
20 potential consequences of viral resistance.
21 At present, evaluation of specific
22 combinations of direct acting agents by a

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1 single sponsor has been the norm and it is the
2 approach that Vertex is also currently taking.

3 As we see it, evaluating combinations of
4 direct acting agents from different sponsors
5 should be considered based on scientific
6 merit, just as in evaluating two agents from
7 the same company. The primary potential
8 impediment is the need for sponsors to find a
9 workable business structure that could
10 accommodate this type of collaboration and I
11 would say this certainly can happen. It would
12 be much more difficult for this to happen in
13 the setting of expanded access where drugs are
14 being put together without a lot of
15 preliminary work to explore drug interactions
16 although I would also say that the choice of
17 agents to combine would also be informed by
18 the potential drug interactions and one might
19 choose agents to put together where drug
20 interactions, for example, could be minimized.

21 At present, evaluation of specific
22 combinations of a direct acting agent by a

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1 single sponsor has been the norm as I said
2 before. There aren't very many examples of
3 collaborations with compounds in early stages
4 of development. We have little doubt however,
5 that if a compelling scientific case can be
6 made and business issues resolved, exploratory
7 studies of direct acting agents from different
8 sponsors will occur through carefully
9 controlled and monitored protocols and
10 separate from consideration of expanded
11 access.

12 We think it would be inappropriate
13 to provide expanded access to two direct
14 acting agents until sufficient clinical data
15 have been obtained to permit reasonably safe
16 use of such combinations and I think this
17 would likely be Phase II data, almost
18 certainly containing some SVR data as was
19 pointed out by the other speakers although
20 combinations of agents without peg and
21 ribavirin have great promise. There has not
22 yet been a demonstration that SVR can be

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1 achieved with those combinations although we
2 certainly hope those data will come soon.

3 We should also consider whether
4 implementation of these carefully controlled
5 trials might better achieve the goal of rapid
6 access to newer therapies. FDA could consider
7 incentives for earlier trials in these
8 patients such as accepting and support of
9 approval, data collected in an expanded access
10 or clinical trial setting using historical
11 controls. Particularly in those populations
12 where current outcomes are very poor in
13 conjunction with controlled data obtained in
14 larger populations.

15 In summary Vertex is committed to
16 the continued advancement of new therapies for
17 hepatitis C. Expanded access may be one way
18 to provide these therapies sooner to those
19 most in need with careful and broad
20 consideration of the potential benefits and
21 risks. Thank you again for the opportunity to
22 present our views on this important topic.

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1 (Applause.)

2 CHAIR MURRAY: Questions. Jules?

3 DR. O'REAR: I have the same
4 question for you, in terms of what's the
5 shortest time you have observed an SVR be
6 obtained -- shortest length of treatment? So
7 what sort of goal you think you might be able
8 to achieve realistically?

9 DR. KAUFFMAN: Yes so we included a
10 treatment arm in one of our Phase II studies
11 in which 12 weeks of three drug combination
12 were used and then treatment was stopped and
13 patients observed for SVR. The SVR rate in
14 that arm was 60 percent. However, the relapse
15 rate in that arm was also fairly high. It was
16 above 20 percent.

17 Therefore we are left with not
18 really understanding under that paradigm
19 whether that really is a viable regimen or
20 not. As you know we have chosen to study a
21 longer duration in Phase III. But that 12-
22 week data I think provides a proof of concept

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1 at least that treatments as short as 12 weeks
2 could be feasible, perhaps shorter. There are
3 some anecdotal reports of patients who
4 discontinued treatment early and then were
5 followed and some of whom got an SVR that is
6 shorter treatment than 12 weeks. But that is
7 very sparse and anecdotal data. So the data
8 set that I mentioned to you is probably the
9 most reliable one we have. It is a small
10 group, only 60 patients.

11 DR. O'REAR: In terms of your
12 anecdotal what's the shortest time?

13 DR. KAUFFMAN: I don't know. I hear
14 about anecdotes of fairly short therapy, you
15 know, eight weeks or so, but you know, you
16 have to take those with what they are. It is
17 just individual anecdotes. I think it points
18 the way to exploring these things but
19 obviously much more work needs to be done.

20 CHAIR MURRAY: All right, thank
21 you. This part of the meeting was just for
22 open public comment for anybody that had not

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1 pre-registered or during the meeting decided
2 to make some comments. One person, actually
3 Jules Levin would like to do an encore
4 presentation to clarify a couple of issues.
5 So Jules, now is the time for you to take the
6 podium again.

7 MR. LEVIN: So this will just take
8 two minutes. I know it is probably obvious to
9 everybody but I didn't sleep well the last
10 couple of nights. I left out something that
11 was in my slides and I think it is obvious to
12 everyone. I just want to clarify. I am in
13 favor except for unusual circumstances, unique
14 situations, as Jan Albrecht addressed where
15 one oral might be appropriate. Generally
16 speaking I'm talking about at least two orals
17 for studies for advanced population patients
18 and for the early access.

19 These are patients who have
20 advanced disease, who are at risk of dying or
21 advancing so far in disease that they may not
22 be eligible for therapy when they get

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1 approved. So my proposal for early access
2 studies is for patients getting at least two
3 orals plus or minus peg ribavirin and then
4 patients who are contraindicated for peg
5 ribavirin two or three orals would be a great
6 opportunity to study two or three orals at
7 that stage without peg and ribavirin and in
8 that patient population. So, and again, so
9 that's my clarification, the two orals in the
10 high risk population only. People who can
11 meet as said people said should wait for
12 approval.

13 And so the other part which I just
14 -- is to repeat is that I'm proposing to do
15 this in Phase II, which means so the last
16 thing that I want to say is that I think it is
17 time now. It was great. All the companies
18 are here. They all spoke and said I think
19 very good things, very encouraging things,
20 showing obviously an interest and desire to do
21 this.

22 So I think it is time now for the

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1 companies to go home and put together study
2 ideas. Put together some study ideas, submit
3 them to the FDA. Let the FDA review them and
4 give you comments. And do your safety data
5 and PK studies so you can do the studies. I
6 think the whole point of this is to move this
7 ahead as quickly as possible. And again I
8 don't want to couch this in the context of and
9 I also I would like the FDA to go home and
10 talk about accelerated approval for the
11 companies and be able to offer them advice and
12 tell us what they think about that. Consider
13 that please. And then so I think we are ready
14 to move ahead on this. That is how I feel
15 after hearing today. And I guess that is it.

16 One last comment I'm going to make
17 is that without going into too much detail it
18 is kind of obvious that hepatitis C is very
19 unique. It is not lifetime therapy. It is
20 short term therapy at 24-12 weeks perhaps.
21 And so it creates a very unique way we can
22 cure people and then off, we're gone with hep

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1 C. We can tell everybody we can go on to
2 another disease. I see that as perhaps
3 happening in a window of ten-twelve years. So

4 I think that what we need to really
5 think about and I have talked to a lot of
6 people about this in the room is there is
7 three components to being successful here.
8 Proper testing and screening, linkage to care
9 and then services in the clinics for patients
10 in clinics. And without that being done
11 properly at launch and being prepared to do
12 that we're headed towards perhaps failure. We
13 need to do that properly for success. So
14 that's it for my comments. Thank you very
15 much.

16 (Applause.)

17 CHAIR MURRAY: I'd like to thank
18 everybody who presented and came to the
19 meeting today. I think it was very productive
20 and I learned a lot. I was actually inspired.
21 I have a couple of ideas.

22 And I want everybody to know just

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1 because you might not hear anything officially
2 right away there's a lot of things going on
3 behind the scenes. There is potential
4 workshops planned with third parties. There
5 are developing guidance. We meet with
6 pharmaceutical companies all the time. And so
7 things are happening and moving ahead even
8 though we can't, you don't always hear about
9 them on a weekly basis. Our comments and
10 guidance come out in a very kind of formal
11 format and once they do they will be open for
12 public comment. I want to thank everybody for
13 a productive session today.

14 (Whereupon the above-entitled
15 meeting was concluded at 3:19 p.m.)
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