

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH
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8 ANTIVIRAL DRUGS ADVISORY COMMITTEE
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11
12 Friday, October 25, 2013

13 8:00 a.m. to 3:30 p.m.
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17
18 Sheraton Silver Spring Hotel

19 Cypress Ballroom

20 8777 Georgia Avenue

21 Silver Spring, Maryland
22

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. MURATA: Let us get started. Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not done so already.

I would also like to identify the FDA press contact, Stephanie Yao. If you are present, please stand. I'm Yoshi Murata, associate professor of infectious diseases and internal medicine at the University of Rochester School of Medicine and Dentistry.

I will ask the members of the FDA panel and the other committee members to introduce themselves. I'll start with the agency.

DR. COX: Good morning. Ed Cox, director of the Office of Antimicrobial Products.

DR. BIRNKRANT: Debbie Birnkrant, director, Division of Antiviral Products.

DR. MURRAY: Jeff Murray, deputy, Division

1 of Antiviral Products.

2 DR. CONNELLY: Sarah Connelly, medical
3 officer, Division of Antiviral Products.

4 DR. MISHRA: Poonam Mishra, medical officer,
5 Division of Antiviral Products.

6 DR. QI: Karen Qi, statistician.

7 DR. DASKALAKIS: Demetre Daskalakis,
8 associate professor, infectious diseases, Mount.
9 Sinai.

10 MR. RAYMOND: Daniel Raymond, policy
11 director, Harm Reduction Coalition.

12 DR. CONNICK: Liz Connick, professor of
13 medicine, infectious disease, University of
14 Colorado, Denver.

15 DR. CORBETT: Amanda Corbett, clinical
16 associate professor of pharmacy at the UNC School
17 of Pharmacy.

18 DR. GIORDANO: Tom Giordano, infectious
19 disease, Baylor College of Medicine, the Michael E.
20 DeBakey VA in Houston, and the medical director for
21 HIV services at Harris Health System.

22 DR. ABRAHAM-BURRELL: Karen Abraham-Burrell,

1 designated federal officer.

2 DR. MURATA: Yoshi Murata, adult infectious
3 diseases, University of Rochester.

4 DR. HAGEDORN: Curt Hagedorn, professor of
5 medicine, University of Arkansas in the Central
6 Arkansas VA Medical System.

7 DR. VAN DYKE: Russell Van Dyke, pediatric
8 infectious diseases, Tulane University.

9 DR. ALCENDOR: Donald Alcendor, associate
10 professor, Meharry Medical College.

11 DR. FOLLMANN: Dean Follmann, head of
12 biostatistics at the National Institute of Allergy
13 and Infectious Diseases.

14 DR. GHANY: Marc Ghany, hepatologist, liver
15 diseases branch, NIDDK, NIH.

16 DR. HONEGGER: Jonathan Honegger, assistant
17 professor of pediatrics at Ohio State University.

18 DR. KORMAN: Louis Korman, community
19 gastroenterologist, Washington, D.C.

20 DR. FRIEDMAN: Lawrence Friedman,
21 gastroenterologist, professor of medicine at
22 Harvard Medical School, and Tufts University School

1 of Medicine, and chair of medicine at Newton-
2 Wellesley Hospital.

3 MS. LUPOLE: Patricia Lupole, executive
4 director of HCVets.com, an educational website and
5 support forum. And I am the patient
6 representative.

7 DR. ISAACS: Robin Isaacs, clinical
8 research, Merck. I'm the industry representative.

9 DR. MURATA: Thank you very much.

10 For topics such as those being discussed at
11 today's meeting, there are often a variety of
12 opinions, some of which are quite strongly held.
13 Our goal is that today's meeting will be a fair and
14 open forum for discussion of these issues and that
15 individuals can express their views without
16 interruption. Thus, as a gentle reminder,
17 individuals will be allowed to speak into the
18 record only if recognized by the chairperson, and
19 we look forward to a productive meeting.

20 In the spirit of the Federal Advisory
21 Committee Act and the Government in the Sunshine
22 Act, we ask that the advisory committee members

1 take care that their conversations about the topic
2 at hand take place in the open forum of the
3 meeting.

4 We are aware that members of the media are
5 anxious to speak with the FDA about these
6 proceedings. However, FDA will refrain from
7 discussing the details of this meeting with the
8 media until its conclusion.

9 Also, the committee is reminded to please
10 refrain from discussing the meeting topic during
11 breaks or lunch. Thank you. And I have one
12 additional comment. I have been reminded by the
13 organizers to please speak into the microphone so
14 that the audience may better be able to hear your
15 comments.

16 Now, I'll pass it to Commander Karen
17 Abraham-Burrell, who will read the Conflict of
18 Interest Statement.

19 **Conflict of Interest Statement**

20 CMDR ABRAHAM-BURRELL: Thank you.

21 The Food and Drug Administration is
22 convening today's meeting of the Antiviral Drugs

1 Advisory Committee under the authority of the
2 Federal Advisory Committee Act of 1972. With the
3 exception of the industry representative, all
4 members and temporary voting members of the
5 committee are special government employees or
6 regular federal employees from other agencies and
7 are subject to federal conflict of interest laws
8 and regulations.

9 The following information on the status of
10 this committee's compliance with federal ethics and
11 conflict of interest laws, covered by but not
12 limited to those found at 18 U.S.C., Section 208,
13 is being provided to participants in today's
14 meeting and to the public.

15 FDA has determined that members and
16 temporary voting members of this committee are in
17 compliance with federal ethics and conflict of
18 interest laws. Under 18 U.S.C., Section 208,
19 Congress has authorized FDA to grant waivers to
20 special government employees and regular federal
21 employees who have potential financial conflicts,
22 when it is determined that the agency's need for a

1 particular individual's services outweighs his or
2 her potential financial conflict of interest.

3 Related to the discussion of today's
4 meeting, members and temporary voting members of
5 this committee have been screened for potential
6 financial conflicts of interest of their own, as
7 well as those imputed to them, including those of
8 their spouses or minor children, and, for purposes
9 of 18 U.S.C. Section 208, their employers.

10 These interests may include investments,
11 consulting, expert witness testimony, contracts,
12 grants, CRADAs, teaching, speaking, writing,
13 patents and royalties, and primary employment.

14 Today's agenda involves a new drug
15 application, NDA 204671, sofosbuvir, an NS5B,
16 polymerase inhibitor, manufactured by Gilead
17 Sciences, Incorporated, with a proposed indication
18 for the treatment of chronic hepatitis C infection
19 in combination with other agents in adult patients
20 with genotypes 1 to 6 and/or adult patients
21 awaiting liver transplantation.

22 This is a particular matters meeting, during

1 which specific matters related to Gilead's NDA will
2 be discussed. Based on the agenda for today's
3 meeting and all financial interests reported by the
4 committee members and temporary members, no
5 conflict of interest waivers have been issued in
6 connection with this meeting. However, we would
7 like to disclose that Dr. Doris Strader has been
8 recused from the meeting.

9 To ensure transparency, we encourage all
10 standing committee members and temporary voting
11 members to disclose any public statements that they
12 have made concerning the product at issue.

13 With respect to FDA's industry representative,
14 we would like to disclose that Dr. Robin Isaacs is
15 participating in this meeting as a nonvoting
16 industry representative, acting on behalf of
17 regulated industry. Dr. Isaacs's role at this
18 meeting is to represent industry in general and not
19 any particular company. Dr. Isaacs is employed by
20 Merck and Company.

21 We would like to remind members and
22 temporary voting members that if the discussions

1 involve any other products, or issues, or firms not
2 already on the agenda for which an FDA participant
3 has a personal or imputed financial interest, the
4 participants need to exclude themselves from such
5 involvement, and their exclusion will be noted for
6 the record.

7 FDA encourages all participants to advise
8 the committee of any financial relationships they
9 may have with the affected firm at issue. Thank
10 you.

11 DR. MURATA: Thank you. We will now proceed
12 with Dr. Birnkrant's introductory remarks.

13 **FDA Introductory Remarks**

14 DR. BIRNKRANT: Good morning. I too would
15 like to welcome everyone to today's advisory
16 committee meeting, where we will be hearing about
17 Gilead's direct-acting antiviral, sofosbuvir, for
18 use with ribavirin, with or without interferon, for
19 multiple genotypes of chronic hepatitis C viral
20 infection. I want to remind everyone that we're
21 presenting our conclusions to date, but this NDA is
22 still under review.

1 I should mention that we were recently made
2 aware of new data that could potentially impact
3 treatment duration to allow for better responses in
4 certain patient populations. We are well into the
5 review of that data, so you will be seeing data
6 today that was not included in the background
7 package.

8 In light of this new information, we won't
9 be discussing bridging analyses for genotype 3
10 treatment-naive patients, nor subgroup analyses for
11 genotype 2.

12 I would also like to mention that we will
13 not be discussing the coinfecting population because
14 our advisory committee members have not been
15 screened for this subject. Lastly, as I mentioned
16 yesterday, drug development for hepatitis C is
17 quite complex and moving very quickly.

18 It not only involves generation and review
19 of clinical data along with biostatistical
20 analyses, but also a review of pharmacology,
21 toxicology, clinical pharmacology, pharmacometrics,
22 virology, and chemistry manufacturing and controls

1 data, as well as inspectional findings.

2 As you will see again in our acknowledgement
3 slide for today's presentations, we have a very
4 large review team, and I would like to thank them
5 for their dedication to public health.

6 Briefly, since we've heard a lot about this
7 yesterday and we'll be hearing more this morning,
8 chronic hepatitis C is both a global and domestic
9 problem. Incident infections in the United States
10 are decreasing, but chronic hepatitis C-related
11 complications are increasing, with more liver-
12 related complications expected in the next 10 to
13 20 years.

14 Chronic hepatitis C-related cirrhosis is
15 already the most common reason for transplantation
16 in this country. Current interferon-based
17 treatments can be highly effective, as we've seen,
18 but there are still populations who are either
19 ineligible or intolerant to the current standard of
20 care.

21 The current standard of care as outlined in
22 AALSD treatment guidelines for genotype 1 chronic

1 hepatitis C is a protease inhibitor plus pegylated
2 interferon and ribavirin.

3 Treatment is based on response-guided
4 therapy. For genotypes 2 and 3, it's 24 weeks of
5 pegylated interferon and ribavirin. Response rates
6 depend on a number of factors, and some of these
7 host and viral factors may be more or less
8 important with the coming antiviral drugs in the
9 pipeline.

10 It is important to note that standard of
11 care regimens for genotype 1 have significant
12 toxicities beyond that same with pegylated
13 interferon and ribavirin. In addition, there are
14 important drug interactions with protease
15 inhibitors. Consequently, new treatment strategies
16 and/or novel agents are desirable. Ideally, future
17 DAA treatment regimens should be comprised of a
18 simple regimen of short duration that involves a
19 low pill burden.

20 There should be limited drug interactions,
21 broad antiviral activity, and a manageable side
22 effects profile. As I showed on the iceberg slide

1 yesterday, there are a lot of new drugs in
2 development. And today, we will be discussing
3 Gilead Science's sofosbuvir.

4 Sofosbuvir is a nucleotide inhibitor of
5 HCV NS5B RNA-dependent RNA polymerase. It has
6 broad genotypic activity. Four pivotal phase 3
7 trials were initially submitted in the NDA. It's
8 been studied in multiple populations, which you
9 will see today, including interferon-ineligible and
10 intolerant populations. However, it has not been
11 studied in a PI-failure population for the purposes
12 of this new drug application. Control arms, as you
13 will see, are variable and population dependent.
14 And I'll have more to say about that.

15 The VALENCE study was recently submitted,
16 and that examined longer durations of an
17 interferon-free treatment regimen in a genotype 3
18 population. And with longer treatment, we saw a
19 decrease in relapse rates for genotype 3.

20 There are limited drug interactions with
21 sofosbuvir, and it is well-tolerated. It was
22 recently designated as a breakthrough therapy under

1 FDASIA, Title IX, as part of an interferon-free
2 regimen in the treatment of chronic hepatitis C.

3 Before turning to breakthrough therapy, a
4 discussion on breakthrough therapy, I just wanted
5 to make a few comments about control arms, as these
6 were different in the various studies in the NDA.

7 So this is outlined in our reissued
8 hepatitis C drug development guidance that was
9 reissued this month. With regard to placebo-
10 controlled designs, this is essentially delayed
11 treatment.

12 Shorter treatment durations, that is 12 to
13 24 weeks, compared to standard of care make it
14 acceptable for those patients not requiring
15 immediate therapy to include a placebo arm, where
16 that is to defer treatment for a period of time.

17 This was seen in the POSITRON trial of
18 interferon-ineligible and interferon-intolerant
19 subjects. In addition, there's no approved drug
20 for that patient population.

21 One of the primary purposes of a placebo-
22 controlled trial in this setting is to allow a

1 safety comparison. With regard to a historical
2 control design, we are recommending historical
3 controls for an all-DAA regimen or regimens with
4 much shorter duration than the approved standard of
5 care, as was seen in the NEUTRINO trial.

6 The expectation is that even a lower
7 response rate than an approved option may be
8 acceptable in a setting of an interferon-free
9 regimen or one that significantly shortens the
10 duration of interferon exposure.

11 Let's now turn to breakthrough therapy and
12 what does it mean. Well, it's been a long-standing
13 FDA goal to facilitate and expedite development and
14 review of drugs to address an unmet medical need
15 for serious conditions.

16 Joining other programs that expedite drug
17 development, such as accelerated approval, priority
18 review, and fast-track designation, is breakthrough
19 therapy. Breakthrough therapy is designated if a
20 drug is intended alone or in combination with one
21 or more drugs to treat a serious or
22 life-threatening disease or condition, and

1 preliminary clinical evidence indicates that the
2 drug may demonstrate substantial improvement over
3 existing therapies on one or more clinically
4 significant endpoints such as substantial treatment
5 effects observed early in clinical development.

6 The features of breakthrough include all
7 fast-track features, intensive guidance on
8 efficient drug development, and organizational
9 commitment.

10 So as I mentioned, the criteria are for a
11 serious condition with preliminary clinical
12 evidence demonstrating substantial improvement over
13 available therapies. What we're looking for are
14 greater response rates, an important safety
15 advantage, and treating the underlying disease or
16 reversing disease progression.

17 So let me tell you a little bit about what
18 we'll be presenting today from the FDA's viewpoint.
19 We will highlight the clinical program, looking at
20 treatment duration and outcomes in different
21 populations, including relapse rates.

22 We'll present exploratory analyses for use

1 of sofosbuvir in genotype 1, PR treatment failures.
2 We'll review the use of sofosbuvir in transplant
3 patients with hepatocellular carcinoma meeting the
4 Milan criteria and awaiting liver transplant.

5 We'll also present our resistance
6 assessment, highlighting our review of next-
7 generation sequencing data. Our safety assessment
8 will cover cardiac issues, as sofosbuvir is in the
9 same class as a drug that had significant cardiac
10 issues. And then we'll present high-level top-line
11 information with regard to drug-drug interactions.

12 Our AC questions and discussion will focus
13 on the risk-benefit of sofosbuvir and various
14 patient populations. And we will ask you to
15 discuss the use of sofosbuvir in the peg ribavirin
16 treatment experience genotype 1 population.

17 We will also ask you to comment on the use
18 of this drug plus ribavirin in HCC patients meeting
19 Milan criteria and awaiting transplant and what
20 additional studies you would recommend to further
21 elucidate the use of this drug.

22 With that, I'll turn it back to the advisors

1 and consulting staff. Thank you very much.

2 DR. MURATA: Thank you, Dr. Birnkrant.

3 Both the Food and Drug Administration and
4 the public believe in a transparent process for
5 information gathering and decision making. To
6 ensure such transparency at the advisory committee
7 meeting, FDA believes that it is important to
8 understand the context of an individual's
9 presentation.

10 For this reason, FDA encourages all
11 participants, including the sponsor's non-employee
12 presenters, to advise the committee of any
13 financial relationship that they may have with the
14 firm at issue such as consulting fees, travel
15 expenses, honoraria, and interest in the sponsor,
16 including equity interests and those based upon the
17 outcome of the meeting.

18 Likewise, FDA encourages you, at the
19 beginning of your presentation, to advise the
20 committee if you do not have any such financial
21 relationships.

22 If you choose not to address this issue of

1 financial relationships at the beginning of your
2 statement, it will not preclude you from speaking.
3 We will now proceed with the sponsor's
4 presentations.

5 **Sponsor Presentation - John McHutchison**

6 DR. MCHUTCHISON: Good morning. I am John
7 McHutchison. I lead the liver diseases group at
8 Gilead Sciences. Over the past few years, we have
9 witnessed rapid unparalleled progress in the
10 development of new therapies that have the
11 potential to transform the lives of patients with
12 hepatitis C infection. It is a privilege to be
13 involved in these efforts to develop all oral
14 therapies that will benefit and cure millions of
15 patients with this infection worldwide.

16 We are pleased to be here today to work with
17 this committee, to bring forward treatment options
18 that have the potential to improve lives of
19 patients with this disease. We are working to
20 develop our first safe, simple, and well-tolerated
21 regimen for all patients with hepatitis C
22 infection.

1 Sofosbuvir is an oral nucleotide analog
2 being developed for the treatment of chronic
3 hepatitis C. It specifically inhibits the HCV NS5B
4 polymerase, a necessary enzyme for viral
5 replication.

6 The drug enables treatment regimens that are
7 short. They are simple. They are well-tolerated.
8 And they are highly efficacious across the
9 hepatitis C genotypes. For these reasons, a
10 broader cross-section of the hepatitis C population
11 can be treated more simply than has been possible
12 before.

13 Now, we heard a lot of this yesterday, but
14 just briefly, the WHO estimates suggest that
15 2 percent of the world's population are infected
16 with hepatitis C and that equates to 170 million
17 individuals worldwide. In the United States,
18 conservative estimates suggest that at least 3.2
19 million individuals are chronically infected with
20 hepatitis C. And over the past decade, our
21 understanding of this epidemic in the U.S. has
22 become clearer.

1 It is estimated that 50 percent or less of
2 those in the U.S. have been identified and are
3 aware of their diagnosis. And as many as
4 30 percent of all diagnosed patients with chronic
5 hepatitis C are ineligible for the current
6 interferon-based therapies. And finally, less than
7 15 percent of those that have been diagnosed are
8 being treated. And the reason for this fall-off
9 are multifactorial.

10 Interferon-containing regimens, which have
11 been the mainstay of treatment, are associated with
12 substantial side effects that can persist for the
13 treatment duration of 24 to 48 weeks. This is a
14 significant deterrent for many patients, as have
15 been the suboptimal response rates.

16 Also, many who do start treatment fail to
17 complete the course because of tolerability issues.
18 As a result, the majority of those who are
19 infected, whether they have been diagnosed or not,
20 have remained untreated or they have failed current
21 treatment options.

22 Since the epidemic began three to four

1 decades ago, a growing proportion of patients have
2 also progressed to develop cirrhosis and its
3 sequelae. This trend will continue to increase
4 over the next two decades.

5 Rates of cirrhosis as high as 30 to 35
6 percent are projected by 2020. And that equates to
7 a million infected individuals with cirrhosis in
8 this country. Similarly, the rates of
9 decompensation, liver cancer, and mortality due to
10 hepatitis C have more than doubled in the past
11 decades, and they will continue to, as shown on the
12 right of this slide and also discussed yesterday.

13 Because of the burden of advancing disease,
14 hepatitis C is now the leading indication for liver
15 transplantation. There are more than 5,000
16 patients with chronic hepatitis C currently
17 awaiting liver transplantation in the U.S., and
18 this number will also continue to increase over
19 coming years.

20 The aging hepatitis C population, increasing
21 rates of advanced disease, and complications of the
22 sequelae will going forward pose a substantial

1 challenge to clinical practice in this country and
2 elsewhere.

3 Clearly, we need more effective
4 interventions to change the trajectory of the
5 disease and the epidemic. The societal burden of
6 chronic hepatitis C has recently been addressed by
7 the Institute of Medicine, the Centers for Disease
8 Control, and the U.S. Preventative Services Task
9 Force.

10 In 2010, the IoM reported that viral
11 hepatitis C accounts for 15,000 preventable deaths
12 per year and that there is a need to improve
13 awareness, diagnosis, and access to care. In
14 particular, it was noted that the underserved have
15 a higher disease prevalence, and they play a major
16 role in terms of disease transmission.

17 Similar recommendations from the CDC in 2012
18 emphasized one-time testing for persons born
19 between 1945 to 1965, the baby boomers, a
20 population with a disproportionately high
21 prevalence of HCV infection and the disease. More
22 recently, the Preventative Services Task Force has

1 also endorsed this screening strategy.

2 As a whole, the bodies have indicated that
3 hepatitis C eradication is an achievable goal,
4 which will reduce disease sequelae and also
5 transmission if there is access and linkage to care
6 and if there is access broadly to effective
7 therapies.

8 Unlike HIV and chronic hepatitis B
9 infection, hepatitis C infection is fortunately
10 curable. A sustained response after therapy,
11 defined as undetectable virus three months after
12 seeking therapy is accepted as an endpoint to
13 demonstrate successful treatment and cure.

14 The linkage between sustained response rates
15 and outcomes have also been evaluated in many other
16 studies. Such a response is durable. In the short
17 term, viral eradication is long-lasting. It's
18 usually associated with normalization of liver
19 enzymes and improved self-perception or quality of
20 life, an improvement in liver histology as well as
21 reversal of cirrhosis in some patients.

22 Longer-term clinical outcomes are also

1 clearly established in prospective and
2 retrospective studies, with documented reductions
3 in the rates of all-cause and liver-related
4 mortality, liver transplantation, and liver cancer,
5 and also reductions in the rates of liver disease
6 progression and rates of decompensation.

7 The linkage between sustained response and
8 clinical outcomes has also been accepted by the
9 Preventive Services Task force, as has the
10 expectation that new or more effective therapies
11 will have even greater benefits.

12 This country is shown here from three
13 different sources. Approximately three-quarters of
14 patients are infected with the hepatitis C,
15 genotype 1 strain of the virus. Of the remaining
16 patients in the U.S., nearly 1 in 5 is infected
17 with genotype 2 and less than 1 in 10 with
18 genotype 3.

19 For those with hepatitis C, genotypes 2 or
20 3, according to current AASLD Society guidelines
21 that Dr. Birnkrant mentioned, it is recommended
22 that these patients receive 24 weeks of pegylated

1 interferon and ribavirin. And two-thirds to three-
2 quarters of these patients will achieve the
3 benefits of a sustained response in this setting.

4 While effective, therapy is lengthy. It's
5 associated and requires weekly injections of
6 pegylated interferon. And it's associated with
7 significant side effects that lead to high rates of
8 dose reductions and discontinuations. And for
9 those that can't take interferon or who have
10 already failed a course of interferon, there are
11 currently no treatment options.

12 For the majority of patients in this country
13 who are infected with genotype 1, if they are
14 eligible, they require 6 to 12 months of an
15 interferon-based triple therapy with a protease
16 inhibitor based upon the guidelines and as we heard
17 yesterday.

18 While also effective in many patients, these
19 triple therapy regimens are even more complex.
20 They have different monitoring and stopping rules,
21 longer treatment durations that are associated with
22 a different and more common side effect profile,

1 more significant side effects, high rates of
2 discontinuation, and the development of viral
3 resistance in most of those that are not cured.

4 Given the current recommended therapies,
5 there is clearly a need for improved therapies that
6 would be simple, that would be short in duration,
7 that would be effective, well-tolerated, free of
8 interferon, and without the risk of viral
9 resistance.

10 Sofosbuvir regimens met the primary efficacy
11 endpoint in all phase 3 clinical trials. The
12 regimens were highly efficacious across all HCV
13 genotypes. And they represent the first
14 interferon-free regimen for patients with genotype
15 2 or 3 infection. The treatment durations in most
16 circumstances are shorter than current therapies
17 and the regimens were safe and well-tolerated, with
18 low discontinuation rates.

19 Finally and importantly, there was no
20 resistance, no clinical breakthrough associated
21 with resistance. The clinical program was also
22 broad in its scope, as you'll hear. We included

1 patients who were historically excluded from
2 current interferon-containing trials and protocols.

3 The phase 3 programs also included many more
4 patients with advanced liver disease, including
5 those with cirrhosis, and we additionally included
6 a small study in patients awaiting liver
7 transplantation.

8 HCV therapy, much like HIV in the past, is
9 rapidly advancing and seeking to bring forward
10 multiple new agents to improve treatment options
11 for patients. Sofosbuvir has been studied in a
12 broad range of patients in combination with other
13 agents, including in combination with ribavirin,
14 including in combination with peg interferon and
15 ribavirin, and there's also undergoing study in
16 combination with other investigational agents.

17 As we have seen with HIV therapies, an
18 indication for sofosbuvir should provide physicians
19 the option of combining with new agents as
20 sufficient evidence becomes available to support
21 those combinations.

22 Given this need and the favorable attributes

1 of the sofosbuvir-based regimens we will describe
2 to you today, we propose that the drug be indicated
3 for the treatment of chronic hepatitis C infection
4 in combination with other agents, in adult patients
5 with genotypes 1 to 6, and also for patients who
6 are awaiting liver transplantation.

7 After this introduction, Dr. Bill Symonds
8 will present the sofosbuvir efficacy data, which
9 will show a consistent benefit across the different
10 populations and the different genotypes. And then
11 Dr. Diana Brainard will discuss the safety of
12 sofosbuvir, which is in large part defined by the
13 other agents with which it is administered. Then I
14 will return to briefly describe the benefit-risk
15 profile of sofosbuvir for the treatment of chronic
16 hepatitis C.

17 We have additionally assembled a group of
18 individuals from our development team to address
19 questions you may have. And we are fortunate to
20 have two highly-regarded external experts with us
21 today who are clinicians, hepatologists, and
22 researchers, Dr. Ira Jacobson from Cornell and

1 Dr. Zobair Younossi from Inova Fairfax.

2 So I'd now like to introduce Dr. Bill
3 Symonds, who's the vice-president in our liver
4 disease group and who has been with sofosbuvir
5 since its inception.

6 **Sponsor Presentation - William Symonds**

7 DR. SYMONDS: My name is Bill Symonds, and I
8 lead the sofosbuvir development program within the
9 liver disease's therapeutic area, Gilead Sciences.
10 Sofosbuvir is a prodrug which delivers the
11 monophosphorylated uridine nucleotide into
12 hepatocytes, where two additional phosphate groups
13 are added by intracellular enzymes to form the
14 active triphosphate.

15 The triphosphate form of sofosbuvir exerts
16 its antiviral activity against the hepatitis C
17 virus by competing with natural uridine nucleotides
18 for incorporation into the growing HCV RNA chain by
19 the NS5B polymerase enzyme. Once incorporated, no
20 further nucleotides can be added and the RNA chain
21 is terminated.

22 The active site on the NS5B enzyme is

1 relatively well conserved across HCV genotypes and
2 that mutations in this region of the viral genome
3 can potentially affect the virus' ability to
4 perform its function and may result in a virus
5 which has reduced fitness.

6 This is evident by the rare appearance of
7 the S282T mutation, which was found to confer
8 resistance to sofosbuvir in vitro and a lack of
9 viral resistance observed in patients who do not
10 achieve a sustained virologic response.

11 Sofosbuvir has been thoroughly evaluated in
12 a series of pre-clinical studies. Sofosbuvir does
13 not inhibit host DNA or RNA polymerases, including
14 mitochondrial polymerases. There were no adverse
15 effects noted in six- to nine-month chronic
16 toxicity studies, with safety margins of at least
17 9- and 13-fold in the rat and dog, respectively.

18 Sofosbuvir is not genotoxic. No adverse
19 effects on fertility or embryo or fetal development
20 were observed in reproductive toxicology studies of
21 sofosbuvir at exposures at least tenfold above the
22 anticipated clinical exposures, supporting the

1 proposed pregnancy category B.

2 Today, the efficacy discussion will focus on
3 the key clinical trials conducted with sofosbuvir
4 and included in the NDA. There were 13 phase 1
5 studies conducted to characterize the
6 pharmacokinetics, drug interactions, and the effect
7 of renal or hepatic impairment upon sofosbuvir.

8 The phase 2 program explored the safety and
9 antiviral activity of sofosbuvir in a series of
10 clinical trials, which provided justification for
11 the dose of sofosbuvir and informed the design of
12 the phase 3 program. We conducted five phase 3
13 trials, including patients with HCV genotypes 1
14 through 6. Approximately 20 percent of these
15 patients had cirrhosis.

16 The majority of these patients were
17 recruited in the United States, except for VALENCE,
18 which was conducted in Europe and included both
19 treatment-naive and treatment-experienced
20 individuals.

21 Sofosbuvir's clinical pharmacology profile
22 also offers a number of potential advantages.

1 Sofosbuvir is administered orally, once daily,
2 based upon the 18-hour intracellular half-life for
3 the active triphosphate.

4 Sofosbuvir is rapidly taken up by the liver
5 and has an elimination half-life of approximately
6 30 minutes. It is gone from the systemic
7 circulation within three to four hours and accounts
8 for only 5 percent of the systemic exposure in
9 humans.

10 The inactive nucleoside metabolite, also
11 known as GS-331007, accounts for greater than
12 90 percent. Of note, only sofosbuvir can enter the
13 hepatocyte and be converted into the active
14 triphosphate form. The 400-milligram dose,
15 administered once daily, does not require
16 adjustment in patients with hepatic impairment, as
17 sofosbuvir is not metabolized by a significant
18 degree to typical hepatic drug-metabolizing enzyme
19 systems. This allowed for the inclusion of a
20 sizeable group of patients with compensated
21 cirrhosis in the phase 3 program.

22 Nucleotide analogs like sofosbuvir and its

1 nucleoside metabolite are removed from the body via
2 the kidney. The 400-milligram dose of sofosbuvir
3 can be used safely in subjects with mild to
4 moderate renal impairment. A creatinine clearance
5 limit of 60 milliliters per minute was used in the
6 phase 3 program, but no dose adjustment is needed
7 down to 30 milliliters per minute. A study is now
8 under way, evaluating sofosbuvir in patients with
9 severe renal impairment, including those receiving
10 hemodialysis.

11 The pharmacokinetics of sofosbuvir and its
12 metabolites are linear and unaffected by BMI, age,
13 race, sex, or cirrhosis. Sofosbuvir also has a
14 favorable drug-drug interaction profile. This
15 allowed for the inclusion of patients receiving
16 stable methadone maintenance therapy in the
17 studies, in the coadministration with
18 immunosuppressants, common antiretrovirals, and
19 other direct-acting antivirals against the HCV
20 virus.

21 The only potential interactions that may be
22 clinically important are with inducers of PGP or

1 BCRP, which may reduce the systemic exposure to
2 sofosbuvir.

3 The objectives of the phase 2 program were
4 to determine an effective dose and duration for
5 sofosbuvir, to demonstrate antiviral activity
6 against HCV genotypes 1 through 6, to determine the
7 need for interferon in the regimen, and to
8 characterize sofosbuvir's resistance profile.

9 In the interest of time, I will only touch
10 upon two key clinical studies from the phase 2
11 program. The first of these was a study named
12 ELECTRON. This study asked a simple question, "How
13 much interferon, if any, is needed to cure
14 treatment-naive patients with HCV genotype 2 or 3
15 infection?"

16 Sofosbuvir, administered at 400 milligrams
17 once a day combined with pegylated interferon and
18 ribavirin for 12 weeks was compared with sofosbuvir
19 plus ribavirin for 12 weeks, with either 8, 4, or
20 zero weeks of interferon.

21 We also evaluated sofosbuvir monotherapy and
22 sofosbuvir plus ribavirin in treatment-experienced

1 patients. Fifty treatment-naive non-cirrhotic
2 patients with genotypes 2 or 3 were enrolled with
3 approximately 10 in each arm. Twenty-five subjects
4 were recruited in the treatment-experienced arm.

5 All treatment-naive patients receiving
6 sofosbuvir plus ribavirin achieved an SVR12,
7 regardless of the duration of interferon therapy
8 employed. When ribavirin was removed from the
9 regimen, sofosbuvir monotherapy achieved a
10 60 percent SVR12 rate, indicating that ribavirin
11 should remain in the regimen.

12 Sixty-eight percent of the treatment-
13 experienced patients also achieved an SVR12, a
14 promising result in this patient population with
15 limited treatment options. The results from this
16 study led to the design of the phase 3 program for
17 patients with genotypes 2 or 3 HCV infection.

18 The second study I will review is ATOMIC.
19 This study was designed to determine if 12 weeks of
20 therapy was sufficient to treat HCV infection with
21 the triple combination.

22 The ATOMIC trial was an open-label study

1 comparing 12 versus 24 weeks of treatment with
2 sofosbuvir in combination with pegylated interferon
3 and ribavirin. This study enrolled mostly HCV
4 genotype 1 patients who were treatment-naive and
5 non-cirrhotic. A small number of patients with
6 genotypes 4 and 6 were included in the 24-week
7 treatment arm.

8 The third arm evaluated 12 weeks of
9 sofosbuvir with pegylated interferon and ribavirin,
10 followed by an additional 12 weeks of sofosbuvir
11 alone or sofosbuvir plus ribavirin. The genotype 1
12 patients were enrolled in a 1:2:3 ratio across
13 these three study arms. 12 weeks of therapy with
14 this regimen in patients with genotype 1 HCV
15 infection resulted in approximately 90 percent of
16 patients achieving an SVR. The longer treatment
17 duration did not improve the response rate above
18 the group receiving 12 weeks of therapy.

19 The small number of genotype 4 or 6 patients
20 also achieved greater than 90 percent SVR in the
21 24-week arm. Results in the two 24-week arms were
22 comparable, indicating that the second 12 weeks of

1 interferon therapy is not required.

2 It was this result demonstrating the
3 efficacy of the 12-week treatment, which led to the
4 design and conduct of a phase 3 trial with this
5 regimen. The SVR results observed across multiple
6 phase 2 studies with sofosbuvir plus ribavirin,
7 administered for 12 weeks, appeared to be variable
8 and somewhat less efficacious.

9 Of note, the 24-week duration performed
10 better in the SPARE trial, in a population
11 considered more difficult to treat with typical
12 standard therapy. I did not review the dose
13 selection studies, but we were able to determine
14 the dose of sofosbuvir with a series of clinical
15 trials, which led us to select the 400-milligram
16 dose level for the phase 3 program.

17 Potent antiviral activity was observed
18 across all HCV genotypes. Results from ELECTRON
19 demonstrated that interferon was not required in
20 genotypes 2 and 3, but that ribavirin enhances SVR
21 rates when combined with sofosbuvir.

22 Sofosbuvir plus pegylated interferon and

1 ribavirin delivered high SVR rates in genotype 1
2 and in a small number of patients with genotypes 3,
3 2, 4, and 6.

4 Finally, we demonstrated that sofosbuvir had
5 a high barrier to resistance as predicted by in
6 vitro experiments with only 1 patient who received
7 sofosbuvir monotherapy, developing the S282T
8 mutation.

9 Based on the phase 2 program, five different
10 studies were conducted with the sofosbuvir phase 3
11 program. Four studies were conducted in patients
12 with HCV genotypes 2 or 3, and one study was
13 conducted in patients with HCV genotypes 1, 4, 5,
14 or 6. The standard of care for all these genotypes
15 currently includes pegylated interferon, the
16 difficulties of which have already been reviewed by
17 Dr. McHutchison.

18 The FISSION study included untreated
19 patients with HCV genotype 2 or 3 infection who
20 could receive interferon.

21 We compared sofosbuvir plus ribavirin
22 against the current standard of care with pegylated

1 interferon and ribavirin. The POSITRON study
2 included patients who could not receive interferon
3 and provided us the important opportunity to
4 characterize the efficacy of sofosbuvir plus
5 ribavirin and to compare the safety of this regimen
6 to a placebo.

7 The FUSION and NEUTRINO study designs
8 necessitated the use of historical controls.
9 Patients in the FUSION study had already failed
10 interferon and ribavirin and treatment guidelines
11 in the United States do not recommend retreatment
12 in these patients. Therefore, we chose to use an
13 historical control in this study for comparison.
14 The calculated SVR rate was based upon the EPIC
15 study, where pegylated interferon and ribavirin
16 were studied in this population.

17 The NEUTRINO study was designed as a
18 single-arm study based upon multiple factors.
19 These included the high SVR rate achieved in the
20 ATOMIC study with this triple combination regimen,
21 the desire to include genotypes 4, 5, and 6, and
22 the complex response-guided treatment algorithms

1 for the current PI-based regimens with treatment
2 durations of 24 to 48 weeks. Again, an historical
3 control was used for comparison with a calculated
4 response rate based upon the telaprevir and
5 boceprevir phase 3 studies.

6 All phase 3 studies shared common study
7 endpoints. The primary endpoint for the studies
8 was a sustained virologic response, assessed 12
9 weeks after the completion of therapy or SVR12, and
10 was defined as an HCV RNA assay result below the
11 lower limit of quantification of less than
12 25 international units per milliliter using the
13 COBAS TaqMan assay version 2.0, for use with a
14 high-pure system.

15 All patients participating in the phase 3
16 program are followed for an additional three years
17 in one of two registries, those who achieved an SVR
18 to determine for the durability of the response and
19 anyone who did not achieve an SVR to monitor for
20 viral resistance.

21 All phase 3 studies included a battery of
22 health-related quality-of-life assessments as an

1 exploratory endpoint to try and characterize the
2 impact of the treatments and the eventual outcomes
3 on the patients enrolled.

4 The first phase 3 trial was conducted in
5 patients who could take interferon. The FISSION
6 trial was an international, multicenter study which
7 evaluated the efficacy and safety of 12 weeks'
8 treatment with sofosbuvir, 400 milligrams,
9 administered once daily, plus ribavirin at 1,000 to
10 1,200 milligrams per day based upon body weight.

11 This was compared to 24 weeks of treatment
12 with pegylated interferon plus 800 milligrams of
13 ribavirin per day in treatment-naive, interferon-
14 eligible genotype 2 or 3 HCV patients.

15 The control group represents the current
16 standard of care for treatment of patients with
17 genotype 2 or 3 HCV infection. Weight-based
18 ribavirin was used throughout the program,
19 irrespective of the HCV genotype under study.

20 Of note, the numbers of patients with
21 genotype 2 versus 3 was prespecified as a 1 to 3
22 ratio in favor of genotype 3 in this trial. The

1 randomization schedule was stratified by HCV
2 genotype, high versus low baseline HCV RNA levels,
3 and by the presence or absence of cirrhosis.

4 A non-inferiority margin of 15 percent was
5 used for the efficacy analysis, based upon the
6 clinical assessment that eliminating pegylated
7 interferon from the regimen, and shortening the
8 duration of treatment from 24 to 12 weeks would
9 result in a substantial benefit for patients and
10 justify the non-inferiority design.

11 These study arms were balanced with respect
12 to demographics and baseline characteristics. Four
13 hundred and ninety-nine patients were randomized in
14 a 1 to 1 ratio to sofosbuvir plus ribavirin or
15 pegylated interferon plus ribavirin, with
16 approximately 20 percent of these patients having
17 evidence of cirrhosis at screening.

18 The mean age was 48, and the majority of the
19 patients were white males with a BMI of 28.
20 Approximately 43 percent of these patients were
21 IL28B CC. Three-quarters had HCV genotype 3, and
22 the mean baseline HCV RNA was similar in both

1 groups at 6 logs of virus.

2 The FISSION study met its primary efficacy
3 endpoint. The SVR12 response rates were 67 percent
4 for both sofosbuvir plus ribavirin and pegylated
5 interferon and ribavirin. Non-inferiority was
6 demonstrated as the lower bound of the two-sided
7 95 percent confidence interval for the difference
8 was minus 7.5 percent. This value is greater than
9 the prespecified non-inferiority margin of minus 15
10 percent.

11 Relapse was the primary reason for not
12 achieving an SVR in both of the study arms.
13 On-treatment failure was rare in the sofosbuvir
14 group, with a lone patient having undetectable drug
15 levels after week 4 of treatment, compared to
16 7 percent of the patients in the control arm.

17 Relapse was the primary reason for failure
18 in both groups. An additional 7 percent failed for
19 other reasons in the control arm, compared to only
20 3 percent in the sofosbuvir arm.

21 Compared to 24 weeks of pegylated interferon
22 and ribavirin, sofosbuvir plus ribavirin,

1 administered for the shorter duration of only
2 12 weeks, resulted in significantly higher response
3 rates in genotype 2 HCV infection and numerically
4 lower response rates with overlapping confidence
5 intervals in patients with genotype 3 HCV
6 infection.

7 Overall, patients with cirrhosis also fared
8 better on the sofosbuvir plus ribavirin treatment
9 compared to the pegylated interferon and ribavirin
10 treatment, as patients with genotype 2 infection
11 maintained high SVR rates regardless of the
12 presence or absence of cirrhosis.

13 As observed in the overall results, patients
14 with genotype 3 and cirrhosis achieved a similar
15 response rate to the control arm, albeit lower than
16 in those without cirrhosis.

17 The second trial was conducted in patients
18 with HCV genotypes 2 or 3 who were unable to
19 receive interferon, as these patients currently
20 have no treatment options.

21 The POSITRON trial was a multicenter,
22 double-blind, placebo-controlled study evaluating

1 the efficacy and safety of 12 weeks of sofosbuvir
2 plus ribavirin versus placebo in patients with
3 chronic genotypes 2 or 3 infection.

4 Patients were either interferon intolerant,
5 ineligible, or unwilling to take interferon
6 therapy. The placebo in control in this study was
7 included because there is no current treatment
8 available for HCV-infected patients who cannot take
9 interferon. All placebo recipients were offered
10 open-label sofosbuvir plus ribavirin after
11 completion of post-treatment follow-up.

12 Unlike FISSION, there was no prespecified
13 ratio of HCV genotypes 2 versus 3. The
14 randomization schedule was stratified by the
15 presence or absence of cirrhosis, and the primary
16 objective was superiority of sofosbuvir plus
17 ribavirin over the placebo group.

18 These treatment arms were balanced with
19 respect to demographics and baseline
20 characteristics. Two hundred and 78 patients were
21 randomized in a 3 to 1 ratio to receive sofosbuvir
22 plus ribavirin or placebo. Sixteen percent of

1 these patients overall had evidence of cirrhosis at
2 baseline.

3 The mean age was slightly older than in
4 FISSION at 52 years, and a majority of the patients
5 were white, but only half of them were male. The
6 mean BMI was 28, as in FISSION, and approximately
7 45 percent of these patients were IL28B CC. Half
8 of the patients had HCV genotype 3 and the mean
9 baseline HCV RNA was similar with 6.3 logs of virus
10 in both groups. The majority of the patients were
11 either unwilling to take interferon or ineligible
12 to do so.

13 When we look at the reasons why these
14 patients could not receive interferon in the
15 POSITRON trial, the majority of the ineligible
16 patients could not receive interferon due to
17 psychiatric conditions, followed by autoimmune and
18 neurologic disorders.

19 Patients who were considered intolerant to
20 prior interferon therapy had suffered significant
21 flu-like symptoms, psychiatric disorders, or
22 thrombocytopenia, which prevented them from

1 completing their previous interferon-based
2 treatment regimens.

3 The POSITRON study met its primary objective
4 of superiority over placebo. Twelve weeks
5 treatment with sofosbuvir plus ribavirin resulted
6 in an SVR12 rate of 78 percent in patients with
7 chronic genotype 2 or 3 HCV infection who are
8 interferon-intolerant, ineligible, or unwilling to
9 take interferon, providing an effective treatment
10 for these patients who had none.

11 SVR results by HCV genotype mirror those
12 observed in FISSION, with 93 percent of those with
13 genotype 2 and 61 percent of those with genotype 3
14 achieving an SVR. When broken down further by
15 genotype and cirrhosis, patients with genotype 2
16 HCV infection maintained high SVR rates regardless
17 of cirrhosis status. SVR rates are lower in
18 patients with genotype 3 and cirrhosis with non-
19 overlapping confidence intervals.

20 Patients with HCV genotypes 2 or 3 who have
21 failed prior therapy with interferon also have
22 limited treatment options and were the population

1 selected for the third phase 3 trial.

2 The FUSION trial is a multicentered, double-
3 blind study evaluating the efficacy and safety of
4 sofosbuvir plus ribavirin, administered for 12 or
5 16 weeks in patients with chronic genotype 2 or 3
6 HCV infection, who have failed prior treatment with
7 an interferon-based regimen.

8 The 16-week duration was chosen to evaluate
9 whether a longer duration of therapy would lead to
10 higher response rates compared to the 12-week
11 duration in this difficult-to-treat population.

12 The randomization schedule was stratified by the
13 presence or absence of cirrhosis and by HCV
14 genotype.

15 The FUSION trial utilized an historical
16 control rate of 25 percent for comparison to both
17 sofosbuvir arms. This rate was calculated based on
18 similar patients in the EPIC study and was deemed
19 to be a clinically meaningful response rate in this
20 patient population who have exhausted their
21 treatment options.

22 As in the previous two studies, the arms are

1 balanced with respect to demographics and baseline
2 characteristics. Two hundred and one patients were
3 randomized in a 1 to 1 ratio to receive 12 or
4 16 weeks of sofosbuvir plus ribavirin, 34 percent
5 of whom had evidence of cirrhosis at baseline. The
6 mean age was again slightly older than in FISSION
7 at 54 years, and the majority of the patients were
8 white males.

9 The mean BMI was the same as the two
10 previous trials, with approximately one-third being
11 IL28B CC and two-thirds having HCV genotype 3. The
12 mean baseline HCV RNA was similar with 6.5 logs of
13 virus in both groups. Three-quarters of these
14 patients were classified as relapsers to their
15 prior therapy and one-quarter were non-responders.

16 The FUSION study met its primary endpoint of
17 superiority over the historical control for both
18 treatment durations. The 12- and 16-week regimens
19 achieved SVR12 rates of 50 and 71 percent,
20 respectively in treatment-experienced patients with
21 genotypes 2 or 3 HCV infection.

22 These results were statistically

1 significant, with p-values of less than 0.001 for
2 both groups when compared with the historical
3 control SVR rate and when comparing the 12- and
4 16-week durations in the combined genotype 2 and 3
5 population. This appears largely due to the
6 improved effect observed in patients with genotype
7 3 HCV infection. The effect in patients with
8 genotype 2 HCV infection was less pronounced, as
9 these patients responded with high SVR12 rates
10 following both durations of therapy.

11 When broken down further by genotype and
12 cirrhosis, patients with genotype 2 maintained high
13 SVR rates, regardless of cirrhosis status. In
14 these genotype 3 treatment-experienced patients
15 with cirrhosis, response rates are lower with the
16 12-week duration, while the 16-week treatment
17 duration appears to enhance SVR12 rates, with a
18 threefold improvement observed.

19 Given the sharp increase in SVR observed and
20 the treatment-experienced genotype 3 patients when
21 the treatment duration was extended by four weeks,
22 data on longer durations are critical to determine

1 what is best for these patients and are now
2 available, as mentioned earlier, from the VALENCE
3 trial, which has been submitted and is currently
4 under review.

5 Data from this trial will also be presented
6 at the AASLD meeting next week. This trial was
7 originally a placebo-controlled trial in genotype 2
8 or 3 patients with sofosbuvir plus ribavirin for
9 12 weeks.

10 The patient population enrolled represented
11 all the populations included in the three trials
12 just discussed. Once the FUSION SVR results were
13 available, demonstrating the benefit of the longer
14 duration in genotype 3 patients, the VALENCE trial
15 was amended to extend the treatment duration in
16 genotype 3 patients to 24 weeks.

17 The genotype 2 patients received 12 weeks as
18 originally planned. A small number of genotype 3
19 patients had completed the original 12-week course
20 prior to the amendment. The placebo arm was
21 stopped and patients were offered treatment in a
22 separate protocol.

1 The majority of the 323 patients in these
2 two arms had genotype 3 HCV infection, were IL28B
3 non-CC, and treatment-experienced. Fourteen to
4 23 percent of these individuals had evidence of
5 cirrhosis at baseline. I will focus on this
6 24-week group with genotype 3, as it is most
7 relevant to our discussion today.

8 SVR results in genotype 3 were high at
9 84 percent overall, especially when we consider the
10 lower SVR rates observed in the prior studies. SVR
11 results in genotype 2 patients were also high at
12 93 percent and are consistent with the phase 3
13 program.

14 Breaking down these genotype 3 results
15 further, we observed that 93 percent of
16 treatment-naïve, non-cirrhotic patients achieved an
17 SVR where only 61 percent had responded in FISSION.
18 Ninety-two percent responded in the small group who
19 also had cirrhosis.

20 Among the treatment-experienced patients,
21 85 percent of those without cirrhosis responded,
22 which represents an improvement over the FUSION

1 trial. Sixty percent with cirrhosis achieved an
2 SVR in the arm who were treatment-experienced with
3 cirrhosis, and this result is similar to the
4 16-week FUSION arm. These results are
5 substantially higher for most subgroups compared
6 with the shorter regimens and indicate that all
7 genotype 3 patients should receive 24 weeks of
8 therapy.

9 Sofosbuvir plus ribavirin offers the first
10 all-oral treatment regimen for patients with HCV
11 genotype 2 or 3 HCV infection. Sofosbuvir plus
12 ribavirin met the primary efficacy endpoint in
13 phase 3 trials conducted in a broad population of
14 patients with chronic HCV infection due to
15 genotypes 2 or 3.

16 Patients with HCV genotype 2 infection
17 experienced consistently high SVR12 rates across
18 all trials and should receive 12 weeks of therapy.
19 Extending the duration of sofosbuvir plus ribavirin
20 to 24 weeks in patients with genotype 3 improves
21 SVR12 rates and is recommended for these patients.

22 In order to make sofosbuvir available as a

1 potential treatment option for the majority of HCV
2 patients, an additional phase 3 study was added to
3 the program in April of 2012 in HCV genotypes 1, 4,
4 5, and 6, based on the high SVR rate observed in
5 the ATOMIC trial with sofosbuvir plus pegylated
6 interferon and ribavirin, administered for only
7 12 weeks.

8 The NEUTRINO trial was an open-label single-
9 arm study evaluating the efficacy, safety, and
10 tolerability of sofosbuvir in combination with
11 pegylated interferon and ribavirin in these
12 treatment-naive patients.

13 This study utilized an historical control
14 rate of 60 percent. This rate was calculated based
15 upon the telaprevir and boceprevir phase 3 data and
16 took into account the higher number of cirrhotics
17 in our trial, the expected safety profile, and
18 shorter treatment duration.

19 The demographic and baseline characteristics
20 were similar to the other trials, but with a few
21 notable differences. Three hundred and 27 patients
22 were enrolled and received at least one dose of

1 study drug. Seventeen percent of these patients
2 had evidence of cirrhosis.

3 The mean age was, again, 52 with the
4 majority being white males. However, 17 percent of
5 these patients were black and 14 percent of them
6 were Hispanic. The mean BMI was 29, and one-third
7 of these patients were IL28B CC. Eighty-nine
8 percent had HCV genotype 1 infection, and most had
9 high viral load.

10 The NEUTRINO trial met its primary endpoint
11 of superiority to the historical control. Twelve
12 weeks of treatment with sofosbuvir plus pegylated
13 interferon and ribavirin achieved an SVR12 rate of
14 90 percent in treatment-naive patients with chronic
15 genotypes 1, 4, 5, or 6 HCV infection.

16 This result was statistically significant
17 with a p-value of less than 0.001 when compared
18 with a historical rate of 60 percent. Prespecified
19 subgroup analyses demonstrated that 80 percent of
20 those with cirrhosis achieved an SVR. Eighty-nine
21 percent of those with HCV genotype 1 achieved an
22 SVR. Ninety-six percent of those with genotype 4

1 responded, and a limited number of patients with
2 genotype 5 and 6 all achieved an SVR.

3 Sofosbuvir plus pegylated interferon and
4 ribavirin for 12 weeks met its primary efficacy
5 endpoint. These results replicate phase 2 data in
6 genotype 1 with the same regimen. Genotype 1
7 patients achieved high SVR rates overall and in all
8 major subpopulations studied.

9 Genotype 4 patients achieved high SVR rates
10 with results consistent with those achieved in
11 phase 2 with the longer treatment duration.

12 Finally, the genotypes 5 and 6 patients all
13 achieved an SVR. Their numbers are small, which
14 reflects their prevalence in the United States.

15 These clinical results are consistent with
16 the in vitro antiviral activity and suggest that
17 these patients should also have access to
18 sofosbuvir.

19 In addition to the phase 3 studies just
20 reviewed, studies are also being conducted in
21 populations with great unmet medical needs; the
22 first of these in patients with HCV infection who

1 are awaiting liver transplantation, as there is
2 currently no standard of care therapy available for
3 these patients, and reinfection following
4 transplantation is universal without therapeutic
5 intervention.

6 The pre-transplant study is a single-arm
7 open-label study for patients with chronic HCV
8 infection of all genotypes who are awaiting liver
9 transplantation due to the presence of
10 hepatocellular carcinoma meeting the Milan
11 criteria. These patients were eligible to receive
12 treatment with sofosbuvir plus ribavirin for up to
13 24 weeks prior to undergoing liver transplantation.

14 A recent amendment has increased the
15 treatment duration up to 48 weeks based upon the
16 preliminary data, which I am about to show you. A
17 total of 61 patients were enrolled, and we have
18 data on 37 patients who had HCV RNA below the lower
19 limit of quantification at the time of
20 transplantation. A number of patients either
21 remain on therapy, have relapsed prior to
22 transplant, or are no longer candidates for

1 transplantation.

2 At baseline, the majority of these patients
3 had high viral load, had HCV genotype 1, or IL28B
4 non-CC, had Childs Pugh A cirrhosis, and were
5 treatment-experienced.

6 Treatment with sofosbuvir plus ribavirin
7 prevented post-transplant reinfection with the
8 hepatitis C virus in the majority of patients who
9 had HCV RNA below the lower limit of quantification
10 at the time of transplantation.

11 At 12 weeks post-transplant, 23 of 36, or
12 64 percent of these patients remained uninfected
13 with no detectible HCV RNA. No patients have
14 become HCV RNA positive after post-transplant
15 week 12 in the patients followed out to week 24.

16 We have conducted a number of exploratory
17 analyses to try and understand the relationship
18 between pre-transplant therapy and the prevention
19 of recurrence. We have looked at the length of
20 therapy and the period of time a patient's HCV RNA
21 is below the lower limit of quantification prior to
22 transplant, but it appears that the number of days

1 with HCV RNA target-not-detected values may be most
2 meaningful.

3 The majority of patients with HCV
4 recurrence, shown in the red bars, were HCV RNA
5 target not detected for less than one month. In
6 contrast, the majority have remained HCV RNA free
7 in the group who were HCV RNA target not detected
8 for one month or more, shown by the green bars.

9 Based on this encouraging preliminary data,
10 sofosbuvir plus ribavirin may provide a treatment
11 option for this population who do not currently
12 have an effective treatment available to prevent
13 recurrence of HCV post-transplantation.

14 The duration of administration of sofosbuvir
15 in these patients awaiting liver transplantation
16 should be guided by an assessment of the benefits
17 and risks to the patient by their physician.

18 Patients who fail to achieve an SVR do not
19 appear to develop resistance to sofosbuvir when
20 administered with ribavirin in the phase 3 program.
21 The S282T mutation was identified as the primary
22 resistance mutation for sofosbuvir in vitro across

1 all HCV genotypes evaluated. Comprehensive
2 virology analyses have demonstrated that genotypic
3 and phenotypic resistance to sofosbuvir was not
4 detected in any patient before treatment or in any
5 of the subjects who did not achieve an SVR within
6 the phase 3 program when sofosbuvir was
7 administered with ribavirin.

8 The L159F mutation was identified in a small
9 number of patients experiencing relapse, but does
10 not appear to be associated with reduced
11 susceptibility to sofosbuvir in vitro.

12 In summary, the sofosbuvir phase 3 program
13 enrolled over 1700 patients with chronic HCV
14 infection, including all relevant HCV genotypes.
15 These were real-world patients based upon the
16 liberal enrollment criteria used, which allowed
17 enrollment of many patient subsets who are normally
18 excluded from HCV clinical trials.

19 Our studies included patients with
20 compensated cirrhosis, with less restriction on
21 platelet counts at entry, no upper limits on age or
22 BMI, and allowed for concomitant use of opioid

1 replacement therapy.

2 To conclude, the treatment of chronic HCV
3 infection with sofosbuvir-based regimens has
4 resulted in high SVR rates across a broad range of
5 patients with the phase 3 studies achieving their
6 primary efficacy endpoints.

7 There was no on-treatment viral breakthrough
8 observed during treatment with sofosbuvir-based
9 regimens in the phase 3 studies and no resistance
10 to sofosbuvir was detected in patients who did not
11 achieve an SVR when combined with ribavirin.

12 Patients with compensated cirrhosis are a
13 population with an unmet medical need and can
14 benefit from sofosbuvir-based regimens. Limited
15 data from an ongoing study indicates that treatment
16 with sofosbuvir plus ribavirin, up until the time
17 of liver transplantation, was effective in
18 preventing recurrence of hepatitis C in a majority
19 of the patients.

20 Based upon the phase 3 data, we are making
21 the following dosing and administration
22 recommendations for sofosbuvir. Treatment-naïve

1 patients with chronic HCV infection due to
2 genotypes 1, 4, 5, or 6 should receive 12 weeks of
3 sofosbuvir plus pegylated interferon and ribavirin.

4 Patients with chronic HCV infection due to
5 genotype 2 should receive 12 weeks of sofosbuvir
6 plus ribavirin. All patients with chronic HCV
7 infection due to genotype 3 should receive 24 weeks
8 of sofosbuvir plus ribavirin.

9 Finally, patients with chronic HCV infection
10 who are awaiting liver transplantation should
11 receive sofosbuvir plus ribavirin until the time of
12 their transplantation.

13 Dr. Diana Brainard will now review the
14 safety profile of sofosbuvir.

15 **Sponsor Presentation - Diana Brainard**

16 DR. BRAINARD: Good morning. I am Diana
17 Brainard, clinical lead for the sofosbuvir program.
18 The safety profile of sofosbuvir is supported by
19 pre-clinical data as well as an extensive exposure
20 in clinical trials that includes patients with
21 chronic HCV infection across a wide range of
22 demographics and treatment durations.

1 Sofosbuvir is well-tolerated when
2 administered with other agents. In phase 2 and
3 phase 3 studies, sofosbuvir plus ribavirin was
4 administered to 1,866 patients for up to 42 weeks.
5 Sofosbuvir plus pegylated interferon and ribavirin
6 was studied in 891 patients for up to 24 weeks.

7 The safety profile of sofosbuvir in these
8 studies was defined by the coadministered
9 antivirals and was similar across all subgroups,
10 including patients with cirrhosis, which made up
11 20 percent of the phase 3 study population.

12 Treatment discontinuations due to adverse events
13 were uncommon, and no additional toxicities were
14 associated with longer treatment duration.

15 In phase 2 and phase 3 studies, nearly 3,000
16 HCV-infected patients have received the
17 400-milligram dose of sofosbuvir; 2,736 patients
18 have been treated for at least 12 weeks, 1,166
19 patients for at least 16 weeks, and just over 1,000
20 patients for 24 weeks.

21 Over the last two decades, the safety
22 profile of interferon and ribavirin has been well

1 characterized. Adverse events across all organ
2 systems may occur with constitutional,
3 neuropsychiatric, hematologic, and autoimmune side
4 effects most frequently reported and most likely to
5 lead to premature treatment discontinuation.

6 The safety profile of ribavirin has largely
7 been assessed when given in combination with
8 interferon, given its lack of efficacy when
9 administered alone. However, small controlled
10 studies of ribavirin monotherapy have been
11 conducted in HCV-infected patients and contribute
12 to the understanding of what adverse events to
13 expect with ribavirin treatment. These include,
14 most notably, hemolytic anemia and teratogenicity,
15 as well as cough, pruritus, and neuropsychiatric
16 side effects such as insomnia and depression.

17 I will first present data on the patients in
18 the four genotype 2 or 3 phase 3 studies, which
19 include the FISSION, POSITRON, and FUSION studies
20 included in the original NDA, as well as the
21 VALENCE study, submitted more recently.

22 In addition, I will review the safety of

1 sofosbuvir plus ribavirin in 61 patients with
2 hepatocellular carcinoma in the pre-transplant
3 study. I will then present data from the NEUTRINO
4 study in 327 patients with genotype 1, 4, 5, or 6
5 infection who receive sofosbuvir plus peg
6 interferon and ribavirin for 12 weeks.

7 FISSION, POSITRON, and FUSION each assessed
8 sofosbuvir plus ribavirin for 12 weeks as compared
9 to pegylated interferon and ribavirin, placebo, or
10 16 weeks of sofosbuvir plus ribavirin,
11 respectively.

12 The safety data were assessed within each
13 study individually, and we also pulled the data
14 from the 12-week arms of each study to perform an
15 integrated analysis.

16 In the phase 3 studies in genotype 2 or 3
17 HCV-infected patients treated with sofosbuvir plus
18 ribavirin for 12 or 16 weeks, 97 to 100 percent of
19 sofosbuvir-treated patients completed therapy.
20 Across all treatment arms, the most common reason
21 for treatment discontinuation was adverse events,
22 occurring in 4 percent of placebo patients and 0 to

1 1 percent of sofosbuvir plus ribavirin-treated
2 patients.

3 Seventy-eight percent of patients treated
4 with peg interferon and ribavirin completed
5 treatment. The most common reasons for
6 discontinuation were adverse events in 11 percent,
7 followed by 7 percent due to virologic failure.

8 The overall adverse event profile with
9 sofosbuvir plus ribavirin was favorable as compared
10 to pegylated interferon and ribavirin.

11 In genotype 2 or 3 treatment-naive patients
12 in the FISSION study, the rates of adverse events
13 or grade 3 or higher adverse events were lower with
14 sofosbuvir plus ribavirin treatment as compared to
15 peg interferon and ribavirin treatment.

16 There was no individual grade 3 or higher
17 adverse event that occurred in more than 1 percent
18 of sofosbuvir-treated patients. In contrast,
19 grade 3 or 4 neutropenia, thrombocytopenia,
20 fatigue, and insomnia all occurred in more than 1
21 percent of peg interferon and ribavirin-treated
22 patients.

1 Serious adverse events occurred in 3 percent
2 of sofosbuvir-treated patients and 1 percent of peg
3 interferon and ribavirin-treated patients. Among
4 the adverse events reported in at least 15 percent
5 of patients, all were significantly more common in
6 the peg interferon and ribavirin-treated patients
7 versus the sofosbuvir and ribavirin-treated
8 patients.

9 Hematologic abnormalities were also more
10 common with peg interferon and ribavirin treatment
11 as compared to sofosbuvir and ribavirin treatment.
12 Few patients had grade 3 or 4 chemistry
13 abnormalities.

14 Grade 3 hyperbilirubinemia occurred in
15 2 percent of sofosbuvir plus ribavirin-treated
16 patients as compared to less than 1 percent of peg
17 interferon and ribavirin-treated patients.

18 Elevations in transaminases were more common
19 with peg interferon and ribavirin treatment,
20 consistent with the known effects of interferon in
21 a minority of patients. Transient asymptomatic
22 elevations and creatine kinase and/or lipase were

1 observed in both treatment arms. There were no
2 cases of pancreatitis in this study.

3 The POSITRON study allowed us a unique
4 opportunity to assess the background rate of
5 adverse events in untreated patients with chronic
6 HCV infection as compared to patients treated with
7 sofosbuvir plus ribavirin for 12 weeks.

8 The rates of adverse events and grade 3 or
9 higher adverse events were higher with sofosbuvir
10 plus ribavirin treatment as compared to placebo
11 treatment. There was no individual grade 3 or 4
12 adverse event that occurred in more than 1 percent
13 of sofosbuvir and ribavirin-treated patients.
14 Serious adverse events were uncommon in both
15 treatment arms, and there was no individual serious
16 adverse event that occurred in more than one
17 patient.

18 In the POSITRON study, there were 6 adverse
19 events that occurred in at least 10 percent of
20 patients in either treatment arm. Among these 6
21 adverse events, fatigue, insomnia, and anemia were
22 significantly more frequent in the sofosbuvir plus

1 ribavirin compared with the placebo group. In
2 contrast, rates of nausea, headache, and pruritus
3 were similar in both groups.

4 Hemoglobin reductions requiring dose
5 modification of ribavirin occurred in 7 percent of
6 patients with less than 1 percent developing a
7 hemoglobin of less than 8.5 grams per deciliter.
8 No other hematologic abnormalities were observed.

9 Few patients had grade 3 or 4 chemistry
10 abnormalities. Hyperbilirubinemia occurred in
11 2 percent of sofosbuvir-treated patients, as
12 compared to none of the placebo patients.
13 Elevations in transaminases were common in placebo
14 patients, consistent with untreated chronic HCV
15 infection. Transient asymptomatic elevations in
16 lipase were observed in both treatment arms. There
17 was one subject in the placebo arm who developed
18 pancreatitis that led to treatment discontinuation.

19 The FUSION study allowed the comparison of
20 12 weeks versus 16 weeks of sofosbuvir plus
21 ribavirin treatment in treatment-experienced
22 genotype 2 or 3 HCV-infected patients, 34 percent

1 of whom had cirrhosis.

2 Extending treatment duration by 4 weeks did
3 not increase the frequency or severity of reported
4 adverse events. Most adverse events were mild to
5 moderate or grade 1 or 2 in severity. Grade 3 or 4
6 adverse events were reported in 4 to 8 percent of
7 patients, and serious adverse events were reported
8 in 3 to 5 percent of patients.

9 Anemia and hepatocellular carcinoma were the
10 only grade 3 events occurring in more than one
11 patient, occurring overall in 2 and 3 patients,
12 respectively. The cases of hepatocellular
13 carcinoma were also the only SAEs that occurring in
14 more than one patient.

15 Given the high percentage of patients with
16 cirrhosis in these studies, the occurrence of
17 hepatocellular carcinoma is not unexpected. There
18 is only one patient across both treatment groups
19 who prematurely discontinued treatment.

20 Most patients in the FUSION study
21 experienced at least one adverse event. However,
22 extending treatment duration for an additional four

1 weeks did not appear to increase the occurrence
2 overall of adverse events.

3 Hemoglobin reductions accounted for the
4 majority of hematologic abnormalities observed in
5 both treatment arms. Extending treatment from 12
6 to 16 weeks did not increase the percentage of
7 patients requiring ribavirin dose reduction due to
8 anemia.

9 Grade 3 and 4 chemistry abnormalities were
10 uncommon and consistent with what was observed in
11 the other sofosbuvir plus ribavirin studies.
12 Hyperbilirubinemia occurred in 2 percent of
13 patients.

14 The grade 3 ALT elevations in the 16-week
15 arm both occurred in patients at the post-treatment
16 week 4 visit in the setting of virologic relapse.
17 Lipase elevations were transient and asymptomatic.

18 The safety of sofosbuvir plus ribavirin for
19 24 weeks provides additional data demonstrating the
20 absence of duration-associated toxicity with this
21 regimen.

22 The phase 3 VALENCE study was originally

1 designed to compare 12 weeks of sofosbuvir plus
2 ribavirin with placebo treatment, but was amended
3 to extend treatment duration to 24 weeks in
4 genotype 3 patients who had not yet completed
5 treatment.

6 Safety data are available from 85 patients
7 who received placebo treatment for a mean treatment
8 duration of 8 weeks prior to the study amendment,
9 which discontinued this treatment arm.

10 From 84 patients who received 12 weeks of
11 sofosbuvir plus ribavirin, that includes 73
12 patients with genotype 2 infection and 11 patients
13 with genotype 3 infection who had already completed
14 treatment at the time of the amendment, and 250
15 genotype 3 HCV-infected patients who were treated
16 with 24 weeks of sofosbuvir plus ribavirin.

17 Rates of adverse events were higher and
18 similar in the active treatment groups. Grade 3 or
19 higher adverse events, serious adverse events, and
20 adverse events leading to treatment discontinuation
21 were uncommon.

22 The numeric differences of grade 3 or higher

1 adverse events and serious adverse events in the
2 24-week treatment arm reflect differences present
3 during the first 12 weeks of treatment.

4 Among the commonly observed adverse events
5 in this study, headache occurred with similar
6 frequency across all groups, including placebo.
7 Other adverse events were more frequent with
8 sofosbuvir plus ribavirin treatment, but extending
9 treatment duration from 12 to 24 weeks did not
10 substantially increase the occurrence of these
11 events.

12 The safety of sofosbuvir and ribavirin has
13 also been demonstrated in patients with more
14 advanced liver disease. In the pre-transplant
15 study, sofosbuvir plus ribavirin was administered
16 to 61 patients with chronic HCV infection and
17 hepatocellular carcinoma, awaiting liver
18 transplant.

19 Study drugs were administered until the time
20 of transplant, with a median exposure of 21 weeks
21 and a range of 2 to 42 weeks of treatment.
22 Eighteen percent of patients had grade 3 or 4

1 adverse events or serious adverse events. These
2 patients had more advanced liver disease and
3 underlying morbidity, with events such as tumor
4 progression, tumor thrombosis, spontaneous
5 bacterial peritonitis, hepatic encephalopathy, and
6 hepatic ischemia, representing expected clinical
7 sequelae in this patient population.

8 Overall, sofosbuvir plus ribavirin was well-
9 tolerated, with only two patients discontinuing
10 treatment due to adverse events, one due to
11 pneumonitis and the other due to spontaneous
12 bacterial peritonitis. These two patients were
13 also the only deaths that occurred pre-transplant
14 in this study.

15 Data from the phase 2 and phase 3 studies
16 have demonstrated that sofosbuvir in combination
17 with ribavirin is a well-tolerated regimen with a
18 readily manageable adverse event profile consistent
19 with that of ribavirin.

20 There are few adverse events leading to
21 treatment discontinuation and low rates of severe
22 or serious adverse events. When compared to

1 current standard of care, 24 weeks of peg
2 interferon and ribavirin, as was done in the
3 FISSION study, the interferon-free regimen of
4 sofosbuvir plus ribavirin demonstrates significant
5 advantages with respect to frequency, and severity
6 of adverse events, and rates of treatment
7 completion.

8 When compared to placebo treatment,
9 sofosbuvir plus ribavirin is characterized by
10 adverse events such as fatigue, insomnia, and
11 anemia that are mostly mild to moderate in severity
12 and occur with a frequency and severity consistent
13 with ribavirin treatment.

14 Extending treatment duration of sofosbuvir
15 plus ribavirin beyond 12 weeks did not impact the
16 safety profile of this regimen, and the safety
17 profile of sofosbuvir plus ribavirin is similar in
18 patients with more advanced liver disease.

19 I'm now going to focus on the NEUTRINO
20 study, in which sofosbuvir plus pegylated
21 interferon and ribavirin was administered for
22 12 weeks in treatment-naïve genotype 1, 4, 5, or 6

1 HCV-infected patients. The safety data from this
2 single-arm study demonstrate that, when sofosbuvir
3 is administered with peg interferon and ribavirin,
4 the safety profile reflects that expected with
5 interferon, ribavirin-based regimens.

6 Of the 327 patients treated with sofosbuvir
7 plus peg interferon and ribavirin for 12 weeks, 98
8 percent completed treatment with 2 percent of
9 patients discontinuing treatment due to adverse
10 events. Anemia was the only adverse event leading
11 to treatment discontinuation in more than one
12 patient. Of note, the two patients who prematurely
13 discontinued treatment due to anemia subsequently
14 achieved a sustained virologic response.

15 Grade 3 or higher adverse events occurred in
16 15 percent of patients, with those occurring in
17 more than 1 percent limited to neutropenia, anemia,
18 fatigue, and headache.

19 Serious adverse events were uncommon,
20 occurring in only 1 percent of patients and no
21 individual serious adverse event occurred in more
22 than one patient. There were no deaths in this

1 study.

2 Most patients treated with sofosbuvir plus
3 peg interferon and ribavirin experienced at least
4 one adverse event, but most adverse events were
5 mild to moderate in severity. The most common
6 adverse events with sofosbuvir plus peg interferon
7 and ribavirin were similar in nature and frequency
8 to those expected with peg interferon and ribavirin
9 alone.

10 Although NEUTRINO was a single-arm study of
11 sofosbuvir plus peg interferon and weight-based
12 ribavirin, the data can be compared with data from
13 the first 12 weeks of treatment, with peg
14 interferon and 800 milligrams fixed-dose ribavirin
15 in the FISSION study.

16 This cross-study comparison suggests that
17 the commonly observed adverse events were similar
18 over 12 weeks of treatment with sofosbuvir plus peg
19 interferon and ribavirin or peg interferon and
20 ribavirin alone, with the exception of anemia,
21 which was more common with the higher weight-based
22 dosing of ribavirin used in all genotype 1

1 patients, versus the lower 800 milligrams
2 fixed-dose ribavirin used with peg interferon in
3 the FISSION study with genotype 2 or 3 patients.

4 Hematologic abnormalities were consistent
5 with the known effects of interferon and ribavirin.
6 Neutropenia and anemia were managed with interferon
7 and ribavirin dose reductions according to the
8 product label. Grade 3 or 4 chemistry
9 abnormalities were uncommon.

10 Elevations in ALT and AST are expected in a
11 minority of patients treated with interferon, and
12 the peg interferon label provides guidance for
13 monitoring transaminases and for dose reductions or
14 discontinuations of interferon.

15 Two to 3 percent of patients receiving
16 sofosbuvir plus peg interferon and ribavirin had
17 grade 3 or higher ALT or AST elevations. None of
18 these patients had a concomitant increase in
19 bilirubin, any change in synthetic function, or
20 clinical signs or symptoms of worsening liver
21 disease, such as jaundice. All of these patients
22 completed 12 weeks of treatment without peg

1 interferon dose reductions or interruptions.

2 Anemia is observed when sofosbuvir is
3 administered with ribavirin with or without
4 interferon. When administered with ribavirin,
5 median hemoglobin reductions are approximately
6 2 grams per deciliter, which is similar to what has
7 been reported in studies of ribavirin monotherapy.

8 Interferon suppresses the bone marrow and
9 increases the degree of anemia observed with
10 ribavirin treatment. Although the anemia is
11 greater in the presence of interferon, interferon
12 causes a reduction in compensatory bone marrow
13 response to anemia, resulting in less reticular
14 cytosis and less hemolysis.

15 Sofosbuvir does not increase the frequency
16 or severity of anemia.

17 Mean hemoglobin levels over 12 weeks of
18 treatment with different regimens show no impact of
19 sofosbuvir on hemoglobin. When sofosbuvir is
20 administered as monotherapy without ribavirin,
21 shown in green, as was done for 10 patients in the
22 phase 2 ELECTRON study, no change in hemoglobin is

1 observed. When sofosbuvir is administered with
2 1,000 to 1,200 milligrams of ribavirin, shown in
3 blue, for the 566 patients in the phase 3 studies,
4 ribavirin associated decreases in hemoglobin are
5 observed.

6 The additional impact on hemoglobin from
7 adding interferon to 1,000 to 1,200 milligrams of
8 ribavirin is shown in red and represents data from
9 25 patients in the phase 2 PROTON study, who were
10 genotype 1 patients in the control arm receiving
11 peg interferon and ribavirin alone.

12 When sofosbuvir is added to peg interferon
13 and weight-based ribavirin, shown in purple, and
14 representing data from the 327 NEUTRINO patients,
15 there is no additional hemoglobin reduction over
16 peg interferon plus weight-based ribavirin alone.
17 These data suggest that sofosbuvir does not
18 contribute to the anemia observed with ribavirin or
19 with pegylated interferon and ribavirin.

20 Dose reductions of either weight-based or
21 fixed-dose ribavirin were performed according to
22 the product label and occurred in 6 to 10 percent

1 of patients receiving sofosbuvir plus ribavirin, as
2 compared to 11 percent of patients receiving peg
3 interferon plus 800 milligrams of ribavirin.

4 Dose reductions were more common in
5 genotype 1 patients who received sofosbuvir plus
6 peg interferon and 1,000 to 1,200 milligrams of
7 ribavirin, occurring in 20 percent of patients.
8 Few patients developed a hemoglobin of less than
9 8.5 grams per deciliter, and only 6 patients or
10 less than 1 percent of sofosbuvir-treated patients
11 required transfusion for anemia.

12 In conclusion, sofosbuvir regimens have
13 favorable safety profiles that are defined by the
14 agents with which sofosbuvir is coadministered.
15 Specifically, in these studies, ribavirin and
16 pegylated interferon and ribavirin. When given
17 with ribavirin, the most common adverse events
18 reflect those associated with ribavirin.

19 Extending treatment duration to 16 or
20 24 weeks did not alter the safety profile or
21 increase the rate of adverse events. When
22 administered with peg interferon and ribavirin,

1 sofosbuvir did not increase the incidence or
2 severity of interferon-associated side effects or
3 hematologic effects.

4 These were successfully managed with peg
5 interferon and/or ribavirin dose reductions. And
6 98 percent of patients completed treatment with
7 sofosbuvir plus peg interferon and ribavirin, a
8 proportion similar to that in the sofosbuvir plus
9 ribavirin treatment arms, suggesting that the short
10 12-week treatment duration is tolerable and allows
11 for the successful management of side effects.

12 Patients enrolled in the phase 3 trials
13 comprising the primary safety population had
14 baseline characteristics similar to the U.S.
15 hepatitis C population. Twenty percent had
16 cirrhosis and women, blacks, older individuals, and
17 obese patients were well-represented.

18 The safety data from the phase 3 trials and
19 the 61 patients awaiting liver transplant support
20 the generalizability of the safety of sofosbuvir.

21 Dr. McHutchison will now return to provide
22 the benefit-risk assessment for sofosbuvir.

Sponsor Presentation - John McHutchison

DR. MCHUTCHISON: Sofosbuvir is the first HCV-specific nucleotide polymerase inhibitor that has demonstrated potent, broad antiviral activity, that's allowed the successful treatment of most patients infected with all hepatitis C genotypes, including several groups of patients for which there are no current treatment options.

The program has demonstrated that sofosbuvir-containing regimens that we have studied have a favorable benefit-risk. These treatment regimens represent a significant advance for patients with chronic hepatitis C in two major ways.

Firstly, sofosbuvir is a single tablet, shown in yellow in the palm, next to the white ribavirin capsules. It's the first all-oral therapy for patients with hepatitis C genotypes 2 or 3 infection, many of whom previously failed treatment or could not be treated.

Secondly, sofosbuvir, in combination with peg interferon and ribavirin provides a shorter,

1 simpler, interferon-limiting regimen for those with
2 hepatitis C genotypes 1, 4, 5, and 6 infection.

3 Sofosbuvir is administered once daily and
4 has few restrictions. It can be taken with or
5 without food with most other medications and it
6 requires no dose adjustments in most circumstances,
7 which will be commonly encountered in clinical
8 practice.

9 The drug's unique mechanism of action allows
10 it to be used effectively for patients with chronic
11 hepatitis C infection of all viral genotypes, with
12 minimal risk for the development and emergence of
13 viral resistance. We have shown in the trials that
14 sofosbuvir provides a simpler, safer, and more
15 effective regimen for these patients.

16 Sofosbuvir-based regimens have demonstrated
17 high sustained response rates. The treatment
18 duration is short, the risk of resistance is low,
19 and the safety and tolerability profile is
20 excellent. Efficacy and safety are importantly
21 maintained in those patients with the greatest
22 need, including the pre-transplant patients.

1 The compassionate use of sofosbuvir in
2 critically ill patients with severe recurrent
3 hepatitis following transplantation also highlights
4 another potential utility of the drug. Given the
5 safety and efficacy profile demonstrated today,
6 there are several potential benefits for a
7 sofosbuvir-containing regimen.

8 The availability of a safer, simpler, and
9 shorter treatment regimen will be welcomed by
10 patients and practitioners alike. Many patients
11 are either ineligible or unwilling to undergo
12 current therapy with 6 to 12 months of an
13 interferon-containing regimen. If and when more
14 patients are successfully treated with sofosbuvir,
15 there should eventually be a measurable and
16 substantial reduction in the rates of progression
17 of patients to advanced disease and a decrease in
18 the need for liver transplantation.

19 With a reduction in the burden and
20 prevalence of the disease, there should also come
21 over time a reduction in the number of new HCV
22 infections, especially among high-risk populations.

1 And finally, the greatest impact in the short term
2 could be observed in patients with hepatitis C who
3 are awaiting liver transplantation.

4 For these patients, suppression of viral
5 replication with a sofosbuvir-containing regimen
6 prior to transplantation could significantly reduce
7 the rate of reinfection of the new liver, which now
8 occurs universally.

9 HCV infection post-transplantation is
10 associated with rapid disease progression, high
11 rates of cirrhosis, diminished graft survival,
12 sometimes requires re-transplantation, and as a
13 consequence, increased morbidity and mortality.
14 Intervention with sofosbuvir could significantly
15 alter the outcomes and lives of these patients.

16 Now, the known risks associated with
17 sofosbuvir are those associated with peg interferon
18 and ribavirin. And after nearly two decades of
19 using these drugs, these risks are well understood.

20 The ribavirin label includes a boxed warning
21 regarding teratogenic effects, and therefore
22 requires care to avoid pregnancy in female patients

1 and female partners of male patients. And anemia
2 is the most common laboratory abnormality observed
3 during therapy, as you've heard today. Other
4 adverse events such as fatigue and insomnia are
5 also commonly associated with ribavirin.

6 The label provides guidance for dose
7 reductions required for the management of anemia
8 and other adverse events. The interferon label
9 also contains a boxed warning for potential serious
10 events that include neuropsychiatric, pulmonary,
11 autoimmune, and infectious events.

12 Interferon should be withdrawn for
13 persisting or worsening signs or symptoms
14 indicative of these serious conditions. The label
15 also provides guidance for dose reductions required
16 for the management of the common hematological
17 toxicities and other common adverse events
18 associated with interferon, such as flu-like
19 symptoms.

20 Now, with any new drug, there are questions
21 that remain to be answered. We recognize the need
22 to further study the use of sofosbuvir-containing

1 regimens in genotype 1 patients, particularly those
2 who have failed treatment. These patients were not
3 specifically included in our phase 3 program.

4 Finally, while we have a compassionate use
5 program for the use of sofosbuvir, this is limited
6 to patients with severe recurrence following liver
7 transplantation. And we do not have adequate data
8 on those who are critically ill or those with the
9 most severe forms of renal and liver dysfunction.
10 We will address ongoing needs in future studies.

11 Gilead is developing a fixed-dose
12 combination of sofosbuvir with an NS5A inhibitor,
13 ledipasvir, for use as an all-oral regimen in all
14 populations of genotype 1 patients, including
15 treatment-experienced patients that have failed
16 protease inhibitors.

17 A second randomized controlled trial is also
18 underway to evaluate in a head-to-head fashion the
19 three different regimens for patients with
20 genotype 3 infection that you heard about today, 16
21 and 24 weeks of sofosbuvir and ribavirin versus a
22 12-week regimen with interferon.

1 We also have ongoing studies in patients
2 with advanced liver disease, those who are
3 coinfected with HIV, those with the most severe
4 form of renal impairment, and other populations.
5 And we will also initiate studies in children
6 infected with hepatitis C with an approach that
7 will include adolescents first.

8 Now, the availability of sofosbuvir will
9 provide clinicians with a new treatment option for
10 patients with chronic hepatitis C infection. The
11 benefits will include high sustained response rates
12 with shorter treatment durations. The sustained
13 response rates in patients infected with
14 genotypes 1 to 6 are the highest reported to date
15 in phase 3 programs.

16 To date, no resistance associated with
17 clinical breakthrough has been observed in the
18 phase 3 programs, and the regimens we are proposing
19 are safe without significant untoward risks that
20 add to the burden of what's usually observed or
21 encountered when using peg interferon and
22 ribavirin.

1 Sofosbuvir also provides the first treatment
2 option for many patients who currently have none,
3 and these include patients who have failed prior
4 therapies or who are ineligible or intolerant to
5 therapies.

6 For all these reasons, we propose that
7 sofosbuvir be made available with a broad
8 indication that allows its use in combination with
9 other agents for the treatment of chronic
10 hepatitis C. Sofosbuvir provides patients with a
11 safe, effective, and simple treatment option that
12 has the potential to become the backbone for
13 future, highly effective, and safe, all-oral
14 regimens for patients with this disease. And today
15 is the first step towards realizing that potential.

16 We sincerely thank the patients and the
17 investigators who participated in the sofosbuvir
18 development program. Thank you.

19 **Clarifying Questions**

20 DR. MURATA: Thank you to the sponsor team
21 for those presentations.

22 Now, are there any clarifying questions for

1 the sponsor? Please remember to state your name
2 for the record before you speak. If you can,
3 please direct questions to a specific presenter.
4 And just as a clarification to the sponsor, if I
5 may ask that the designated responder or responders
6 come back up to the podium as necessary to address
7 those questions.

8 Mr. Raymond?

9 MR. RAYMOND: Thank you. Daniel Raymond. I
10 wondered if you could expand on any kind of safety
11 signals in the overall kind of patient-numbering
12 characteristics for early access, compassionate
13 use.

14 In the original submission, you'd mentioned
15 only 29 patients as of February 15th had received
16 at least one dose. I think you said something
17 about only in a transplant setting, which seems
18 rather limited for a compassionate use program.

19 So I'm wondering, since February 15th, how
20 has that program evolved? How many patients have
21 been treated? What were the requirements, and if
22 there were any particular safety signals?

1 DR. MCHUTCHISON: In the compassionate use
2 program, separate from the pre-transplant studies.
3 So I'll ask Dr. Symonds to give us an outline of
4 where we are currently with the compassionate use
5 program in terms of the numbers and what that looks
6 like, that program, and then also Dr. Brainard to
7 comment briefly on the safety in the compassionate
8 use program.

9 Now, it's a compassionate use program, so
10 one doesn't collect safety in any way, shape, or
11 form similar to what is collected in these trials,
12 so that's the caveat.

13 DR. SYMONDS: Bill Symonds, Gilead Sciences.
14 Our compassionate use program has been running for
15 a little over a year. We take individual requests
16 from investigators in the United States as well as
17 from other countries around the world.

18 The program is targeted towards patients
19 with severe HCV recurrence post-transplantation,
20 including those patients for the fibrosing
21 cholestatic hepatitis, which is one of the most
22 severe forms of recurrence.

1 We provide sofosbuvir at 400 milligrams per
2 day to be used without ribavirin or pegylated
3 interferon. At the time of the NDA submission, we
4 had data on 29 patients which were included in that
5 program, but now we're up into the hundreds of
6 patients who have been treated and receive
7 sofosbuvir in that.

8 I can't summarize the outcome of those
9 patients today, but we are actively working with
10 the investigators and ask them to send us frequent
11 updates on the patients, laboratory findings, and
12 also on the clinical status.

13 I can share with you one quick summary of
14 that data based on the first 45 actually who have
15 been enrolled in that program. When we simply
16 asked the investigators, "Is the patient improved?
17 Are they stable? Or have they declined since going
18 on sofosbuvir?" And we ask for this quarterly.

19 In these patients, in the first 45, 71 of
20 the 45 were considered improved by the
21 investigator, 13 percent were stable, and 16
22 percent had either declined or were deceased at

1 that point in time.

2 We'll continue to track these patients and
3 update these numbers over time, but so far, the
4 experience has been relatively positive for the
5 patients who have participated in the program.

6 DR. MCHUTCHISON: Dr. Brainard, safety?
7 This is a poster at AASLD next week, actually, this
8 program.

9 DR. BRAINARD: Diana Brainard, Gilead
10 Sciences. So as Dr. Symonds mentioned, the
11 majority of patients did have a clinical
12 improvement. We didn't collect safety information
13 in a standardized way, but left it to the
14 investigator to submit updates to us and laboratory
15 results, which we requested.

16 Overall, sofosbuvir plus ribavirin or
17 sofosbuvir plus pegylated interferon and ribavirin
18 were well-tolerated in these patients. And we
19 weren't able to detect any specific sofosbuvir
20 safety signal across the patients in the
21 compassionate use study, including a very small
22 number of patients with severe renal impairment on

1 or off dialysis.

2 MR. RAYMOND: Thank you. Daniel Raymond.
3 And just to clarify, outside of the clinical trials
4 and this post-transplant compassionate use, there
5 were no other earlier expanded access programs?

6 DR. MCHUTCHISON: No. It's a compassionate
7 use program, pre-transplant study. Another study
8 is in patients with advanced liver disease that
9 weren't included in the NDA and we haven't
10 discussed today, post-transplant, decompensated
11 liver disease. But they're ongoing studies. We
12 have no data currently.

13 DR. MURATA: Dr. Van Dyke?

14 DR. VAN DYKE: Yes. Russell Van Dyke. I
15 was surprised that viral resistance was so
16 infrequent among subjects that had treatment
17 failure. I'd be interested in hearing more about
18 that. In particular, in the ELECTRON study, there
19 were 10 subjects who receive monotherapy, and 4 of
20 those failed. Only one were you able to identify a
21 resistance mutation.

22 So I'm wondering if you have any thoughts on

1 that. I assume you looked at adherence, you looked
2 at bioavailability of the drug. I mean, do you
3 have any clues what's going on with those subjects?

4 DR. MCHUTCHISON: So I'll ask Dr. Symonds to
5 discuss some of the clinical information related
6 to -- to answer your question, also the case in
7 question, a few more details about the case in
8 question; Dr. Svarovskaia, also from clinical
9 virology, to provide some further comments from a
10 virologic perspective.

11 DR. SYMONDS: Yes. There were 10 patients
12 who received monotherapy in the ELECTRON trial.
13 They comprised a group of genotype 2 and genotype 3
14 patients. Four patients did fail to achieve an
15 SVR. It's interesting. If you go back and look at
16 those patients because the early viral kinetics
17 were similar. We saw no differences between those
18 monotherapy patients in the ones who achieved an
19 SVR and those who did not. So we saw no
20 differences there. Compliance with the drug
21 therapy was very, very good. And then 1 of 4
22 actually had the S282T that was a genotype 2 B

1 patient.

2 If I could have the viral kinetics on the
3 one patient who failed, please, from the ELECTRON
4 trial.

5 The viral kinetics are shown here. And this
6 patient actually was treated with sofosbuvir
7 monotherapy, developed the S282T, which reverted
8 back to wild type. The patient was subsequently
9 retreated with sofosbuvir plus ribavirin and was
10 subsequently cured after a 12-week course, after
11 receiving sofosbuvir just with the addition of
12 ribavirin the second time.

13 DR. MCHUTCHISON: Jenny?

14 DR. SVAROVSKAIA: There are multiple factors
15 for the lack of resistance observed in our phase 2
16 and phase 3 studies. And I forgot to introduce
17 myself. My name is Jenny Svarovskaia, Gilead
18 Sciences.

19 Sofosbuvir binds to a highly conservative
20 site of NS5B polymerase. S282T is the only
21 mutation identified in in vitro selection that
22 confer phenotypic shift to sofosbuvir. And it's

1 associated with less than 20-fold resistance to
2 sofosbuvir.

3 S282T results in severe reduction of
4 replication capacity. And among all the subjects
5 we sequenced at baseline, we did not detect S282T
6 by population or by deep sequencing.

7 DR. MURATA: Dr. Follmann?

8 DR. FOLLMANN: Yes. I had a comment and
9 then a question. The comment was, I'd be curious
10 to see the success rates 36 weeks post-
11 randomization in the FISSION trial, so that's a
12 comparison that's common to the two groups relative
13 to randomization.

14 The question I have has to do with the lack
15 of a control group for the NEUTRINO trial. So the
16 FISSION trial did compare sofosbuvir plus
17 combination with standard of care. NEUTRINO
18 didn't. NEUTRINO is for genotypes 1, 4, 5, 6,
19 which is the vast majority of people with HCV. And
20 it's a one-arm study, which is kind of unusual to
21 be the sole body of evidence for approval of a
22 drug.

1 So I'm sort of thinking about that as an
2 issue. What's the justification, really, for doing
3 a one-arm study for such an important population?

4 DR. MCHUTCHISON: So I'll ask Dr. Symonds to
5 address both questions. Firstly, the answer to the
6 time point, at a common time point. We have that
7 data; and secondly, our clinical rationale for the
8 single-arm NEUTRINO study.

9 DR. SYMONDS: In the FISSION trial, the
10 patients continued to be followed at post-study
11 time points, out to week 24 post-study in both
12 arms. So we can go back and look at those. And if
13 you look at the red numbers, so for sofosbuvir plus
14 ribavirin, the red numbers are SVR24, 65.6 percent,
15 which compares to 66.7 percent in pegylated
16 interferon, and ribavirin 12 weeks after that. So
17 it's a similar rate if you look at the same time
18 point for both arms.

19 Now, if I can move on to the NEUTRINO
20 question, the NEUTRINO study was designed as a
21 single-arm trial based mainly on clinical
22 considerations. We have seen high efficacy with

1 this same regimen in the ATOMIC trial, greater than
2 90 percent in those patients.

3 We also wanted to include genotypes 4, 5,
4 and 6 in that trial, and the PI-based regimens
5 aren't indicated for those genotypes, so we
6 couldn't have included them in the trial. If we
7 had a protease inhibitor-based control arm in
8 there, the protease inhibitors have a number of
9 drug interactions, which cause a lot of
10 complications in terms of the patients that can
11 come in, what drugs they're able to take when they
12 come in the trial.

13 Sofosbuvir does not have that in terms of
14 its drug-drug interaction profile. Given the
15 response-guided therapies as well with the protease
16 inhibitors, it's very difficult to conduct a trial
17 like that, and we certainly couldn't have blinded
18 it.

19 We also had feedback from our investigators
20 and physicians that it'd be very difficult to
21 recruit a trial with a PI-based control because the
22 patients all knew about the data from the ATOMIC

1 trial and would probably be unwilling to come in
2 and do that.

3 So it made us go down the path of choosing a
4 single-arm trial. We thus decided to use a
5 historical control to have some comparison in the
6 study.

7 DR. FOLLMANN: The telaprevir trial was able
8 to successfully recruit, and compare, and so on,
9 and so on. So it seems like, in principle, it
10 could have been done. It would have been more
11 difficult to do, more dropout, more restrictive
12 inclusion criteria, et cetera, I guess.

13 DR. MCHUTCHISON: Yes. It would have been
14 possible but difficult to do. And the field was
15 moving very rapidly at this stage. And as
16 Dr. Symonds had said, we had very high response
17 rates in a very short duration, albeit the caveat
18 was, it was in phase 2.

19 Perhaps I could ask Dr. Jacobson as a
20 clinician to recall this period of time and his
21 views on potentially enrolling such a study. It's
22 an important point.

1 DR. JACOBSON: Good morning. Ira Jacobson,
2 Weill Cornell Medical College. I have received
3 consulting honoraria for my time. I have no
4 financial interest in the company nor in the
5 outcome of this meeting.

6 The NEUTRINO trial was formulated at a time
7 when clinicians were already aware of the
8 arduousness, if you will, of protease inhibitor-
9 based therapy, both from the pivotal trials and
10 from our early clinical experience. The duration
11 of therapy is part of that consideration along with
12 the side effect profile.

13 We had a very strong indication that what
14 became the NEUTRINO regimen, based on the ATOMIC
15 study, was very well tolerated and led to
16 compellingly high SVR rates. Patients were aware
17 of this. They were also aware of ongoing studies
18 or studies being initiated with oral antiviral
19 regimens. And by the time the NEUTRINO study was
20 begun or even conceived of, many patients were
21 already unwilling to go on interferon-based
22 protease inhibitor-containing therapy.

1 Indeed, a common observation amongst
2 investigators who participated in NEUTRINO is that
3 most of the patients who jumped into the
4 study -- and the study did enroll remarkably
5 quickly -- were patients who had historically and
6 consistently declared that they were not interested
7 in taking interferon-based therapy.

8 DR. MURATA: Dr. Friedman?

9 DR. FRIEDMAN: Lawrence Friedman. Two quick
10 questions. One is, clinicians are conditioned to
11 checking an HCV RNA level at four weeks. And I
12 wonder whether the detectability of HCV RNA at
13 four weeks has any significance whatsoever with
14 sofosbuvir-containing regimens.

15 My other question is, do you have enough
16 data to comment on whether ribavirin dose reduction
17 has any effect on SVR?

18 DR. MCHUTCHISON: So I'll ask Dr. Symonds
19 again to answer both questions. But we've looked
20 fairly carefully at HCV RNA at week 4. The vast
21 majority of people are negative at week 4. We can
22 show you its positive predictive value. And then,

1 Bill, ribavirin dose reductions and their lack of
2 effect on sustained response.

3 DR. SYMONDS: Bill Symonds, Gilead Sciences.
4 So in terms of the utility of a week 4 HCV RNA
5 result to determine eventual outcome in a patient,
6 in the overall program, if we look at week 4 across
7 the studies in genotype 1, 2, and 3, and then in
8 genotype 3 in VALENCE, in genotype 1 in particular,
9 only 4 patients had quantifiable HCV RNA at the
10 week 4 time point. One of 4 of those patients
11 achieved an SVR as well, who did not have
12 undetectable HCV RNA.

13 So genotype 2 and 3 VALENCE excluded, there
14 were only 7 patients across the trial who had
15 quantifiable HCV RNA, and in the POSITRON trial,
16 14 percent of those achieved an SVR.

17 In VALENCE, only three patients out of the
18 entire sample size of 250 had quantifiable HCV RNA.
19 So very low numbers of patients who did not have
20 HCV RNA below the lower limit of quantification and
21 small numbers of those who did. So it's difficult
22 to say if these rates really translate into a

1 significant decline in SVR, but they do appear to
2 be lower in these very small numbers of patients.

3 When we've looked at ribavirin -- we've
4 actually done two studies where we looked at
5 ribavirin, once in genotype 1 with a 600-milligram
6 once a day, and it appeared to be a little bit
7 worse than weight-based dosing in genotype 1
8 patients who received sofosbuvir plus ribavirin for
9 24 weeks.

10 We've also done a study in genotype 3
11 patients where we gave 800 milligrams, or split
12 dosing, but 800 milligrams with sofosbuvir in the
13 ELECTRON trial in just genotype 3 patients. Sixty
14 percent of those patients responded. So the two
15 times we've tried to reduce the ribavirin dose,
16 we've seen lower rates of efficacy.

17 DR. FRIEDMAN: And adherence?

18 DR. SYMONDS: We also have gone back and
19 looked at adherence in terms of how patients have
20 taken their ribavirin. And in general, when you
21 look at the dose reductions of patients across
22 trials and compare that with the patient's eventual

1 outcomes, SVR12 or not -- that's shown here for
2 genotype 2 and 3 patients across the phase 3
3 program -- what you really notice is that the
4 patients who have ribavirin dose reductions or
5 interruptions typically have numerically higher SVR
6 rates. This probably correlates with the patients
7 getting higher milligram per kilogram doses of
8 ribavirin. So those patients do, do a little bit
9 better. We also see the same trend if you look at
10 anemia. Patients who have anemia tend to have
11 slightly higher SVR rates than those who do not.

12 We've also looked at this in genotype 1 with
13 the NEUTRINO regimen. And on this slide, it's a
14 little bit complicated, but the line at the top are
15 the patients who did not have any reduction in
16 their ribavirin or peg, so no dose interruptions
17 overall, SVR12 rate of 92 percent in those 63
18 patients.

19 Peg dose reductions or interruptions are on
20 the next line, the same SVR rate; ribavirin-only
21 dose reductions, no effect on the SVR; and then
22 patients who have modified both peg and ribavirin

1 had a similar SVR rate as well to those who did
2 not.

3 DR. MURATA: Dr. Giordano?

4 DR. GIORDANO: Tom Giordano. Question on
5 the pre-transplant population that was studied. I
6 guess my question boils down to, what proportion of
7 the patients in that protocol were actually on
8 treatment still at the time of transplant? Because
9 it sounds like there was a 24-week stopping point
10 initially that was extended to 48 weeks. And so
11 did the fact that the person was either on or off
12 therapy at transplant predict their eventual
13 outcome post-transplant as opposed to the 30-day
14 analysis that you presented?

15 DR. MCHUTCHISON: Dr. Symonds? It's a
16 complicated study and flow to follow, but
17 Dr. Symonds will take you through it again.

18 DR. SYMONDS: I'm afraid it might be a
19 complicated answer as well. So basically, before
20 transplantation in that study, you could take
21 24 weeks of therapy. If you got to that point
22 before transplantation, prior to the amendment, you

1 had to stop.

2 Of the patients who stopped, 73 percent of
3 those patients relapsed. According to the
4 protocol, once we identified that the patients who
5 are relapsing after stopping did not have
6 resistance, we were able to put the patients back
7 on and subsequently amended the protocol to both
8 increase the duration to 48 weeks. And it also
9 allowed us to put the patients who had stopped back
10 on to therapy as well in the pre-transplant period.

11 So we recognized very early it was very
12 important to be less than LLOQ at the time of
13 transplantation. So we made efforts in the
14 protocol to make sure that we could give the
15 patients the greatest likelihood of remaining below
16 the lower limit of quantification at the time of
17 transplant.

18 The data I showed you is based upon further
19 analysis, where we tried to dig deeper and find a
20 more sensitive measure of determining who these
21 patients really are because the TND measure
22 actually gives us a much better idea of who these

1 patients are who have a higher likelihood of not
2 recurring post-therapy.

3 I would note, I would say as well, that this
4 is the only population where TND has mattered
5 compared to LLOQ. We've used LLOQ everywhere else
6 and haven't seen a difference. But in this
7 population, TND does appear to be important.

8 DR. GIORDANO: So essentially, all the
9 patients were on therapy at the time of the
10 transplant?

11 DR. SYMONDS: No. No. We actually had some
12 patients who had come off therapy and finished
13 24 weeks, or I think in maybe one case, 48 weeks,
14 and remained undetectable. So basically, they were
15 probably an SVR before transplant and then were
16 transplanted.

17 DR. MCHUTCHISON: So it was somewhat
18 difficult to judge the timing of transplantation,
19 which is why we chose this population. But certain
20 people went to transplantation very early, perhaps
21 earlier than the drug had time to have effect. And
22 then they relapsed and got transplanted shortly

1 thereafter. We couldn't modify the time of
2 transplantation.

3 So anybody who was positive at the time of
4 the transplantation, of course they had recurrence.
5 We haven't counted them, but they recurred.

6 DR. MURATA: Dr. Alcendor?

7 DR. ALCENDOR: Yes. I noticed there was no
8 virology presentation made. Also, drug-drug
9 interactions, I really haven't heard enough that,
10 and I'd like to hear more, specifically the classes
11 of drugs that were looked at in terms of drug-drug
12 interactions.

13 Now, in the immunosuppression regimens used
14 in the transplantations, I'd like to know if
15 seropositive donor to seropositive recipient
16 differed in terms of outcome when the donor was
17 positive or negative for HCV, and the kind of
18 immunosuppression, whether it be in cyclosporine or
19 tacrolimus. Also, in the presence of ganciclovir
20 prophylaxis, do you see a difference for some of
21 those transplantations?

22 Finally, in the patient recruitment, I

1 notice only in the NEUTRINO that African-Americans
2 and Hispanics were included in a significant way.
3 I'd like you to explain why that is.

4 DR. MCHUTCHISON: I'll see if I can answer
5 all your questions. So firstly, Dr. Symonds will
6 talk to you about the immunosuppressive regimens,
7 but we did not include people who weren't
8 transplanted with hepatitis C positive organs. So
9 that excludes that.

10 Secondly, 95 percent of African-Americans
11 are infected with genotype 1, so there's a
12 preponderance of African-American in the NEUTRINO
13 and SPARE trials, and Dr. Symonds will go into that
14 further.

15 Then Dr. Kearney, we'll ask, from clinical
16 pharmacology, to give you a broader overview of the
17 drug-drug interaction program because we haven't
18 discussed it in great detail. So those two things
19 first, please, Bill.

20 DR. SYMONDS: Just in terms of the
21 representation of African-Americans, I'll take that
22 one first, maybe in reverse order of your

1 questions. So we have looked across the program,
2 and as Dr. McHutchison pointed out, they do have
3 mainly genotype 1.

4 In the program, 186 patients who are
5 African-American have been treated. A hundred of
6 them received a triple combination, 86 of them
7 received sofosbuvir plus ribavirin. This includes
8 50 patients from the NIAID-sponsored SPARE trial,
9 where they actually ran that study in inner city
10 Washington, D.C.

11 So we have recognized early on in the
12 program that we didn't have as high numbers of
13 blacks and African-Americans. So one thing I'll
14 point out that we did, in the conduct of the
15 NEUTRINO trial, we had a cap on each center in
16 terms of the number of patients that they could
17 enroll in the trial. That did not apply to
18 African-American patients.

19 So if a center was able to enroll more
20 African-American patients, they could have more
21 than their allotted share overall. So we did that
22 as a way to encourage them to recruit more

1 patients. And we were successful in NEUTRINO and
2 actually got the number up to 17 percent there.

3 Actually, if you look at the two trials that
4 were the latest trials run in genotype 1, that was
5 the SPARE trial and NEUTRINO, approximately
6 27 percent of those populations were African-
7 American in those trials. Fourteen percent were
8 Hispanic in the NEUTRINO trial as well.

9 In terms of how those patients did,
10 77 percent of the African-American patients
11 achieved an SVR. And if we look at here, at the
12 influence of race on results from NEUTRINO, it's
13 broken down here that blacks versus non-black
14 patients, we don't see a difference in the response
15 right there. We see a similar thing in genotype 2,
16 although there are much smaller numbers in
17 genotypes 2 and 3 and, in genotype 3, very small
18 numbers, only 9 patients, but that the patients did
19 fairly well.

20 Yes. In terms of the immunosuppressive
21 regimen in the pre-transplant study, it was
22 standardized across centers. We didn't want high-

1 dose steroids to be used after. It mainly focused
2 on tacrolimus in combination with a couple other
3 compounds.

4 I can get you the exact regimen after the
5 break, which was used, but it was standardized
6 across all the centers, so we tried to remove that
7 variable. And it's actually very difficult to
8 standardize that across centers as well, as you can
9 imagine.

10 DR. KEARNEY: Brian Kearney, Gilead
11 Sciences. We have done a comprehensive clinical
12 pharmacology program. I think the short answer
13 regarding drug interactions is a nuc. It's not
14 subject to a lot of drug interactions. We followed
15 FDA guidance and international regulatory guidance
16 in terms of assessing the drug-drug interaction
17 potential.

18 The compound is not metabolized to any
19 extent by cytochrome P450s or UGT enzymes. We have
20 evaluated drug-drug interactions to support various
21 aspects of the program. This includes our HIV
22 coinfection population. We have looked at a

1 variety of antiretrovirals.

2 Then we've also tried to get a sense of
3 drug-drug interaction potential. We conducted
4 population PK analysis in 986 patients in the
5 phase 3 study and looked where there was any
6 evidence of an impact of any of these medications
7 on sofosbuvir pharmacokinetics, and we've not found
8 any impact.

9 The kinetics of sofosbuvir are equivalent in
10 patients taking these agents versus not taking
11 these agents. And these represent the most common
12 medications coadministered in patients in the phase
13 3 program.

14 As is reflected in the primary presentation,
15 we do prospectively recommend not using certain
16 agents with sofosbuvir, and this is because
17 sofosbuvir is a PGP substrate. These are potent
18 inducers of PXR, and therefore could reduce the
19 oral bioavailability of sofosbuvir.

20 So this is based on our strong in vitro
21 program, really trying to avoid suboptimal exposure
22 of the drug.

1 DR. MURATA: Dr. Ghany?

2 DR. GHANY: Yes. I have some questions
3 about the pre-transplant study, probably directed
4 to Dr. Symonds.

5 Could you just expand a little bit and tell
6 us how quickly patients became negative while on
7 treatment? And were the kinetics of oral decline
8 different in this population compared to those with
9 stable disease, without cirrhosis?

10 The second question is, what was the highest
11 MELD score of a patient to receive this drug? And
12 were there any toxicity concerns in patients with
13 more advanced disease?

14 DR. MCHUTCHISON: So I'll ask Dr. Symonds to
15 show the kinetics in the patients in that study,
16 perhaps compare them to the kinetics in their other
17 study, and then Dr. Brainard to provide an update
18 in the safety split by the severity of liver
19 disease in the 61 patients.

20 DR. SYMONDS: Bill Symonds, Gilead Sciences.
21 The highest MELD was 14 in this study. So in terms
22 of HCV RNA kinetics, the kinetics were similar in

1 these patients to what we see in other populations.

2 Here, I have the kinetics actually broken
3 down by Childs A and Childs B in the overall
4 population, so of the 61 patients, not the ones who
5 we have for post-transplant data.

6 The CPT A's are in green. The B's are in
7 orange. And you really don't see a difference in
8 those in terms of median declines over time. We
9 can look more closely though at week 1, 2, and 4 at
10 these patients and look at the green bars, are
11 patients who were less than LLOQ but above target
12 detected, and then target not detected are in
13 orange. And you really don't see a difference in
14 the Childs A and Childs B patients when you look
15 over time here at the early viral kinetics.

16 DR. BRAINARD: So the safety in the pre-
17 transplant study, we looked at the overall safety
18 and then the safety in Childs Class A patients,
19 which are approximately two-thirds of the study
20 population and, in Childs Class B patients, about
21 one-third of the population. And we didn't see any
22 differences in the safety of sofosbuvir plus

1 ribavirin by Childs class.

2 There was a slight numeric increase in the
3 serious adverse events, but because of the small
4 numbers, this just represents a discrepancy in one
5 additional serious adverse event.

6 Again, as I mentioned in the core
7 presentation, these patients overall had higher
8 numbers of serious adverse events and grade 3 or
9 higher adverse events that were reflective of their
10 more advanced liver disease. We weren't able to
11 detect any specific signal related to sofosbuvir
12 being less well-tolerated in these patients.

13 DR. GHANY: So do you think they can go into
14 patients with higher MELD scores? Because the
15 population that was studied seems to be well
16 compensated.

17 DR. MCHUTCHISON: So being the initial foray
18 into the field, this was carefully selected, and
19 the patients were collected because they had less
20 severe liver disease. They had the Milan exception
21 criteria. And they would be transplanted more
22 expeditiously, which allows us to test the

1 hypothesis that we could prevent recurrence. That
2 was the hypothesis of the trial.

3 Dr. Symonds can talk about another ongoing
4 study -- we have no data today -- looking at people
5 with more advanced liver disease. Aside from the
6 compassionate use program, we don't have good data,
7 but we will from the trial that Dr. Symonds will
8 describe.

9 DR. SYMONDS: We currently have an ongoing
10 trial in genotypes 1 through 6 in patients with
11 decompensated liver disease, as shown here on this
12 slide. The trial is fully enrolled, and the
13 patients are currently on therapy.

14 This trial is looking at 48 weeks of
15 sofosbuvir, 400 milligrams, with ribavirin.
16 There's also an observation cohort in there who
17 will switch over to active therapy after six
18 months. You note that we're doing portal pressures
19 at baseline, also at week 24 and 48 in these
20 patients.

21 The endpoint here, aside from looking at SVR
22 in these patients, is really trying to see if we

1 can see clinical benefits of the therapy in these
2 fairly sick patients. So if we're monitoring this
3 over time, the patients are all on study now.

4 It is a 48-week treatment, so it's going to
5 take a while, so probably sometime next year, we'll
6 have the data from this trial.

7 DR. MCHUTCHISON: But to answer your
8 question, Dr. Ghany, we don't know whether the
9 safety profile will be the same in patients with
10 more advanced liver disease. From our
11 compassionate use program, we haven't seen
12 anything. The data is collected in a different
13 fashion. The drug is very well-behaved.

14 We are hopeful that the drug's safety
15 profile will look the same in patients with more
16 advanced liver disease. We haven't collected that
17 information yet, to a great degree.

18 DR. MURATA: Dr. Korman?

19 DR. KORMAN: I have a question about the
20 adverse event CK elevation in the FISSION trial,
21 which was 2 percent, and in the NEUTRINO trial, was
22 less than 1 percent, I have a suggestion that the

1 physicist who's been naming your trials actually
2 use Boson for the next one, since it won the Nobel
3 Prize. You probably have already thought of it,
4 but just in case.

5 (Laughter.)

6 DR. MCHUTCHISON: It has been discussed.

7 (Laughter.)

8 DR. MCHUTCHISON: Dr. Brainard will discuss
9 the isolated asymptomatic increase in CK
10 elevations.

11 DR. BRAINARD: So we assessed creatine
12 kinase levels in the FISSION and in the NEUTRINO
13 studies. May I have the table of graded laboratory
14 abnormalities, please?

15 Across the arms of these studies, a total of
16 7 percent of patients in the sofosbuvir plus
17 ribavirin treatment arm of the FISSION study,
18 4 percent in the peg interferon and ribavirin
19 treatment arm of the FISSION study, and 3 percent
20 of patients in the sofosbuvir plus peg interferon
21 and ribavirin NEUTRINO study experienced graded
22 creatinine kinase elevations.

1 Most of these elevations were mild to
2 moderate or grade 1 or 2 in severity. These
3 elevations tended to be asymptomatic and associated
4 with increases in exercise or activity.

5 In the FISSION study, these are the five
6 patients with grade 3 or higher creatine kinase
7 elevations. The plots are there, creatine kinase
8 over time. And the asterisks represent the
9 elevations, and the asterisks represent
10 associations with increased activity and exercise.

11 DR. KORMAN: The patients were asymptomatic,
12 all the ones with CKs of 1,000 and 4,000?

13 DR. BRAINARD: May I have that slide back,
14 please? And now I'll take the next slide.

15 So all of these patients did not have
16 systems temporally associated with the elevation in
17 creatine kinase. The third patient to the right
18 with the highest creatine kinase elevation in the
19 FISSION study did discontinue treatment, as is
20 shown here, due to the creatine kinase elevation.

21 This was a male patient with cirrhosis who
22 was a manual laborer, and prior to the week 3

1 visit, had requested additional work because he was
2 feeling good and wanted to make additional money.

3 When he came into the visit, his creatine
4 kinase was in the 8,000s. He came back for a
5 repeat visit after this initial result was
6 obtained, and because his creatine kinase was still
7 elevated, he was discontinued from treatment.

8 This is that single patient's creatine
9 kinase over time. You can see he was discontinued
10 from treatment shortly after the week 4 visit.
11 During follow-up at the 24-week post-treatment
12 visit, he had another elevation in creatine kinase
13 six months after stopping study drugs.

14 This patient was evaluated by a
15 rheumatologist at that time point and underwent a
16 muscle biopsy as well as additional evaluations for
17 myopathy or autoimmune disease. All of these were
18 negative, but the muscle biopsy did show an
19 idiopathic myopathy.

20 DR. MURATA: Dr. Daskalakis?

21 DR. DASKALAKIS: So one really, I think,
22 easy question and then one probably more complex,

1 which is, I know that we've heard about some
2 drug-drug interactions, but I'm curious if -- I
3 imagine that there are none postulated for
4 cobicistat and elvitegravir, but I'd love a comment
5 on that. So that's question 1.

6 The second question, I think we're all
7 focusing on this pre-transplant population because
8 they're pretty interesting from the perspective of
9 history. And I see that 75 percent of them have a
10 prior history of being treated for HCV.

11 Do you have a break-down of how they were
12 treated and how that treatment interacted with
13 their post-transplant virologic response?

14 DR. MCHUTCHISON: So I'll ask Dr. Kearney to
15 make a brief comment related to the boosting agent
16 cobicistat and elvitegravir, and then Dr. Symonds
17 to talk about prior treatment characteristics in
18 the pre-transplant population.

19 DR. KEARNEY: We would not expect a
20 significant interaction with either boosting
21 ritonavir or cobicistat. And we have studied
22 sofosbuvir with ritonavir-boosted regimens as part

1 of our coinfection program, and there's no dose
2 regimen for either agent.

3 DR. SYMONDS: In terms of the pre-transplant
4 question, first I can come back and answer the
5 original question. The post-transplant
6 immunosuppressive regimen was a seven-day steroid
7 taper maximum, and then tacrolimus, and MMF,
8 mycophenolate.

9 In terms of the HCV RNA reductions by prior
10 treatment -- and I'll start with that. So if we
11 look at viral declines in the patients who were
12 treatment naive versus treatment experienced, we
13 have that data here. Treatment naives are in
14 green. You can't see them because they're actually
15 behind the orange line of the treatment
16 experienced. So we see no difference in terms of
17 viral kinetics if someone was previously treated.

18 When we look at the baseline characteristics
19 of the patients who had recurrence versus no
20 recurrence across the study, we have those here.
21 And you'll see that most of the patients who had
22 recurrence for genotype 1a or 1b, we don't really

1 see any impact of Childs A versus B. And in terms
2 of treatment naive, 1 out of 10 who had recurrence
3 was treatment naive versus 7 out of 28. So 10 to
4 25 percent, small numbers in the recurrence group,
5 but it doesn't seem to be a very strong factor in
6 terms of this, but it is a small data set.

7 I don't have specific data on the types of
8 prior treatment, but I'd be happy to try and get
9 back to you after the break with the types of
10 regimens that the patients were on.

11 DR. MURATA: Dr. Hagedorn?

12 DR. HAGEDORN: My question is related to
13 ribavirin dosing. In the patients that required
14 reduction of ribavirin, what was the lowest dose in
15 either of the protocols, the ones for genotype 1,
16 4, 5, and 6 and genotype 2, 3?

17 DR. MCHUTCHISON: So I'll ask Dr. Brainard
18 to talk about the ribavirin dose reductions, lowest
19 dose, and the schedule for the clinical trials.

20 DR. BRAINARD: We recommended in all of our
21 phase 3 studies that ribavirin dose reduction for
22 anemia be performed according to the Copegus label,

1 which suggests that, for patients without cardiac
2 disease, the dose is reduced to 600 milligrams once
3 the hemoglobin is less than 10 grams per deciliter.
4 And the dose is interrupted or discontinued if the
5 hemoglobin is less than 8.5 grams per deciliter.

6 That said, we did allow for investigator
7 discretion to use their clinical judgment to
8 justify an alternate dose reduction and/or to
9 increase the dose once the dose had been reduced.

10 The lowest dose of ribavirin that was
11 administered to a patient in the phase 3 study was
12 200 milligrams. However, this was just a temporary
13 dose reduction and of the over 600 patients who
14 received sofosbuvir plus ribavirin, there was only
15 1 patient who received 200 milligrams. The
16 majority of dose reductions were down to
17 600 milligrams with approximately 30 percent of
18 patients having a subsequent dose increase after
19 the hemoglobin increased.

20 DR. MURATA: Dr. Corbett?

21 DR. CORBETT: Amanda Corbett, University of
22 North Carolina. So one of my questions was

1 answered about cobicistat, so thank you. But maybe
2 Dr. Kearney can maybe help me understanding a
3 little bit about the boosted PI interactions.

4 So it looks like, with daurunavir or
5 ritonavir, it was about a 30 to 40 percent overall
6 in increases in PK. And I guess I would have
7 expected that maybe to be a little bit higher with
8 ritonavir inhibiting P-gp, but maybe I'm incorrect
9 and that's pretty much expected.

10 Would that similar increase likely be seen
11 with other boosted protease inhibitors, aside from
12 tipranavir, obviously?

13 DR. KEARNEY: Yes. In our experience, the
14 effect of a ritonavir-boosted PI, either with
15 ritonavir or with cobicistat, on either tenofovir
16 P-gp substrate or sofosbuvir, is in this 30 to
17 35 percent range.

18 In terms of whether we would see this
19 interaction with other boosted PI regimens, we're
20 collecting additional data with other boosted
21 regimens as part of coinfection programs for our
22 fixed-dose combination program. I think we're

1 expecting the interaction profile to be generally
2 consistent with this and be very permissive in
3 terms of use.

4 DR. CORBETT: That's very good news. And
5 just to follow up, I would assume there would be no
6 dolutegravir interactions, no OCT2 substrate? I
7 guess you guys asses that transporter as well. I
8 can't remember.

9 DR. KEARNEY: We wouldn't expect there to be
10 an interaction with dolutegravir.

11 DR. CORBETT: Okay.

12 DR. MURATA: Dr. Giordano?

13 DR. GIORDANO: Tom Giordano. This question
14 relates to the reproducibility of the results, and
15 so maybe the agency needs to comment on that. But
16 typically, the standard is that there be two
17 similar trials that show similar results. In this
18 case, I think there's enough data in the genotype 2
19 and 3 to meet that standard, but in the other
20 genotypes and in the pre-transplant population, we
21 have a single study.

22 So I guess, is there an agency standard that

1 there needs to be two studies? What is the
2 company's, the sponsor's position on why there are
3 not two studies showing some other results?

4 DR. MURRAY: Do you want me to answer that?

5 Well, in our guidance and for previous drugs
6 and indications, generally trials in different
7 patient populations, a genotype 1 trial can support
8 genotype 2. And actually doing studies in a lot of
9 different populations in subgroups, we think,
10 offers a lot of strength that actually you don't
11 get from just repeating the same trial in the same
12 population. So you do get to see kind of the
13 versatility of the drug.

14 So we have thought that trials in different
15 populations actually support each other. And
16 sometimes a drug is approved for one indication.
17 We don't always require two trials to expand to
18 another population or for a related indication.

19 DR. MURATA: Dr. Honegger?

20 DR. HONEGGER: Jonathan Honegger. I just
21 had a quick question about the 12-week treatment
22 for genotype 2. SVR rates were over 90 percent or

1 higher for every population, except the treatment-
2 experienced group with cirrhosis. Those were small
3 numbers in the FUSION study. But I just wondered
4 if there was any consideration for testing a
5 24-week duration in that group.

6 DR. MCHUTCHISON: So I'll ask Dr. Symonds to
7 address the duration in genotype 2. The data set
8 is small. There's 27 total patients with those
9 unfavorable characteristics. And if you think
10 about, in the U.S., 20 percent of patients have
11 genotype 2, 80 percent of them are cured with peg
12 and ribavirin. So that leaves 4 out of 100, and
13 then perhaps half of them have cirrhosis.

14 So these decisions are affecting perhaps 1
15 or 2 out of 100 individuals, but we've given it due
16 thought, and Dr. Symonds will take you through all
17 of it.

18 DR. SYMONDS: Bill Symonds, Gilead Sciences.
19 So comparing the genotype 2 treatment-experienced
20 population across the study, in treatment
21 experience, we have the FUSION trial, of which I
22 showed you the detailed results. But in VALENCE, I

1 did not show you a breakdown of genotype 2 in these
2 populations.

3 So over on the right-hand side are the
4 patients with cirrhosis. And you can see FUSION,
5 there were only 10 patients who got 12 weeks. Six
6 out of 10, or 60 percent, achieved an SVR. In the
7 longer arm, 7 out of 9, or 78 percent. However, in
8 VALENCE, it was 7 out of 8 with only 12 weeks.

9 So there is no clear evidence that going
10 longer in the genotype 2 patients would actually
11 provide additional benefit. However, in the study
12 which Dr. McHutchison mentioned at the
13 beginning -- or I guess it was at the end of his
14 presentation about ongoing studies, we do have a
15 randomized control trial comparing 16 versus
16 24 weeks of sofosbuvir plus ribavirin, and also
17 including a triple combination with pegylated
18 interferon added to that regimen as well.

19 It's mostly genotype 3, but we have
20 included genotype 2 treatment-experienced cirrhosis
21 to see if we can find more of these patients, and
22 get the numbers up, and have a better estimate for

1 what the true response rate is of these durations.

2 DR. MURATA: In the interest of time, for
3 the morning clarifying questions, I would like to
4 just call on two additional questions.

5 Dr. Connick?

6 DR. CONNICK: Liz Connick. I just had a
7 quick question. Why was erythropoietin prohibited?
8 Was there a concern about an interaction?

9 DR. MCHUTCHISON: No concern about an
10 interaction, but a willingness and wanting to
11 understand what the profile of the regimens were,
12 particularly the profiles without interferon. And
13 erythropoietin would have muddied those waters in
14 terms of understanding the profiles.

15 We also felt that ribavirin dose reductions
16 could be managed, and the phase 2 data suggested
17 strong efficacy in phase 2. So there was not as
18 much great concern about dose reductions of
19 ribavirin.

20 DR. MURATA: The last question for the
21 morning, Mr. Raymond?

22 MR. RAYMOND: Thank you. Daniel Raymond. I

1 wanted to go back to the proposed indication that
2 sofosbuvir is indicated for the treatment of
3 chronic hepatitis C infection in combination with
4 other agents in adult patients with genotypes 1 to
5 6 or awaiting liver transplantation, because we had
6 a bit of a discussion about this at yesterday's
7 meeting about the relative pros and cons or timing
8 of a broad versus narrow but specific indication.

9 So I wanted to hear a little bit more about
10 the thinking of this proposal and perhaps maybe a
11 clinician's perspective on how they would use and
12 interpret that.

13 DR. MCHUTCHISON: I heard all the comments
14 yesterday, as you've mentioned, and I'll ask
15 Dr. Jacobson to comment, as you said, from a
16 clinician's perspective as well. But I think the
17 field is moving very rapidly.

18 Sofosbuvir is combined with ribavirin. It's
19 combined with interferon and ribavirin. There are
20 numerous ongoing studies with multiple other
21 antiviral agents. So the approach could be a broad
22 approach that will allow practitioners and patients

1 alike to incorporate new regimens as they are shown
2 to be effective and safe and as that strength of
3 evidence becomes evident. The other approach is
4 just to be more conservative and then to open up
5 subsequently. So it's a timing issue, as Dr.
6 Murray said yesterday.

7 We have lots of durations. We have lots of
8 regimens with interferon and ribavirin, with
9 ribavirin, and with other regimens in the future.
10 So it was that concept of broadness in a rapidly
11 evolving field, similar to HIV, that would be
12 supportive of such an indication.

13 Dr. Jacobson?

14 DR. JACOBSON: Let me preface my answer by
15 saying that I'm acutely aware of my position in
16 discussing potential applications of this drug and
17 this regimen in the near future, that we don't
18 necessarily examine phase 3 trials at a meeting of
19 the U.S. Food and Drug Administration.

20 However, at this time, the drug and the
21 associated regimens do inevitably lend themselves
22 to such considerations. For instance, the NEUTRINO

1 trial only involved treatment-naive patients, but
2 that leaves a lot of treatment-experienced patients
3 who have failed peg interferon and ribavirin or
4 perhaps peg-riba and a protease inhibitor.

5 It seems quite clear from the SVR rates in
6 ATOMIC and NEUTRINO that that regimen cures a great
7 majority of the people who would have been
8 biologically destined to fail peg interferon and
9 ribavirin. And in fact, a substantial number, if
10 not a majority, of the patients would have failed a
11 protease inhibitor regimen as well. And so I think
12 clinicians need to have the option to give that
13 particular regimen to treatment-experienced
14 genotype 1 patients.

15 Similarly, there are many interferon-
16 ineligible patients who really do need treatment
17 rather urgently. And of course, three years ago,
18 we would have regarding the SVR rates obtained with
19 sofosbuvir and ribavirin alone in genotype 1 as
20 nothing short of miraculous.

21 Now, of course, with SVR rates of 90 to
22 100 percent on the horizon in phase 2 trials, we

1 think of it differently. But those SVR rates are
2 sufficient to lead clinicians perhaps to give
3 strong consideration to selective treatment of
4 patients who are interferon-ineligible in the near
5 future with a regimen that certainly will be
6 suppressive and perhaps curative.

7 Also, patients with genotypes 2 and 3 were
8 not studied in phase 3, although they were in
9 phase 2, to some extent, with peg interferon,
10 sofosbuvir, and ribavirin. And that might be a
11 compelling option in light of the very high rates
12 of SVR in the genotype 3 patients in the PROTON and
13 ELECTRON studies, where in fact 38 out of 39
14 patients were cured, and one was missing; so
15 perhaps 100 percent SVR rate.

16 Also, I think given the incredible pace with
17 which this field is progressing, we do expect other
18 regimens to come along shortly. And I think that
19 in general terms, the proposed label would position
20 the drug ideally and appropriately to be combined
21 with other antiviral agents, both ones that we have
22 now, namely ribavirin and interferon, but others

1 that we hope will come along, soon.

2 DR. MURATA: Thank you very much. We will
3 hopefully open up further clarifying questions of
4 the sponsor in the afternoon discussion session.

5 So we will now take, again, an almost
6 15-minute break. Panel members, please remember
7 that there should be no discussion of the meeting
8 topic during the break amongst yourselves or with
9 any member of the audience. We will resume at
10 10:45 a.m.

11 (Whereupon, a brief recess was taken.)

12 DR. MURATA: Let's get started. We will now
13 proceed with the FDA presentation.

14 **FDA Presentation - Poonam Mishra**

15 DR. MISHRA: Good morning. My name is
16 Poonam Mishra. Today, Dr. Karen Qi and I will be
17 presenting the FDA analyses for sofosbuvir on
18 behalf of the review team.

19 I will start with a brief background,
20 followed by the key efficacy and safety results
21 pertinent to today's discussion. The detailed
22 efficacy and safety analyses have been provided by

1 the applicant in their presentation earlier today.
2 I will briefly discuss the resistance data
3 currently available for sofosbuvir and will also
4 discuss drug-drug interaction data pertinent to
5 specific populations.

6 Following my presentation, Dr. Qi will
7 discuss the exploratory analyses performed using
8 the baseline predictive factors of treatment
9 response to predict a response rate in genotype 1
10 patient population who have failed a previous
11 course of interferon and ribavirin therapy.

12 Sofosbuvir, also referred to as GS7977, is a
13 nucleotide inhibitor of hepatitis C virus, NS5B
14 RNA-dependent RNA polymerase. Sofosbuvir is the
15 first-drug-in class submitted for marketing
16 application in the United States. The proposed
17 indication by the applicant is for sofosbuvir use
18 in combination with other agents for the treatment
19 of chronic hepatitis C in adult patients.

20 Of note, in the registration trials, the
21 sofosbuvir and ribavirin combination was evaluated
22 in genotypes 2 and 3 subjects. And sofosbuvir, in

1 combination with pegylated interferon and
2 ribavirin, was evaluated in subjects with
3 genotype 1, 4, 5, and 6.

4 Now, I will provide the efficacy results for
5 phase 3 trials. My discussion will focus on
6 primary efficacy endpoint and relapse rates for
7 each trial. First, I will start with the efficacy
8 data from the trials done in genotypes 2 and 3
9 subjects.

10 Details of the phase 3 trials have been
11 described by the applicant earlier. I will go over
12 some of the key terms and briefly describe the
13 trial designs to reiterate the different regimens
14 and duration of therapy evaluated for genotypes 2
15 and 3.

16 I will be referring to these trials by their
17 names to be consistent with the applicant's
18 presentation. I may occasionally use the last
19 three or four digits of the trials interchangeably
20 as well.

21 Trial P7977-1231 or FISSION enrolled
22 treatment-naïve subjects with HCV genotype 2 or 3

1 infection. In this trial, 12 weeks of sofosbuvir
2 and ribavirin therapy was compared with 24 weeks of
3 pegylated interferon and ribavirin therapy, which
4 is the current standard of care for genotypes 2 or
5 3.

6 Trial 107 or POSITRON enrolled subjects with
7 chronic genotype 2 or 3 HCV infection who were
8 interferon-ineligible, interferon-intolerant, or
9 unwilling to take interferon, also collectively
10 referred to as interferon-unable.

11 Subjects were treated with 12 weeks of
12 sofosbuvir and ribavirin, and the treatment arm was
13 compared to placebo group, as currently there is no
14 available therapy for subjects who are
15 interferon-unable.

16 Trial 108 or FUSION enrolled subjects with
17 chronic genotype 2 or 3 HCV infection who had
18 failed prior treatment with an interferon-based
19 regimen, also referred to as treatment experienced.

20 This trial has two different durations of
21 sofosbuvir and ribavirin treatment, 12 weeks or
22 16 weeks. A historical response rate of 25 percent

1 was used for comparison.

2 Trial 133 or VALENCE enrolled treatment-
3 naive subjects and treatment-experienced subjects
4 with chronic genotype 2 or 3 HCV infection,
5 including those subjects classified as interferon-
6 unable. As the applicant discussed, the original
7 trial design was 4 to 1 randomization to either
8 sofosbuvir and ribavirin for 12 weeks or placebo.

9 Based on the emerging data, this trial was
10 unblinded, and all genotype 3 subjects, still on
11 sofosbuvir and ribavirin treatment, were extended
12 to 24 weeks, while genotype 2 subjects continued
13 the original 12-week duration.

14 All trials included a subset of subjects
15 with compensated cirrhosis, which represents a
16 harder-to-treat subgroup. All sofosbuvir-
17 containing arms used sofosbuvir, 400 milligrams
18 once daily and weight-based ribavirin.

19 In the pegylated interferon and ribavirin
20 arm, the ribavirin dose was 800 milligrams daily,
21 which is the approved regimen. It should be noted
22 that the primary endpoint in all trials is

1 sustained virologic response defined as HCV RNA
2 below the lower limit of quantification, or LLOQ,
3 12 weeks after the discontinuation of active
4 treatment, referred to as SVR12.

5 This schematic shows the trial designs for
6 four phase 3 trials done in genotypes 2 and 3. To
7 orient everyone with the schematic, the left side
8 shows the trial number, trial name, genotypes
9 studied, and the populations studied, which are
10 genotypes 2 and 3.

11 The top line of the schematic shows the
12 treatment duration in weeks. The treatment regimen
13 and the number of subjects in each treatment group
14 are shown on the horizontal bars itself.

15 I will reiterate the treatment regimen,
16 duration, and control arm in each trial before I
17 discuss the efficacy results. First, I will start
18 with FISSION. As I mentioned earlier, in FISSION,
19 12 weeks of sofosbuvir and ribavirin therapy was
20 compared with 24 weeks of pegylated interferon and
21 ribavirin therapy. Primary endpoint was SVR12.

22 This slide shows the SVR12 and relapse rates

1 observed in the FISSION trial. A total of 256
2 subjects received treatment in the sofosbuvir and
3 ribavirin group and 243 subjects in the pegylated
4 interferon and ribavirin group. Twenty percent of
5 study subjects had compensated cirrhosis.

6 The overall SVR12 rate was 67 percent in
7 both groups, as shown in this table. The
8 difference in proportions was 0.1 percent. The
9 lower bound of the two-sided 95 percent confidence
10 interval for the difference between groups was
11 within the prespecified non-inferiority margin of
12 minus 15 percent.

13 Within the sofosbuvir and ribavirin group,
14 genotype 2 subjects had higher SVR12 rates compared
15 with genotype 3 subjects, 95 percent versus
16 56 percent, respectively.

17 The overall relapse rate was 30 percent in
18 the sofosbuvir and ribavirin group and 21 percent
19 in the pegylated interferon and ribavirin group.
20 Within the sofosbuvir and ribavirin group,
21 genotype 3 subjects had a relapse rate of
22 40 percent compared with a 5 percent relapse rate

1 in genotype 2 subjects.

2 Moving on to the next trial, POSITRON,
3 POSITRON enrolled subjects who were
4 interferon-unable. Twelve weeks of sofosbuvir and
5 ribavirin was compared to placebo with subjects
6 randomized 3 to 1; to sofosbuvir and ribavirin, and
7 placebo arm, respectively.

8 This slide displays the SVR12 and relapse
9 rates observed in the POSITRON trial. A total of
10 207 subjects received treatment in the sofosbuvir
11 and ribavirin group and 71 subjects in the placebo
12 group, including 16 percent with compensated
13 cirrhosis.

14 The sofosbuvir and ribavirin 12-week regimen
15 was superior to placebo with SVR12 rates of
16 78 percent and zero percent, respectively. Within
17 the sofosbuvir and ribavirin group, genotype 2
18 subjects had higher SVR12 rates compared with
19 genotype 3 subjects, 93 percent versus 61 percent,
20 respectively.

21 The overall relapse rate in the sofosbuvir
22 and ribavirin group was 20 percent. Within each

1 genotype, relapse accounted for most treatment
2 failures, with genotype 3 subjects having a relapse
3 rate of 38 percent compared with a 5 percent
4 relapse rate in genotype 2 subjects.

5 The next trial is FUSION, which was done in
6 treatment-experienced subjects. This trial
7 assessed two different durations of sofosbuvir and
8 ribavirin treatment, 12 weeks or 16 weeks.
9 Subjects enrolled in the 12-week group received
10 placebo for an additional four weeks.

11 This slide shows the observed SVR12 and
12 relapse rates in the FUSION trial. A total of 103
13 subjects were enrolled in the sofosbuvir and
14 ribavirin 12-week group and 98 subjects received
15 treatment in the sofosbuvir and ribavirin 16-week
16 group, including 34 percent with compensated
17 cirrhosis. A higher percentage than enrolled in
18 the other phase 3 trials.

19 The SVR12 rate in the sofosbuvir and
20 ribavirin group was 50 percent and in the
21 sofosbuvir and ribavirin 16-week group was
22 71 percent, each significantly higher compared to

1 the historical rate of 25 percent. In the
2 sofosbuvir and ribavirin 12-week group, SVR12 rates
3 were 82 percent and 30 percent for genotype 2 and 3
4 subjects, respectively.

5 In the sofosbuvir and ribavirin 16-week
6 group, SVR12 rates were 89 percent and 62 percent,
7 respectively. In both the sofosbuvir-ribavirin
8 12-week group and 16-week groups, genotype 2
9 subjects had higher SVR12 rates compared with
10 genotype 3 subjects.

11 Extending the treatment duration by 4 weeks
12 increased SVR12 rates in genotype 2 subjects from
13 82 to 89 percent, and in genotype 3 subjects from
14 30 percent to 62 percent.

15 The overall relapse rate was 48 percent in
16 the 12-week treatment group compared to 29 percent
17 in the 16-week treatment group. Extending the
18 treatment duration by 4 weeks decreased relapse
19 rates in genotype 2 subjects from 18 percent to
20 11 percent, and in genotype 3 subjects, from
21 66 percent to 38 percent.

22 This bar graph shows the difference in SVR12

1 rates observed between genotype 2 and 3 across
2 three trials described so far. On the X axis are
3 the different treatment durations and the Y axis
4 shows the SVR12 rates. The light blue bar
5 represents SVR12 rates in genotype 2 subjects, and
6 the dark blue bar represents SVR12 rates in
7 genotype 3 subjects. The top of the bar shows
8 SVR12 results in each group.

9 As shown in the graph, SVR12 rates for
10 genotype 3 subjects, as shown in dark blue bars,
11 were consistently lower than genotype 2 subjects
12 shown in the light blue bar across all three
13 trials.

14 The FUSION trial, shown on the right-most
15 side of the graph, demonstrated genotype 3
16 treatment-experienced subjects receiving sofosbuvir
17 and ribavirin for 16 weeks had significantly
18 increased SVR12 rates compared with the same
19 regimen for 12 weeks, 62 percent versus 30 percent,
20 respectively.

21 The collective evidence from these three
22 trials indicated that 12 or 16 weeks of sofosbuvir

1 and ribavirin is not the optimal regimen for
2 genotype 3 patients, and the SVR12 rates can be
3 further optimized by a longer treatment duration in
4 the genotype 3 population.

5 This led to review of data from ongoing
6 trial VALENCE, described in the next slide.
7 VALENCE enrolled treatment-naïve and
8 treatment-experienced subjects with chronic
9 genotype 2 or 3 HCV infection, including those
10 classified as interferon-unable. The original
11 trial design was 4 to 1 randomization to either
12 sofosbuvir and ribavirin for 12 weeks or placebo.

13 Based on emerging data primarily from
14 FISSION, POSITRON, and FUSION, this trial was
15 unblinded, and all genotype 3 subjects still on
16 sofosbuvir and ribavirin treatment were extended to
17 24 weeks, while genotype 2 subjects continued the
18 original 12-week duration. Of note, only 11
19 genotype 3 subjects had already completed 12 weeks
20 of treatment at the time of the protocol amendment.

21 This slide shows the SVR12 and relapse rate
22 noted in the VALENCE trial. A total of 73

1 genotype 2 subjects received treatment in the
2 sofosbuvir and ribavirin 12-week group, and 250
3 genotype 3 subjects received treatment in the
4 sofosbuvir and ribavirin 24-week group, including
5 approximately 19 percent with compensated
6 cirrhosis.

7 The overall SVR12 rate for genotype 2
8 subjects was 93 percent, with treatment-naïve
9 subjects achieving an SVR12 rate of 97 percent and
10 treatment-experienced subjects an SVR12 rate of
11 90 percent.

12 The overall SVR12 rate for genotype 3
13 subjects was 84 percent, with treatment-naïve
14 subjects achieving an SVR12 rate of 93 percent, and
15 treatment-experienced genotype 3 subjects an SVR12
16 rate of 77 percent.

17 The overall relapse rate in genotype 2
18 subjects was 7 percent, with a relapse rate of
19 3 percent and 10 percent in treatment-naïve and
20 treatment-experienced subjects, respectively.
21 Genotype 3 relapse rates were 14 percent overall
22 and 5 percent and 20 percent in treatment-naïve and

1 treatment-experienced subjects, respectively.

2 Extending the sofosbuvir and ribavirin
3 treatment duration to 24 weeks in genotype 3
4 subjects improved SVR12 rates primarily by
5 decreasing relapse. This point will be illustrated
6 further in the next few slides.

7 This slide recaps the SVR12 rates and
8 relapse rates observed for genotype 3 subjects in
9 all trials and their different treatment durations.
10 I will walk you through the slide.

11 First, I will start with treatment-naive
12 subjects. Different treatment durations and study
13 populations are shown on the X axis. The Y axis
14 shows the SVR12 rates. The light blue bar
15 represents SVR12 rates, and the dark blue bar shows
16 the relapse rates.

17 The SVR12 rate was 56 percent, and relapse
18 rate was 40 percent with 12 weeks of sofosbuvir and
19 ribavirin treatment in treatment-naive subjects.
20 Extending the treatment duration to 24 weeks
21 improved SVR12 rates to 93 percent and decreased
22 the relapse rate to 5 percent in treatment-naive

1 subjects.

2 Moving to the treatment-experienced
3 subjects, with 12 weeks, SVR12 rate was 30 percent
4 and relapse rate was 66 percent. Increasing the
5 duration to 16 weeks resulted in an SVR12 rate of
6 62 percent and a relapse rate of 38 percent, which
7 was still very high.

8 In the VALENCE trial, treatment duration was
9 24 weeks, which resulted in an SVR12 rate of
10 77 percent and a relapse rate of 20 percent.

11 In conclusion, by extending the treatment
12 duration from 12 weeks to 24 weeks in
13 treatment-experienced genotype 3 subjects, relapse
14 rate decreased from 66 to 20 percent.

15 Now, I will switch gears to the trial done
16 in subjects with genotypes 1, 4, 5, and 6. This
17 schematic shows the trial design for NEUTRINO.
18 NEUTRINO was an open-label single-arm trial in
19 treatment-naive subjects with chronic genotype 1,
20 4, 5, or 6 HCV infection. Subjects received
21 sofosbuvir in combination with pegylated interferon
22 and ribavirin for 12 weeks.

1 Overall, 90 percent of subjects achieved
2 SVR12 in the NEUTRINO trial compared with a
3 historical SVR12 rate of 60 percent in this
4 population. Subjects with genotype 1 had an
5 overall SVR12 rate of 89 percent. Genotype 1a
6 subjects had 10 percent higher SVR12 rates than
7 genotype 1b subjects, SVR12 rates of 92 percent and
8 82 percent, respectively.

9 Post hoc analyses between the two genotype
10 subtypes across demographics and baseline
11 characteristics found that HCV genotype 1a subjects
12 had numerically higher SVR12 rates than HCV
13 genotype 1b subjects in almost all subgroups, as
14 was illustrated in the FDA background document.
15 Thus, the HCV genotype 1 subtype, SVR12 rate
16 differences are not clearly explained by
17 demographic and baseline factors.

18 Subjects with genotype 4 had an SVR12 rate
19 of 96 percent. There were 28 subjects with
20 genotype 4 in this trial. It should be noted that
21 only one subject with genotype 5 and 6 subjects
22 with genotype 6 were included in this trial.

1 Hence, the available data are believed to be
2 insufficient to make definitive dosing
3 recommendations for patients with HCV genotype 5 or
4 6 infection at this time.

5 So to summarize the efficacy results from
6 phase 3 trials, the 12 weeks of sofosbuvir and
7 ribavirin therapy resulted in SVR rates from 93 to
8 97 percent in treatment-naive genotype 2 subjects.
9 The SVR12 rates in treatment-experienced genotype 2
10 subjects ranged from 82 to 90 percent after
11 12 weeks of sofosbuvir and ribavirin therapy.

12 Twenty-four weeks of sofosbuvir and
13 ribavirin regimen resulted in SVR12 rates of
14 93 percent in treatment-naive genotype 3 subjects.
15 The SVR12 rates in treatment-experienced genotype 3
16 subjects was 77 percent after 12 weeks of
17 sofosbuvir and ribavirin therapy.

18 SVR rates of 89 percent were observed in
19 genotype 1 treatment-naive subjects treated with
20 12 weeks of triple therapy with sofosbuvir in
21 combination with pegylated interferon and
22 ribavirin. SVR12 rates in genotype 4 subjects was

1 96 percent, which is from data in 28 subjects.

2 Now, I will move on to discuss
3 pre-transplant population. Recurrence of HCV
4 infection after liver transplantation is almost
5 universal. Rate of fibrosis progression in these
6 patients is accelerated compared to non-transplant
7 hepatitis C patients with approximately 10 to
8 25 percent of patients developing cirrhosis within
9 the next 5 to 10 years of liver transplantation.

10 There are currently no approved therapies to
11 prevent recurrence of HCV infection post-liver
12 transplant. Thus, this represents an area of unmet
13 medical need.

14 Trial P7977-2025 is an ongoing phase 2
15 open-label trial evaluating the efficacy and safety
16 of sofosbuvir and ribavirin in subjects with
17 genotype 1 through 6 HCV infection, and
18 hepatocellular carcinoma specifically meeting the
19 Milan criteria, and listed for liver
20 transplantation with an anticipated time until
21 liver transplantation within one year.

22 Milan criteria are defined as the presence

1 of a tumor, 5 centimeters or less, in subjects with
2 single hepatocellular carcinoma, and no more than
3 3 tumor nodules, each 3 centimeters or less, in
4 subjects with multiple tumors. There should be no
5 extra hepatic manifestations and no evidence of
6 vascular invasion of the tumor.

7 Eligible subjects were those listed for
8 liver transplant with an MELD model for end-stage
9 liver disease score of less than 22, and its
10 HCC-weighted MELD score of greater than or equal to
11 22. Child-Pugh Turcotte score was less than or
12 equal to 7.

13 Enrolled subjects received sofosbuvir and
14 ribavirin prior to undergoing liver
15 transplantation. The original protocol specified
16 treatment duration was for a maximum of 24 weeks,
17 which was later extended via protocol amendment to
18 48 weeks or until transplant, whichever comes
19 first. Treatment is discontinued within 24 hours
20 prior to liver transplant if it occurs before the
21 subject has completed their treatment course as
22 appropriate.

1 This trial evaluated the efficacy of
2 sofosbuvir and ribavirin in preventing HCV
3 recurrence post-liver transplant. Prevention of
4 post-transplant reinfection is determined by a
5 sustained post-transplant virologic response
6 HCV RNA below lower limit of quantification at
7 12 weeks' post-transplant, also referred to as
8 pTVR12.

9 Thirty-seven subjects had HCV RNA below LLOQ
10 at the time of liver transplantation, out of which
11 36 have been followed to post-transplant week 12.
12 Of those subjects, 64 percent achieved sustained
13 pTVR12 as shown in this table.

14 In genotype 1 subjects, those with genotype
15 1a had improved pTVR12 rates compared with genotype
16 1b subjects, 62 percent versus 46 percent,
17 respectively. Please note the number of subjects
18 in each of these subgroups is limited. Genotype 2-
19 and genotype 3-infected subjects had improved
20 virologic outcomes ranging from 75 to 100 percent.

21 Moreover, the sustained virologic response
22 post-transplantation was maintained through week 24

1 in a subset of subjects. pTVR12 -- pTVR24 of 71
2 percent was observed in 17 out of 24 subjects.

3 Although the number of subjects in this
4 trial is limited at this time, the observed
5 response rates in this subgroup of pre-transplant
6 population addresses an unmet medical need.

7 To summarize, this trial in pre-transplant
8 population included patients who were eligible to
9 undergo liver transplant due to an upgrade in their
10 MELD scores due to HCC and may not necessarily
11 because of worsening liver disease. An overall
12 response rate of 64 percent is encouraging and
13 provides the therapeutic option for these subgroup
14 of patients undergoing liver transplantation for
15 HCC.

16 Higher rates of grade 3 or 4 adverse events,
17 serious adverse events, and deaths were reported in
18 this pre-transplant population compared to the
19 adverse events profile noted in the other phase 3
20 trials. This difference in safety profile can be
21 attributed to the more advanced stage of liver
22 disease and due to underlying disease progression

1 in these advanced liver disease patients.

2 Some of the adverse events noted were
3 associated with liver transplant itself. After
4 accounting for all these factors, the safety
5 profile in the subpopulation does not appear to
6 differ from the overall safety profile of a
7 sofosbuvir and ribavirin regimen in subjects not
8 undergoing liver transplantation. The demonstrated
9 efficacy, as measured by pTVR12 of 64 percent,
10 coupled with a generally well-tolerated safety
11 profile in this pre-transplant addresses an unmet
12 medical need.

13 Now, I will present the safety analyses
14 done. The primary safety analysis evaluated the
15 data from phase 3 trials described earlier. Safety
16 review from non-pivotal trials provided the
17 supportive safety data.

18 Please note that the safety analysis from
19 the VALENCE trial are still ongoing and these
20 slides may not have been updated with the most
21 recent data. Our safety review focused on
22 treatment-emergent, adverse events, deaths, serious

1 adverse events, severe and life-threatening adverse
2 events, and adverse events leading to treatment
3 discontinuations. Laboratory abnormalities
4 reported in phase 3 trials were also evaluated.

5 In general, the division agrees with the
6 applicant's safety assessments, which were
7 presented earlier today.

8 I will discuss the overall safety summary
9 briefly followed by evaluation of cardiac safety.
10 This slide provides an overall summary of adverse
11 events of the pooled data. Each column indicates
12 the name of the trial or trials from which the
13 pooled data is taken.

14 Data from 16-week sofosbuvir and ribavirin
15 treatment group and pegylated interferon and
16 ribavirin 24 group is not shown in this table.
17 However, they were presented in the applicant's
18 presentation earlier today.

19 A majority of the subjects experienced
20 adverse events in these trials. Incidence of
21 serious adverse events was low across all treatment
22 groups with similar incidence in the 12-week and

1 24-week treatment group. Grade 3 or grade 4
2 adverse events was also 12-week and 24-week
3 sofosbuvir and ribavirin treatment groups.

4 At this time, extending treatment duration
5 of the sofosbuvir and ribavirin combination regimen
6 from 12 weeks to 24 weeks does not appear to
7 increase adverse events associated with sofosbuvir
8 use.

9 AEs leading to permanent discontinuation
10 from sofosbuvir were very low in all treatment
11 groups. Most of the adverse events leading to
12 modification or interruption of study drugs were
13 with ribavirin or pegylated interferon.

14 Incidence of serious adverse events was low
15 and comparable between the sofosbuvir and ribavirin
16 12-week group and sofosbuvir and ribavirin 24-week
17 group. Most of the serious adverse events observed
18 are consistent with the study population and the
19 disease under study.

20 Incidence of serious adverse events that
21 were considered related to the study drug by the
22 investigators was very low and the investigators'

1 causality assessment for relatedness seems
2 reasonable for the observed adverse events.

3 There was no apparent clustering of serious
4 adverse events within the MedDRA system organ
5 classes. The only serious adverse events seen in
6 three or more subjects in the sofosbuvir and
7 ribavirin group were malignant hepatic neoplasm,
8 which is a well-known complication of cirrhosis in
9 this patient population.

10 The drug development for another
11 investigational agent in the same class being
12 developed for the treatment of chronic hepatitis C
13 was halted in 2012 after cardiac safety concerns
14 were noted.

15 A detailed safety evaluation focused on
16 cardiac disorders was done by FDA to identify any
17 potential cardiac toxicity signals in the
18 sofosbuvir development program. Please note that
19 the review of the VALENCE trial data is ongoing,
20 and this slide has not been updated with the
21 cardiac adverse event noted from the VALENCE trial.
22 This event was also not included in the FDA

1 background package.

2 The evaluation was done based on adverse
3 events reported in the MedDRA system organ class of
4 cardiac disorders. There have been no cases of
5 cardiomyopathy reported to date. No serious
6 cardiac adverse events have been reported, and
7 there has been 1 serious adverse event of grade 3
8 arrhythmia reported in trial VALENCE in the
9 24 weeks of sofosbuvir and ribavirin treatment
10 group.

11 This adverse event is not included in the
12 summary slide. However, this adverse event was not
13 considered related to study drugs by the
14 investigator as subject had a medical history of
15 previous episodes of cardiac arrhythmia prior to
16 participation in trial.

17 Investigators' causality assessment seems
18 reasonable. No treatment discontinuations due to
19 cardiac adverse events were noted. No clustering
20 of cardiac-related adverse events was seen. A
21 detailed table, including preferred terms for the
22 observed adverse events is provided in the FDA

1 background package.

2 Based on the review of the submitted data to
3 date, no obvious safety issue related to cardiac
4 toxicity has been identified in the sofosbuvir
5 clinical development program. We will continue to
6 monitor for any such events in our routine
7 postmarketing surveillance program.

8 In summary, sofosbuvir regimens in
9 combination with ribavirin, or in combination with
10 pegylated interferon and ribavirin, were well
11 tolerated in all patient populations studied. No
12 clustering or trends of any specific adverse events
13 were noted. At this time, no safety concerns
14 specific to cardiac toxicity associated with
15 sofosbuvir use have been identified.

16 I will now turn to a brief discussion of
17 treatment-emergent resistance data available from
18 sofosbuvir clinical trials. For the FDA analysis
19 of sofosbuvir-resistant substitution emergence,
20 next-generation nucleotide sequencing and NGS data
21 were analyzed for four phase 3 clinical trials. A
22 total of 224 subjects in sofosbuvir-containing arms

1 had next-generation data, and 676 raw data files
2 were analyzed by the Division.

3 This slide shows the treatment-emergent NS5B
4 substitutions that were noted in subjects with
5 treatment-failures. The sofosbuvir-resistant
6 substitution, S282T, which was selected in cell
7 culture, was also detected in 1 genotype 2b
8 relapsed subject who received sofosbuvir
9 monotherapy for 12 weeks in phase 2 study.

10 The L159F substitution emerged in 6
11 genotype 3a relapsers and the V321A substitution
12 emerged in 5 genotype 3a relapsers from the phase 3
13 trials. We are highlighting these substitutions as
14 contributing to genotypic resistance because they
15 emerged at highly conserved amino acid positions
16 and occurred in multiple subjects and multiple
17 trials.

18 The resistance data from pre-transplant
19 trial 2025 provided supportive information for the
20 FDA resistance findings in sofosbuvir phase 2 and 3
21 studies. In study 2025, where subjects received
22 sofosbuvir and ribavirin, there were 5 on-treatment

1 failures and 20 subjects who relapsed.

2 S282R and L320F substitutions were detected
3 in the on-treatment sample from a subject infected
4 with genotype 1a HCV, who did not respond to
5 sofosbuvir. The L320F substitution is a previously
6 identified HCV nucleotide polymerase inhibitor-
7 associated resistant substitution.

8 In addition, the L159F substitution emerged
9 in two subjects who had breakthrough and one
10 subject who relapsed. The presence of substitution
11 L159F at baseline was also associated with
12 sofosbuvir breakthrough and relapse in four
13 subjects. This substitution emerged in multiple
14 genotypes.

15 Overall, these results indicate that in
16 cases where sofosbuvir is not used in an optimal
17 regimen or duration, resistance may emerge. There
18 is evidence of genotypic changes associated with
19 breakthroughs and relapses. S282T emerged with
20 sofosbuvir monotherapy and showed a mean,
21 13.5-fold, reduced susceptibility to sofosbuvir.

22 The S282R and L320F substitutions emerged

1 with breakthrough on sofosbuvir and ribavirin in
2 genotype 1 pre-transplant subjects. And even
3 though substitutions L159F and V321A showed no
4 detectable shift in sofosbuvir phenotypic
5 susceptibility assays, these substitutions occurred
6 at conserved sites and emerged in multiple subjects
7 who experienced breakthrough or relapse in multiple
8 trials in genotypes.

9 Now, I will move on to the discussion of
10 available data and specific populations. The
11 pharmacokinetics of sofosbuvir was studied in
12 subjects with varying degrees of renal impairment.
13 No clinically significant effect on the exposures
14 of sofosbuvir and its major metabolite GS-331007
15 was observed for subjects with mild to moderate
16 renal impairment, that no dose adjustment is needed
17 for these patients.

18 However, a significant effect on GS-331007
19 concentrations was observed for subjects with
20 severe renal impairment and end-stage renal
21 disease. Hence, sofosbuvir use is not recommended
22 in these patients. And an additional

1 pharmacokinetic efficacy and safety study is
2 ongoing for subjects with severe renal impairment
3 and end-stage renal disease.

4 The pharmacokinetics of sofosbuvir were
5 studied in HCV-infected subjects with moderate and
6 severe hepatic impairment. No clinically
7 significant PK effect was observed for any degree
8 of hepatic impairment. Thus, sofosbuvir may be
9 administered to patients with any degree of hepatic
10 impairment without dose adjustment.

11 Furthermore, population PK analysis in HCV-
12 infected subjects indicated that cirrhosis had no
13 clinically relevant effect on the exposure of
14 sofosbuvir and GS-331007. However, as pegylated
15 interferon is contraindicated for use in patients
16 with decompensated cirrhosis and the safety
17 efficacy and safety of sofosbuvir have not been
18 established in these patients, sofosbuvir should
19 not be used in this patient population who would
20 receive a pegylated interferon-based regimen.

21 This slide shows drugs that may have a
22 significant effect on sofosbuvir. Because

1 sofosbuvir is a P-gp substrate, P-gp inducers have
2 the potential to decrease sofosbuvir exposures,
3 thus leading to lowered efficacy. These drugs were
4 not studied in a drug-drug interaction trial with
5 sofosbuvir. However, based on their known
6 mechanism of inducing P-gp transport, they have a
7 high potential for affecting sofosbuvir and should
8 not be coadministered.

9 This slide shows drugs for which an in vivo
10 drug-drug interaction trial was conducted, and the
11 results indicated that no clinically significant
12 changes in the exposures of either sofosbuvir, its
13 major metabolite, GS-331007, or the interacting
14 drugs were detected. Thus, any of these drugs
15 listed on this slide, which includes some
16 antiretroviral drugs, methadone, and some
17 immunosuppressive drugs, can be coadministered with
18 sofosbuvir with no dose adjustment of either drug.

19 Sofosbuvir may be given to patients with
20 mild or moderate renal impairment with no dose
21 adjustment. Sofosbuvir can be used in patients
22 with hepatic impairment with no dose adjustment.

1 There is the potential for a reduction in the
2 efficacy of sofosbuvir when it is coadministered
3 with P-gp or BRCP inducers.

4 Drug interaction studies conducted to date
5 have demonstrated no clinically significant changes
6 for either sofosbuvir or the interacting drug.

7 To conclude, sofosbuvir in combination with
8 ribavirin provides the first all-oral
9 interferon-free regimen for chronic hepatitis C
10 patients with genotype 2 or 3 HCV infection.

11 Sofosbuvir in combination with pegylated interferon
12 and ribavirin provides improved efficacy and
13 shorter treatment duration for chronic hepatitis C
14 patients with genotype 1 or 4 hepatitis C virus
15 infection.

16 Sofosbuvir and ribavirin regimen provides a
17 therapeutic option for chronic hepatitis C patients
18 with HCC, awaiting liver transplantation, thus
19 addressing an unmet need for this patient
20 population. No major safety issues associated with
21 sofosbuvir use have been identified to date.

22 This concludes my presentation. Dr. Karen

1 Qi will now present exploratory analyses done to
2 predict a response in treatment-experienced
3 genotype 1 population. I would like to thank the
4 committee for their attention.

5 **FDA Presentation - Karen Qi**

6 DR. QI: Good morning. My name is Karen Qi.
7 I'm here to present an exploratory analysis
8 performed to support the use of sofosbuvir in the
9 genotype 1 pegylated interferon and ribavirin or
10 P/R treatment-experienced population. This will
11 provide you background information to assist you in
12 the discussion this afternoon.

13 The question for today's discussion is
14 whether the high SVR rates demonstrated in the
15 genotype 1 treatment-naive population provides
16 evidence that 12-weeks of sofosbuvir plus P/R is
17 also effective in genotype 1 P/R treatment-
18 experienced population.

19 The NEUTRINO study evaluated the 12-week
20 sofosbuvir plus P/R treatment in genotype 1
21 treatment-naive subjects. The SVR12 rate was
22 89 percent, however, there's no available data from

1 sofosbuvir studies that investigates the regimen in
2 the genotype 1 P/R treatment-experienced
3 population.

4 Because this regimen might offer an
5 important treatment option for genotype 1 P/R
6 treatment-experienced patients, I will present two
7 exploratory analyses to predict the SVR rate for
8 the sofosbuvir regimen for this population.

9 The first analysis was conducted to predict
10 the SVR rates for the sofosbuvir regimen in the
11 overall genotype 1 P/R treatment-experienced
12 population. The analysis was based on the
13 historical SVR rate for P/R treatment. Across P/R
14 arms in multiple historical studies, the observed
15 SVR rates on P/R treatment ranged from 40 to
16 50 percent. Those subjects who do not achieve SVR
17 are classified as P/R treatment failures and become
18 the P/R treatment-experienced population.

19 In the NEUTRINO study, 89 percent of
20 subjects achieved SVR12, and 11 percent failed
21 treatment. This increase in SVR rates over that
22 typically observed for P/R treatment most likely

1 comes from the population that would have been
2 classified as P/R treatment failures.

3 Among the 50 percent P/R treatment failures
4 observed historically, if we assume 11 percent do
5 not respond to the sofosbuvir regimen as seen in
6 the NEUTRINO study, then 39 percent of historical
7 P/R treatment failures will respond. It follows
8 that the predicted SVR rate for the sofosbuvir
9 regimen in the NEUTRINO genotype 1 P/R treatment-
10 experienced population will be 78 percent.

11 The previous analysis evaluated the
12 predicted SVR rates in the overall genotype 1 P/R
13 treatment-experienced population. We also explored
14 the predicted SVR rates from the sofosbuvir
15 regimen, based on the baseline predictive factors
16 for lower response to P/R.

17 A review of published literature identified
18 baseline factors, which are more likely to result
19 in P/R treatment failure in genotype 1
20 treatment-naïve patients. These factors include
21 high baseline viral load, fibrosis score of F3 or
22 F4, presence of cirrhosis, pre-diabetes or

1 diabetes, high baseline ALT level, and
2 African-American race. Recent published analysis
3 have also identified that IL28B is associated with
4 a response to P/R treatment, which might partly
5 explain the impact of race.

6 The second analysis focuses on P/R partial
7 and non-responders, which are the more difficult-
8 to-treat patients in P/R treatment-experienced
9 population. According to published literature and
10 HCV treatment guidelines, IL28B non-CC, high
11 baseline viral load, and METAVIR score of F3 or F4
12 are important baseline characteristics to predict
13 the lower response to PR treatment in genotype 1
14 treatment-naive subjects.

15 These factors have been consistently
16 identified as associated with the increased
17 likelihood of P/R treatment failure. Based on
18 these baseline predictors, the accrued knowledge
19 has shown that the observed SVR rates between the
20 harder-to-treat treatment-naive population and the
21 documented P/R and null responders in a treatment-
22 experienced population were similar.

1 The observed SVR rates in the harder-to-
2 treat treatment-naive population ranges from 43 to
3 51 percent compared to 44 to 59 percent in the
4 partial and null responders.

5 The same baseline predictors were applied to
6 the NEUTRINO data. This figure displays the SVR
7 rates for the three baseline characteristics in the
8 NEUTRINO study. For example, in IL28B, the red bar
9 represents 98 percent of CC subjects achieving SVR
10 and blue bar represents 86 percent of non-CC
11 subjects having SVR.

12 The non-CC subject had a lower response
13 rate. From the baseline HCV viral load, more
14 subjects with lower viral load achieved SVR
15 compared to those with higher viral load. For
16 METAVIR score, the SVR rate was lower in the
17 subjects with METAVIR score of F3 or F4.

18 The SVR rates are among the harder-to-treat
19 treatment-naive subjects, defined by combining
20 those three baseline covariates in the NEUTRINO
21 study was 71 percent. Based on the accrued
22 knowledge, the SVR rates for the P/R partial and

1 null-responder is predicted to be close to
2 71 percent.

3 Finally, I will reiterate the considerations
4 and limitations of sofosbuvir use in the genotype 1
5 P/R treatment-experienced population. The NEUTRINO
6 study resulted in a high SVR rate for 12 weeks of
7 sofosbuvir plus P/R in genotype 1 treatment-naive
8 subjects. However, the submission did not include
9 data for the genotype 1 P/R treatment-experienced
10 population.

11 The exploratory analysis led to 78 percent
12 predicted SVR rates for the overall genotype 1 P/R
13 treatment-experienced population and 71 percent for
14 P/R partial and null -responders, but these
15 predictions were based on assumptions.

16 In summary, the 12-week sofosbuvir plus P/R
17 might provide treatment options for the genotype 1
18 P/R treatment-experienced population. The 12-week
19 regimen is shorter, which might result in an
20 improved safety profile.

21 Finally, on behalf of Dr. Mishra and myself,
22 I would like to acknowledge the contributions of

1 the entire review team and many others who
2 contributed and provide support throughout the
3 review. Thank you for your attention.

4 **Clarifying Questions**

5 DR. MURATA: Thank you to the agency
6 presenters for their talk and slides. Now, I'd
7 like to open up for clarifying questions for the
8 FDA. And please remember to state your name for
9 the record before you speak.

10 Dr. Korman?

11 DR. KORMAN: I'd like to continue to explore
12 the issue of the CK abnormality that was identified
13 and maybe understand the cardiomyopathy that
14 occurred in another class.

15 I understand that, if you get peg, you're
16 not going to go out and run a marathon. And that
17 might explain the difference between the ones who
18 got two drugs and the ones who got peg. But these
19 are asymptomatic patients. What's your assessment
20 of this event -- of these events?

21 DR. MISHRA: So first, I will address the
22 creatine kinase elevations. The number of subjects

1 with grade 3 or grade 4 CK elevations was low.
2 There were no cases of rhabdomyolysis in the
3 development program. And due to the presence of
4 confounding factors, which were noted earlier by
5 the applicant, such as increased physical activity
6 in subjects with grade 3 or grade 4 levels, it is
7 really challenging for us to assess any causal
8 relationship between sofosbuvir use and CK
9 elevations.

10 Additional data from ongoing or future
11 trials evaluating sofosbuvir may be helpful in
12 further assessment of this finding. And as I
13 mentioned earlier, we do a routine safety
14 monitoring once a new drug is approved. So this
15 will be a part of a routine monitoring and, if we
16 see anything, we will make a note of it.

17 Regarding cardiac events, based on the
18 reported data so far, there have been no reports of
19 cardiomyopathy with sofosbuvir use so far. The
20 events, which I noted in the FDA background package
21 are mainly arrhythmia palpitations or tachycardia.
22 I don't recall some others. But other than

1 that -- and please note, all these patients were
2 also on concomitant ribavirin therapy, which gives
3 hemolytic anemia. And some of these symptoms could
4 also be seen in patients with anemia.

5 But to discuss further about cardiovascular
6 events, with your permission, I would like the
7 sponsor to add anything that they can add for
8 cardiovascular assessment.

9 DR. MURATA: To facilitate the discussion,
10 perhaps, if it's okay with you, Dr. McHutchison, we
11 will try to work that into the afternoon
12 discussions.

13 Dr. Birnkrant?

14 DR. BIRNKRANT: I'd like to add to what was
15 just said. With regard to cardiomyopathy and
16 another investigational agent, although sofosbuvir
17 and another investigational agent were in the same
18 overall class of the NS5B, polymerase inhibitors,
19 they were structurally somewhat dissimilar in that
20 this drug is a uridine derivative, and the other
21 drug was a guanosine derivative.

22 Those who had cardiomyopathy with the other

1 investigational agent were quite symptomatic.

2 DR. MURATA: Dr. Giordano?

3 DR. GIORDANO: Tom Giordano. Perhaps if
4 this meeting were being held at a Holiday Inn, I'd
5 get it, but I have to admit, I don't understand at
6 all the attempt to extrapolate from the
7 treatment-naïve data to the treatment-experienced
8 population. And could you please try to explain
9 that again?

10 DR. MISHRA: I will ask our colleague,
11 Dr. Jeff Florian, from pharmacometrics group to
12 address that question.

13 DR. FLORIAN: Jeffry Florian, FDA. So we've
14 taken a look at the P/R treatment response from
15 treatment-naïve subjects as well as prior P/R
16 treatment failures. And what we ended up seeing
17 was the on-treatment response as assessed by week 4
18 change HCV RNA was similar. We used that
19 observation with some of the previous reviews to
20 leverage information from the treatment-experienced
21 population to treatment-naïve, and used the
22 treatment-naïve data to help inform the use of

1 those regimens in those populations.

2 We weren't able to use on-treatment
3 assessments in this case because, as actually was
4 noted by you, the phase 3 trial was not controlled.
5 It did not have a comparator arm.

6 But this led us to take a step back and
7 think about what have we seen from P/R treatment
8 arms throughout the past 10 years of experience.
9 And when we look across it, there's this consistent
10 overall SVR response rate, genotype 1 subjects,
11 ranging upward to 50 percent. Then we're thinking,
12 "What is going on? What's happening in the other
13 50 percent?" These are the group of patients that
14 we now call prior treatment failures. And we
15 classify them by how they failed on P/R treatment.

16 This got us further thinking, then, how to
17 consider these classifications going forward.
18 Already, in genotype 1 subjects, P/R is no longer
19 the standard of care. So these classifications,
20 these definitions, are going on the wayside.

21 Taking a closer look, what exactly is
22 contributing to these various on-treatment

1 responses? And a lot of things were brought up
2 yesterday that what's driving these responses are
3 baseline factors. And there are a number of
4 publications showing these various factors that
5 were brought up in Dr. Qi's talk that contribute to
6 varying degrees of P/R non-response.

7 So what was presented there was an
8 exploratory analysis looking at these baseline
9 factors to try and identify a patient population
10 from treatment-naive, similar to what are these P/R
11 non responders, prior P/R non-responders that we
12 would normally classify at the end of treatment.
13 But really, that P/R treatment is not changing
14 their response.

15 Does that address your question?

16 DR. GIORDANO: No. I'm sorry, but I still
17 don't -- so, yes. You have people who have failed
18 treatment in the past. You know that that's half
19 the population, roughly. And then you say some of
20 those patients, maybe that half of the population,
21 is enriched for characteristics that make him more
22 likely to fail therapy. Fair enough. But you

1 apply some estimate of the efficacy of this
2 treatment to arrive at some proportion that's going
3 to have a response to the experimental treatment.

4 What is that estimate based on? That's my
5 question. You have no data in treatment-
6 experienced patients.

7 DR. FOLLMANN: Could I take a stab at this?

8 DR. MURATA: Dr. Follmann?

9 DR. FOLLMANN: Yes. I thought about
10 slide 47 that Karen Qi presented. This seemed in
11 my mind a more clear kind of analysis. So the way
12 I think about this is that if we had a baseline
13 characteristic that said P/R response versus
14 non-response in NEUTRINO -- and this would be these
15 patients who would ultimately fail or not fail P/R
16 therapy. And we figure there's about half of them
17 that would fail and half of them that wouldn't
18 fail.

19 So that's where the 50/50 split goes. If
20 you can go to slide 46, 47.

21 DR. MURATA: This is 47.

22 DR. FOLLMANN: It's not quite what I had

1 in -- one more, I guess. So the way I think of
2 this, the right-hand side is the people who -- the
3 white part is the 50 percent of the population that
4 would be P/R responders. And if we knew at
5 baseline who -- and you're going to conservatively
6 assume that they would all be successes.

7 So the other half is the non-responders, and
8 you're going to figure that all the failures must
9 be in the people who would be non-responders. And
10 that's where you assign all the 11 failures to the
11 people here sort of assuming would be P/R
12 non-responders.

13 So in my mind, this is kind of a
14 conservative calculation to extrapolate what the
15 success rate would be in P/R non-responders.
16 You're saying all the failures in this population
17 belong to the P/R non-responder pool who we're
18 identifying here through this thinking.

19 DR. MURATA: Dr. Cox, you had a comment?

20 DR. COX: Yes. So maybe I'll just try and
21 back up a minute. And I agree completely with what
22 Dean's describing. And they will try and describe

1 this as two ways of trying to understand the
2 treatment-experienced population.

3 So as Dean's described, I think there's sort
4 of an empirical attempt, and that's sort of the pie
5 chart. I would summarize it as that they must be
6 there. They must be in the population. That's the
7 argument. So that's sort of the empirical
8 approach.

9 Now, a second approach I would describe is
10 the biological approach in essence. What is a
11 patient who is a P/R non-responder, partial
12 responder? And do we understand the biology of
13 that disease state in essence? And that's what's
14 attempted to try -- what we're trying to understand
15 by looking at non-CC high-viral load and cirrhosis
16 or METAVIR score.

17 So we're trying to understand the
18 characteristics of that patient population that may
19 define a group that's more difficult to treat, and
20 then trying to see if we can understand what the
21 biology of more difficult-to-treat or who might be
22 a treatment-experienced patient population if they

1 had been exposed to P/R, how did they do from the
2 available data.

3 It seems there's one other question in here,
4 too, and that is, does treatment with P/R change
5 what will happen subsequently? And so that's one
6 more component in this overall equation.

7 But you can see we're trying to look at,
8 empirically, what can we estimate what happened
9 here. Biologically, what do we know about a P/R
10 partial, null responder, relapser, and have we
11 actually studied that biology in the existing data?
12 And then there's the other question of does prior
13 P/R treatment change things?

14 Does that help some to try and
15 compartmentalize this and what the underlying
16 rationales are for this effort?

17 DR. MURATA: Dr. Giordano?

18 DR. GIORDANO: It does. Thank you. So do
19 we know? Does prior P/R treatment, would that
20 influence response? It's ultimately a very
21 important question, I would think, even in some
22 earlier phase 1 or 2 data.

1 DR. COX: So we think there's evidence that
2 it doesn't, but I'm going to ask some others to
3 contribute to that discussion.

4 DR. MURATA: Dr. Soon?

5 DR. SOON: Guo Soon, FDA. I want to add on
6 to what Dr. Florian said earlier, to close the loop
7 of the assumptions here. As Dr. Florian explained,
8 this is a conservative analysis, but there is an
9 implicit assumption here, which is biological, and
10 so really put this forward to clarify.

11 That is, we assume that the patients who are
12 taken -- for any treatment-naive patients, if they
13 are started with P/R for 48 weeks, then followed by
14 the sofosbuvir for 12 weeks -- which will not do
15 any worse than if you start the same patient on the
16 sofosbuvir directly for 12 weeks -- that's the
17 assumption here being made. If you believe in that
18 assumption, then the analysis -- whatever you put
19 forward is a conservative analysis. Thank you.

20 DR. MURATA: Dr. Florian?

21 DR. FLORIAN: Jeff Florian, FDA. So there
22 are two pieces of evidence. One, we can see with

1 retreatment that, like, prior relapsers, prior
2 partials, nulls with retreatment, you can get some
3 of them to respond. So it's not as if they've gone
4 from zero to staying at zero. You're able to get
5 some of them. And even those response rates from
6 those subgroups are along the same lines of what
7 their original response was with prior partial
8 nulls having a lower response rate when retreated
9 with P/R than prior relapsers.

10 The second piece of evidence came when we
11 took a look at what were the on-treatment P/R
12 response across this litany of prior submitted P/R
13 treatment arms, P/R control arms, looking at what
14 is the week 4 response for treatment-naive patients
15 grouped according to their end-of-study outcome, as
16 well as then what were patients who had been
17 classified as prior relapsers, prior partial, prior
18 null, and looking at that on treatment.

19 Actually, what slide is that? Pictures are
20 much more valuable than all the words.

21 So this is the analysis taken from patients
22 who are treatment-naive, grouped according to what

1 is their end-of-treatment outcome responder,
2 relapser, partial null shown in red, pink, orange,
3 and green as you go from left to right.

4 What is shown then is what is the
5 on-treatment response assessed at week 4 for those
6 groups from the treatment-naïve, and then we also
7 have that data for our prior relapsers, partials,
8 prior nulls, same colors, but above what is the
9 untreated data.

10 What we saw was the week 4 response when
11 they were on the first line of treatment, as well
12 as then what was second consequent P/R treatments,
13 was similar.

14 This was a piece of evidence that
15 retreatment was similar. We also had what are the
16 actual SVR rates that have been seen from
17 retreatment, as well as what is the ranking order
18 of the SVR rates from those prior P/R treatment
19 failure subgroups when retreated.

20 DR. MURATA: Dr. Giordano?

21 DR. GIORDANO: So thank you for the
22 clarification. It helps me understand it quite a

1 bit. The data you just presented, though, had
2 nothing to do with the drug under consideration.
3 Correct? And so let me ask a straightforward
4 question perhaps of the sponsor.

5 Do you have any data of the drug under study
6 being used in people who are treatment-experienced
7 prior non-responders?

8 DR. MURATA: As the chair, I'd like to defer
9 that for the afternoon session.

10 In the interest of time, I think we should
11 break. At the moment, I have three people who are
12 listed for questions for the agency clarifications,
13 Dr. Ghany, Dr. Daskalakis, and Dr. Raymond.

14 So at this moment, I would like to propose
15 that we will now break for lunch. We will
16 reconvene in this room in one hour at 1:00, at
17 which time we will begin the open public hearing
18 session.

19 (Whereupon, at 11:59 a.m., a luncheon recess
20 was taken.)

21

22

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

(1:00 p.m.)

Open Public Hearing

DR. MURATA: Let's get started.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement,

1 to advise the committee if you do not have any such
2 financial relationships. If you choose not to
3 address this issue of financial relationships at
4 the beginning of your statement, it will not
5 preclude you from speaking.

6 The FDA and this committee place great
7 importance in the open public hearing process. The
8 insights and comments provided can help the agency
9 and this committee in their consideration of the
10 issues before them.

11 That said, in many instances and for many
12 topics, there will be a variety of opinions. One
13 of our goals today is for this open public hearing
14 to be conducted in a fair and open way, where every
15 participant is listened to carefully, and treated
16 with dignity, courtesy, and respect. Therefore,
17 please speak only when recognized by the
18 chairperson. Thank you for your cooperation.

19 Will speaker number 1 step up to the podium
20 and introduce yourself? Please state your name and
21 any organization you are representing for the
22 record.

1 MR. BRAYSHAW: Hi. My name is Paul
2 Brayshaw, and I'm here on behalf of People with
3 Bleeding Disorders in Hepatitis C. And I'd like to
4 thank the committee for the opportunity to provide
5 testimony today, as well as in support of this new
6 drug application.

7 I represent patients and supporters affected
8 by hepatitis C. It's a crisis among people with
9 bleeding disorders. As an organization, we
10 organize and advocate for urgent development and
11 access to new, better hepatitis C therapies.

12 Among people with factor-dependent bleeding
13 disorders over the age of 30, nearly the entire
14 cohort was exposed to hepatitis C via contaminated
15 blood products.

16 We have a long-term disease associated with
17 these therapies, which were used for the treatment
18 of bleeding disorders. I actually had my first
19 factor-concentrate injection shortly after birth,
20 so I think I've probably had it since 1973.

21 About four years ago, we first encountered
22 many of you at a similar hearing for the approval

1 of telaprevir and boceprevir. Since then, one
2 effective, low side effect therapy, which has
3 proven to be a cure, was demonstrated in a clinical
4 trial. This was sofosbuvir and declatasvir.

5 Yet, we as a society haven't figured out how
6 to make it available. We know this cure exists and
7 people in our community are becoming more ill and
8 even dying because they can't obtain it. The rest
9 of our testimony comes out of our profound desire
10 to create a cure as quickly as possible.

11 This new drug application under discussion
12 today allows the marketing of sofosbuvir.
13 Sofosbuvir is one step closer to a cure that we're
14 looking for. It has the high-activity, specific
15 low side effect, and as well as a high barrier to
16 resistance. People with bleeding disorders have
17 been allowed into some clinical trials where
18 sofosbuvir is tested, yet we have little data
19 specific to our community.

20 For most situations, the current application
21 requires coadministration of pegylated interferon
22 and ribavirin. This is particularly significant to

1 our aging hemostasis-challenged community because
2 it's very powerful. The side effects are very
3 powerful. The combination is not so much. And
4 we're not satisfied with this mediocre reported
5 effectiveness.

6 We support this application because it moves
7 sofosbuvir towards a cure -- because sofosbuvir
8 moves us towards a cure. And we can't ignore that
9 it's far and away better than any other drug on the
10 market.

11 We hope for more rapid access programs. We
12 need early compassionate access, particularly for
13 patients with advanced liver disease. And we
14 expect for trials to continue to include people
15 with bleeding disorders because our treaters, the
16 hematologists, tend to recommend the go-slow
17 approach on most new things, new therapies, prior
18 to the accumulation of community-specific
19 experience.

20 I'd like to thank you for the time today.

21 DR. MURATA: Thank you very much.

22 Will speaker number 2 step up to the podium

1 and introduce yourself? Please state your name and
2 any organization you are representing for the
3 record.

4 MR. OGBOMO: Good afternoon, ladies and
5 gentlemen. My name is Onaiwu Ogbomo. Let me
6 spell, O-N-A-I-W-U, last name O-G-B-O-M-O. Most
7 people pronounce it Obama. Even though I'm black,
8 I'm from Africa, but I'm not related to the
9 President. I'm from Nigeria. His father is from
10 Kenya

11 (Laughter.)

12 MR. OGBOMO: I first had experience with
13 hep C about 15 years ago, when I was diagnosed.
14 Then my doctors told me that there is a long life
15 expectancy for me, and I didn't take it seriously
16 that I would get to this stage where my life would
17 be in danger.

18 About three or four years ago, I found out
19 that my situation was deteriorating. And so I was
20 recommended for transplant enlistment, and I did
21 put my name on the list.

22 Just about a year after, I was called for a

1 transplant. Then I rejected the transplant because
2 I had a son in the university, and my second child,
3 a daughter, was preparing to enter the university.
4 I was so afraid that I might die on the operating
5 table, and they will not have a father to take care
6 of them.

7 However, by May last year, it came to a
8 point where I had to make the final decision,
9 whether to do the transplant or not. And I did
10 sign up to do it. I successfully underwent the
11 transplant on the 1st of June, 2012. And I came
12 out of the operation room very well, spent about
13 two months without any problem. But by about the
14 first week or second week of August last year, I
15 discovered there's a recurrence of the disease with
16 the new liver that I got.

17 At that time, my doctors told me that I
18 should go home and prepare for my final departure
19 from this earth because my situation was getting
20 very bad. Not knowing that my doctors were working
21 behind the scene, a few weeks later I was told by
22 my doctor that there's approval by the FDA and

1 Gilead Sciences, that I could get an experimental
2 drug.

3 The question was, "Would you be willing to
4 take it?" At that point, I had no choice anyway.
5 If I take it, I might die. If I don't, I will die.
6 So I decided to sign up on compassionate grounds to
7 take the medication.

8 I started on August 24th, 2012. The viral
9 level or the baseline level at that time was
10 16 million. I don't know what you scientists call
11 it, but there was 16 million, whatever level, in my
12 blood. By the fourth week, the number had -- after
13 taking sofosbuvir, the number had reduced to
14 44,290. And by November 15th, 2012, it has come
15 down to 4,304. And week 12, it was now less than
16 43. And by week 24 -- that is, I had taken it for
17 24 weeks -- the viral level was now undetectable.

18 By February 2012 -- no, September 6th, 2012,
19 ribavirin, 200 milligrams, was added to my
20 protocol. And then by November 9th -- initially, I
21 was taking 200 milligrams once a day. And then by
22 November 9th, milligrams was now the level I was

1 taking.

2 On the whole, by May 2nd, 2013, I stopped
3 taking the drug. Since May to today, my lab work
4 has shown that I no longer have hepatitis C in my
5 system.

6 Being told that you are going to die was a
7 very serious experience. I was like a prisoner who
8 had been told that you're are being condemned to
9 death. But the time the doctors, called me and
10 gave me the drug, I was still very much at the
11 level whether the governor would pardon me or not,
12 but I now was still on the drug.

13 I must say that, in my situation, I regards
14 sofosbuvir as a magical drug because, otherwise, if
15 I had not taken it, I wouldn't be here talking to
16 you today. And today, I am very, very confident
17 that at least I've been given a second chance. And
18 that is why I have offered to come here to appeal
19 to you to please approve this drug for the benefit
20 of those like me who are suffering somewhere that
21 you may not know.

22 Those of you in the United States will not

1 understand what it means to come from a developing
2 world. I don't know how I got the disease, but I
3 suspect I may have gotten it through vaccinations
4 because, in those days, they used to use needles
5 for 10, 50, 100 people, only to put it in a trough
6 and boil it. I have never been sexually
7 promiscuous, so I don't think I got it through that
8 way. I would have preferred that this drug was
9 available when I was first diagnosed. However, I
10 am very grateful because a half-full in a cup is
11 better than none.

12 I know I will live throughout my life,
13 taking anti-rejection medication, but I also know
14 that God has given me, the medical doctors who
15 treated me, the nurses who took care of me, have
16 given me a second opportunity to represent the
17 interests of those who, incidentally, find
18 themselves in my situation.

19 Ladies and gentlemen, that is my story, and
20 I hope in a few months from now, other people,
21 whether in Nigeria, Ghana, Sierra Leone, India,
22 Bangladesh, United States, or elsewhere, we'll be

1 in a position to benefit from the magic of this
2 drug. In my family, we call sobosprevir, "that
3 drug." And that drug is the drug that has saved a
4 son, a father, a brother, a cousin, a nephew, so
5 on. Thank you very much.

6 DR. MURATA: Thank you very much. Will
7 speaker number 3 step up to the podium and
8 introduce yourself? Please state your name and any
9 organization you are representing for the record.

10 MS. DEE: Hi. Yes. I'm Lynda Dee from AIDS
11 Action Baltimore and the Fair Pricing Coalition.
12 My organization gets funding from a number of drug
13 companies, including Janssen and Gilead. And
14 nobody paid for me to get here today.

15 So first, if I may say, oh, happy day. This
16 is very exciting for me and for I think all the
17 committee people here. I'm actually cured of HCV
18 using sofosbuvir, and I'm really elated to see this
19 day come. And I think that most everybody in the
20 HCV community feels that way.

21 I'm here also to support approval of this
22 drug with interferon and ribavirin for 12 weeks in

1 genotype 1, 2, and 4, although if I was a person
2 that was still infected, and I was a prior null
3 responder, and to make it more interesting, if I
4 had cirrhosis, I wonder what guidance you could
5 give my doctor as to what dose, duration of
6 treatment I might really need with this drug.
7 Anyway, I'll leave that to the wisdom of the agency
8 to figure out.

9 I'm really glad that this genotype 3 issue
10 is cleared up. I mean, it makes it a lot easier to
11 recommend -- support approval of genotype 3 and 2,
12 12 weeks for 2 and 24 weeks for genotype 3.

13 It was really interesting to hear the
14 comments about the pre-liver transplant patients.
15 And I say amen to you, brother, for people -- I
16 mean, the compelling need there, actually, I think
17 really supports approval for patients in that
18 horrible situation.

19 The problem is for how long. And I think it
20 looks clearer that it's not -- 24 weeks is not
21 enough; 48 weeks might be better. But again, the
22 agency will give us guidance on that.

1 I was really elated to hear about how there
2 are more African-Americans and women. And people
3 like me have been coming to these meetings for
4 years screaming about inclusion of underrepresented
5 people. And I agree with what Daniel said
6 yesterday about not exposing more people to
7 interferon-ribavirin regimens and hopefully, having
8 the sponsors include typically underrepresented
9 people in the next round of trials that are going
10 to be interferon-sparing.

11 But the idea of putting caps on enrollment
12 of whites and waiting for other populations to
13 enroll in the trial is just really fantastic. I
14 mean, we've been begging for this, and I'm really
15 glad to see it. And I hope that other companies
16 will follow suit with that.

17 I'm glad to see that you're doing the trial
18 for people with severe renal insufficiency. I
19 would love to see -- I'm cured with
20 sofosbuvir -- sofosbuvir and daclatasvir. So I
21 really would hope that Gilead would continue or
22 restart their collaborations with other drug

1 companies, like Janssen for simeprevir and BMS for
2 daclatasvir, to see what's really going to happen
3 to larger groups of people on those combinations.
4 I think the communities would be extremely
5 interested in seeing that.

6 I also hope that -- you know, it's America.
7 There are no rules about what you can charge. But
8 it would be a shame that this drug would not be
9 accessible to people because it cost too much. I
10 would urge you. I would say I would beg you to
11 consider pricing this drug reasonably. We all know
12 that it's going to be cost-effective, but that
13 scale of what's cost-effective is I think an
14 unreasonable way to look at it.

15 I mean, if the price of telaprevir and
16 boceprevir I think is already exorbitant. I mean,
17 if you could price it even close to what those
18 drugs are, I think that would be reasonable under
19 the circumstances, and you'd still make a fortune.
20 The volume that you're going to get for this I
21 think it's outstanding.

22 Anyway, I'm just extremely happy that, as

1 Paul said, we're one step closer to the day when
2 interferon and ribavirin will be obsolete. I think
3 the risk-benefit ratio that Dr. McHutchison showed
4 really says it all, easier to take as far as side
5 effects, better efficacy, no food effect, limited
6 drug-drug interactions.

7 Yay is all I can say. So thank you for the
8 good work and I hope we can get this drug out to
9 people and as many people that need it as possible.
10 Thank you.

11 DR. MURATA: Thank you very much. Our
12 understanding is that speaker 4 is no longer on the
13 list, so we will proceed with speaker number 5.

14 Will speaker number 5 step up to the podium
15 and introduce yourself? Now, please state your
16 name and any organization you are representing for
17 the record.

18 MR. LABRECQUE: Good afternoon. My name is
19 Fred LaBrecque from the Caring Ambassadors program.
20 I don't have any financial relationships to
21 disclose. Our organization has received industry
22 support for various activities, but no one has paid

1 for my travel today.

2 Caring Ambassadors is a nonprofit patient
3 advocacy organization working to improve the lives
4 of people living with hepatitis C. Lorren Sandt,
5 the executive director of Caring Ambassadors, has
6 been a leader in the viral hepatitis community
7 since 1999. She could not be here today, so I'm
8 here to read a statement on her behalf.

9 "I'm here today to ask that the FDA not only
10 approve sofosbuvir for the treatment of
11 hepatitis C, but do so in a manner that will allow
12 it to help as many people as quickly as possible.
13 There is no doubt that sofosbuvir markedly improves
14 current treatment when used in a variety of
15 context. As such, we encourage the FDA to consider
16 a broad approval for the application of sofosbuvir.

17 "Given its safety profile, we ask that
18 clinicians be given the freedom to prescribe
19 sofosbuvir in patients with various genotypes and
20 in a multitude of durations and combinations,
21 especially those that exclude pegylated interferon,
22 the harsh side effects of which can be a major

1 barrier to care for many patients.

2 "A structured and measured approach to
3 expanding the use of sofosbuvir would accelerate
4 our understanding of the drug and more importantly,
5 positively impact many more patients. Giving
6 clinicians the flexibility to prescribe sofosbuvir
7 as part of the interferon-free combinations in
8 patients of all genotypes will allow many more
9 patients living with hepatitis C to enter
10 treatment.

11 "Finally, we ask that the FDA consider a
12 more expansive approval of classes of drugs to be
13 used in the treatment of hepatitis C. Where
14 preliminary data exist on cross-class use of drugs
15 and where these data identify no contraindications,
16 we ask that cross-class use be approved.

17 "By doing so, the FDA would be filing its
18 own successful example in the development of
19 treatment regimens for HIV. With all the new drugs
20 coming into the market, we do not have the time to
21 conduct large-scale phase 3 trials on every
22 potential iteration. Thousands would die

1 unnecessarily before such trials could be
2 completed.

3 "Sofosbuvir is a powerful new tool in the
4 treatment of hepatitis C. On behalf of the
5 patients that Caring Ambassadors fights for every
6 day, we ask that the FDA approve its use as broadly
7 as possible. We believe that doing so will help
8 save the lives of millions of Americans. Thank
9 you."

10 DR. MURATA: Thank you very much. And will
11 speaker number 6 step up to the podium and
12 introduce yourself? Please state your name and any
13 organization you are representing for the record.

14 MS. SMITH: My name is Robin Lord Smith. I
15 represent Hepatitis C Association. I also, for
16 Hepatitis C Association, work for Help for Hep, the
17 national peer helpline that's part of the support
18 partnership. We do receive financial support from
19 Gilead and many other companies that are working on
20 medication development, and nobody paid for me to
21 come here today.

22 I have three minutes, so I'm just going to

1 real quickly tell you that I'm cured from
2 hepatitis C, was able to do that about nine years
3 ago with pegylated interferon and ribavirin. I was
4 genotype 2b. It was not easy.

5 I have gone on to be very involved in
6 advocacy and support for others. And that's why
7 I'm here today. On the helpline, we get many calls
8 from people that are not able to do the standard of
9 care, and are very anxious to hear what's going on,
10 and looking forward to a time when they can do a
11 medication treatment that's going to give them a
12 cure.

13 So basically, I'm here to say I hope that
14 fewer and fewer people have to experience the
15 difficulties and the side effects that I did
16 experience under standard of care. It was at great
17 cost, quite frankly; not to say that I'm not very
18 grateful for that and I'm very happy to be cured
19 from hep C, but there are a lot of people out there
20 that are waiting for this.

21 So I'm here in support of that, and asking
22 you to kind of reiterate what some of the other

1 people said about making this available as quickly
2 as possible and making this available to as many
3 people as possible so that we can all be a part of
4 seeing a cure for this virus.

5 That's it. Thank you.

6 **Clarifying Questions (continued)**

7 DR. MURATA: Thank you very much. Now, the
8 open public hearing portion of this meeting has now
9 concluded, and we will no longer take comments from
10 the audience. The committee will now turn its
11 attention to address the task at hand, the careful
12 consideration of the data before the committee as
13 well as the public comments.

14 So now this is our opportunity to tie up
15 loose ends from the morning discussion. And so
16 that we remain on task and to proceed in a rational
17 way, I propose the following. First, the agency,
18 Dr. Cox and Dr. Birnkrant, requested that they
19 issue clarifying comments.

20 Number two, there are three colleagues
21 amongst our fellow committee members who have
22 outstanding questions specifically towards the

1 agency's presentation. And number three, the
2 sponsor was requested to be given an opportunity to
3 address residual clarifying issues from the
4 morning.

5 So I would like to start there before we
6 open the committee for discussion -- and
7 clarification questions to both the agency and the
8 sponsor. So with that preamble, Dr. Cox and
9 Dr. Birnkrant?

10 DR. COX: Thank you. So I thought it might
11 be helpful just for a minute just to provide a
12 little bit of perspective in regards to
13 Dr. Giordano's question and our presentation by
14 Karen Qi and Jeff Florian in response to the
15 questions.

16 So if you think about it, we're learning
17 about hepatitis C. We're learning about the
18 disease as we see the results of trials. And
19 that's very important as we understand more about
20 the biology of the disease. And you can see that
21 the analysis that they're presenting is trying to
22 get a greater understanding of what is difficult to

1 treat, in essence. What is a treatment-experienced
2 patient in the era of pegylated interferon and
3 ribavirin.

4 If you think about it and you think about
5 the importance of this, if we look to the future
6 and we think about, what do we understand about the
7 biology of difficult-to-treat, and we also think
8 about pegylated interferon and ribavirin,
9 encountering treatment-experienced patients with
10 pegylated interferon and ribavirin is sort of an
11 identifier of difficult-to-treat, maybe something
12 that we encounter very infrequently in the future.

13 So to the extent that we can understand the
14 biology of that today, that will help us, I think,
15 in how we're evaluating drugs and how drugs, in
16 essence, are tested.

17 So I hope that provides a little more
18 perspective on some of the learnings here about the
19 disease of hepatitis C and how we're trying to look
20 at the available data.

21 I think Dr. Florian may have a comment,
22 also, too, if that's okay, Dr. Murata.

1 DR. MURATA: Not a problem. Dr. Florian?

2 DR. FLORIAN: A lot of the items have
3 already been addressed in Dr. Cox's opening
4 comments. Just getting back to one of the
5 questions that was asked, what do we know about the
6 characteristics of treatment naive versus what
7 we're seeing in these prior P/R treatment failures?

8 One of the ways we're looking is, in
9 treatment-naive patients, we have this list of
10 factors. And once they're treated, they've now
11 been exposed to this drug, but those factors aren't
12 changed.

13 So now, we want to know to what extent have
14 maybe viral factors changed. How has their
15 response to P/R altered? And what we were relying
16 on were two pieces of evidence, one, the
17 retreatment results, which shows that you can
18 actually get some of them to respond. So if their
19 response is biased, you can actually get a
20 response, so it's not biased on what would be a
21 negative direction. They were getting zero. Now
22 you can get some of those patients to actually

1 respond.

2 Then the second piece was looking at what
3 were on-treatment viral response, so looking at
4 this week 4 changing viral load from patients based
5 upon when we didn't know their classification and
6 how they went, and then when we knew their
7 classification and their week 4 change in viral
8 load was. So that was a figure that was put up at
9 the end of the morning session.

10 So what we have is, in treatment-naive, to
11 that prior P/R responder, the factors are the same.
12 The only thing that has changed is we now have what
13 is a very useful label that tells us how responsive
14 they are to interferon, but that's also a label
15 that we may not have available going forward.

16 So going back to what Dr. Cox said, is there
17 a way to learn from the biology so that we can
18 continue to have that useful information for
19 guiding patient treatment decisions.

20 DR. MURATA: Thank you very much.

21 Dr. Birnkrant?

22 DR. BIRNKRANT: Just to attempt to further

1 clarify, on slide 49, the second bullet says,
2 "Based on these baseline predictors, accrued
3 knowledge has shown overlapping SVR rates between
4 the harder-to-treat naive population and documented
5 partial/null responders." And we showed ranges of
6 response rates for the harder-to-treat naive and
7 for the partial/null responders.

8 What we actually did was, we don't have a
9 slide to show you, but we applied our approach to
10 our in-house databases of the other drugs we've
11 reviewed and approved over the years. And we get
12 similar findings. So it reassured us that we could
13 go ahead with this particular product and present
14 the analyses that we did today to show you that,
15 within the treatment-naive population, there are
16 these harder-to-treat groups.

17 So I just wanted to make that clear that
18 we've done this using our in-house knowledge, which
19 means the databases from the other drugs that are
20 approved, just in case that bullet was a little too
21 big.

22 DR. MURATA: Thank you very much. I'd like

1 to hold off on any questions on the agency until we
2 were through with the second two parts of the
3 unfinished business.

4 Now, if we are done with Dr. Cox and
5 Dr. Birnkrant, the three people that I have listed
6 for questions to the agency from the morning are
7 Drs. Ghany, Daskalakis, and Raymond. So I would
8 like to give them an opportunity to ask agency
9 questions.

10 Dr. Ghany?

11 DR. GHANY: Thank you. Marc Ghany. My
12 question is for Dr. Mishra. So among the pie of
13 people undergoing transplantation for hepatitis C,
14 those undergoing transplantation for hepatocellular
15 carcinoma represents really a small slice. And the
16 majority are not being transplanted for
17 hepatocellular carcinoma. But they are being
18 transplanted with MELD scores that are, on average,
19 25 or higher.

20 So does the agency have any concerns about
21 using sofosbuvir in this patient population? And
22 is the agency planning on providing any guidance to

1 general practitioners on the use of sofosbuvir in
2 this population? Obviously, this is the population
3 at perhaps greatest need for receiving antiviral
4 therapy. And if you can cure patients going into
5 transplantation, the outcome of transplantation is
6 significantly better.

7 DR. MISHRA: So we fully acknowledge all
8 your concerns, and we are aware that that is the
9 patient population which is in most need of
10 therapy, but we are limited with the data, what we
11 have now, and the data we have reviewed.

12 That's why I made a point during my
13 presentation that this group of pre-transplant
14 population is a subgroup. It's not an overall
15 broad pre-transplant population because these
16 patients receive transplantation due to an upgrade
17 in their MELD scores, which you're pointing out,
18 and not necessarily due to worsening of their liver
19 disease. Because, as you said, patients who
20 undergo liver transplant, not because of their HCC,
21 but worsening liver disease, are maybe different
22 from these HCC-weighted liver transplantations.

1 Unfortunately, we don't have much data. We
2 have some limited data from an individual
3 investigator or compassionate use programs. And I
4 think at this time, we believe that the data is
5 insufficient to make any conclusive determination
6 about the safety and efficacy of sofosbuvir in this
7 patient population.

8 We believe that the optimal treatment
9 regimen and duration of therapy in overall
10 pre-transplant population has not been fully
11 explored at this time.

12 DR. MURATA: Thank you. Next for the
13 question is Dr. Daskalakis.

14 DR. DASKALAKIS: Demetre Daskalakis, Mount
15 Sinai. So I am not sure who I'm directing the
16 question to. I think it's sort of a follow-up
17 question to the conversation about extending the
18 use of the drug to individuals who have been
19 non-responders previously to pegylated interferon
20 and ribavirin.

21 So my question is, how does that interact
22 with what the proposed indication is? The proposed

1 indication reads that it's a treatment of chronic
2 hep C infection in combination with other agents in
3 adult patients with 1 to 6 and/or adult patients
4 who are awaiting liver transplantation.

5 So unlike some HIV drugs, where it'll say
6 "approved for use in naive" or "approved for use in
7 experienced patients," technically this approval
8 would sort of allow the use of this by positions,
9 even in a salvage situation.

10 So my question is, this conversation that
11 we're having I think may influence what the
12 recommended doses are on the package, but does it
13 affect the actual approval?

14 DR. MURRAY: So the actual approval takes
15 into account the overall safety and efficacy of the
16 drug, and then for individual patient subgroups or
17 individual genotypes, that is handled within the
18 prescribing information.

19 If a decision to approve the drug is made,
20 then all these subgroups are handled under
21 indications and usage. And we try to convey the
22 message to healthcare providers that this is what

1 was seen in the clinical trials. This is the
2 response rate in this particular subgroup or
3 population to guide them to make the best decision
4 for the patients.

5 DR. DASKALAKIS: Just a follow-up question.
6 So ultimately, can we interpret that that means
7 that from the agency perspective, the extrapolation
8 of the data into the experienced population is
9 adequate to approve the drug as listed here?

10 DR. BIRNKRANT: I think that's why we're
11 asking you the question later this afternoon.

12 DR. DASKALAKIS: Yes.

13 DR. BIRNKRANT: In other words, what is your
14 opinion or how can we best study? I mean, do we
15 study all groups in order for indications to be
16 granted?

17 DR. DASKALAKIS: Got it.

18 DR. BIRNKRANT: Or can we learn from other
19 groups with key characteristics and use that to
20 craft an indication that's acceptable?

21 DR. DASKALAKIS: Very valuable
22 clarification. Thank you.

1 DR. MURATA: Thank you for the
2 clarification, Dr. Birnkrant.

3 Then last of the three outstanding
4 questioneers is Mr. Raymond.

5 MR. RAYMOND: Thank you. Daniel Raymond.
6 So this is, again, about the extrapolation for
7 genotype 1 previous treatment non-responders. And
8 I'll just say two caveats. I'm okay in principle
9 with this kind of analysis. And I guess my other
10 caveat is that I look further to the day that we
11 don't talk about prior, non-, null relapse
12 responders at all. But while we're still here, I
13 had two questions.

14 One is that you talked, especially in your
15 second analysis, about baseline predictive factors.
16 And when I think about people who do not get an SVR
17 on peg-riba treatment, I also think about
18 on-treatment factors like lower adherence of people
19 who are lost to follow-up, of people who drop out
20 due to side effects and toxicities.

21 So my first question is how you considered
22 that in doing this kind of analysis, that

1 non-response is more than just about baseline
2 predictive factors. And does that actually make
3 your analysis more conservative, more liberal?

4 My second question is whether you try to
5 apply that to the data set for the ATOMIC trial to
6 sort of validate that that range in the 70's kind
7 of holds across what we know about the experience
8 with sofosbuvir in genotype 1.

9 I'm asking these two questions not because I
10 question the thrust of the analysis, but because I
11 think that genotype 1 people who are non-responders
12 will have some difficult choices to make next year.

13 While it might not be possible to have exact
14 precision and a projected SVR rate, they're going
15 to have to compare this against, do I go into an
16 investigational trial for a different regimen? Do
17 I talk to my doctor about combining sofosbuvir with
18 simeprevir, where we have some data? Do I talk to
19 my doctor about extending the duration to 16 or
20 24 weeks, as we talked about in a different context
21 for genotype 3?

22 So I'm just trying to get a little more

1 color to the analysis.

2 DR. MISHRA: Sure. Thank you for all your
3 comments. I think all of these are very important
4 questions which you brought up. And regarding
5 on-treatment factors, of course, adherence, and
6 side effect profile, and discontinuations due to
7 side effects, all those factors play into response
8 rates.

9 What the agency is trying to do here is help
10 those subgroups of patients who are treatment-
11 experienced and who we believe are in the most need
12 of therapy. So this is an area now where we
13 believe that 12 weeks' shorter duration will
14 somehow translate into maybe more adherent therapy,
15 so to say, because if you have longer duration of
16 treatment, patients are more likely to not adhere
17 with all that interferon-related side effects.

18 So maybe 12 weeks of therapy will translate
19 into improved safety and improved efficacy.

20 Regarding your other question about data
21 from the ATOMIC study, I will have to ask one of my
22 colleagues to address that.

1 DR. MURATA: Dr. Florian?

2 DR. FLORIAN: Jeffry Florian, FDA. Did not
3 look back at ATOMIC. It did not include cirrhotics
4 in it, so it would be a much different demographic
5 with one of the factors that was looked at. It was
6 also 52 subjects, so looking for subjects who would
7 have three factors is going to be a miniscule or
8 very small total in.

9 To what was one of the original questions,
10 using along the lines of what Poonam said, did not
11 go and take what were these post-randomization
12 factors with the analysis. This was just trying to
13 use what was baseline information to get a sense of
14 treatment response, things that have been
15 identified as associated with poor non-response.

16 I would also have the caveat that it
17 shouldn't be taken that these factors are a
18 definitive representation of the population. This
19 was something the agency was doing as an
20 exploration of known factors associated with poor
21 response, but to better try and characterize such
22 patients.

1 I think what you're asking for is a much
2 more involved analysis. And I think there would be
3 value in having that done.

4 DR. MURATA: Dr. Birnkrant?

5 DR. BIRNKRANT: Our approach that we're
6 describing today, at this point in time, just
7 applies to those who may have a history of using
8 P/R. It doesn't apply yet to those using a
9 PI-based regimen.

10 So we're taking small steps, but at the same
11 time, we're trying to use our expansive experience
12 at the agency over the years with the approvals of
13 these drugs to try, as was said, to leverage that
14 data to be able to help other populations in need.

15 Again, I also mentioned working with the
16 target group as well. I think that will also help
17 to advance her understanding and use of these drugs
18 on the market.

19 DR. MURATA: Thank you for the
20 clarification. Now, the last of the business from
21 this morning is the opportunity for the sponsor to
22 address some of the outstanding queries for their

1 presentations.

2 DR. MCHUTCHISON: Yes. So we wanted to
3 follow up on three things that we were asked about
4 this morning before lunch. And the first -- we'll
5 have Dr. Symonds address -- was the characteristics
6 of the people who had previously been treated who
7 had recurrence after transplantation; and then
8 secondly, some flavor and quantitation around the
9 compassionate use program.

10 So Dr. Symonds will do that first.

11 DR. SYMONDS: Bill Symonds, Gilead Sciences.
12 The data I have to show you is what the patients
13 were actually receiving, who were the treatment-
14 experienced patients. It was asked this morning.
15 In the pre-transplant setting, what was the nature
16 of their prior experience?

17 I have that data here among those patients.
18 The majority were peg and riba failures. So 38 of
19 those patients, 5 of them had been treated with peg
20 only, and then 3 of them were PI plus peg-riba
21 failures.

22 You can see their ultimate response rates at

1 this point in time, anyway. Among those PI,
2 peg-riba, 2 out of 3 have no recurrence; peg, 2 of
3 the patients have recurrence, 3 of them do not; and
4 then about half of them with peg-riba.

5 So I just wanted to share that information
6 and clear that question up. And then the other one
7 was, I didn't really answer your question on the
8 number of patients who were being treated in the
9 compassionate use program. That is shown here at
10 the present time, 285 patients, almost 300, are
11 being treated, about half of them in North America,
12 about half of them in Europe.

13 DR. MCHUTCHISON: Thank you. The second
14 question was a complex question, so I'm going to
15 ask three people to respond. And it was related to
16 other drugs, other drugs in the class, muscle,
17 cardiac, toxicity. So I'm going to ask Adrian Ray
18 to compare and contrast the non-clinical profiles
19 of the drugs; secondly, Dr. Tay to talk about the
20 animal toxicology experiments that we've
21 undertaken, particularly as they relate to muscle;
22 and then thirdly, Dr. Brainard to follow up on

1 something else that was asked, which was a careful
2 look at the safety module or data from the VALENCE
3 24-week trial related to cardiac symptoms.

4 DR. RAY: Adrian Ray, Gilead Sciences.
5 Sofosbuvir has a distinct structure from the other
6 agent that was discussed this morning that showed
7 cardiac toxicity during clinical studies. The two
8 structures are shown here on the left-hand side of
9 the two molecules.

10 There is a difference in the pro-drug
11 moieties. There's two differences between the two
12 compounds. Sofosbuvir is a uridine analog, and the
13 other agent is a guanosine analog. There's also a
14 difference in the ribose substitutions of these two
15 compounds. One has one modification of a methyl
16 group at the 2-prime position. Sofosbuvir has a 2-
17 prime fluoro and a 2-prime C-methyl, so two
18 modifications within the ribose ring.

19 We have also compared these two agents in
20 in vitro assays for their general cytotoxicity
21 profiles. This may be relevant to the clinical
22 observations that were made.

1 Here, the cytotoxicity in cell lines is
2 summarized, showing different cell lines for
3 different tissues, liver, lymphoid cells, and
4 others. Sofosbuvir showed little or no
5 cytotoxicity across these cell types. And we're
6 testing concentrations that are a hundredfold
7 higher than the plasma Cmax concentrations that are
8 observed in the clinic.

9 In contrast, the other agent showed toxicity
10 around 1 micromolar in these assays, so a marked
11 difference.

12 Similar results were obtained across
13 different primary cells. One target that data
14 supports may differentiate molecules in this class
15 is the mitochondrial RNA polymerase, which is a
16 possible mechanism for toxicity of some
17 ribonucleotide analogs.

18 Looking at these two compounds, the active
19 triphosphates that are formed by these two prodrugs
20 in biochemical assays with their purified
21 triphosphates, the active triphosphate of
22 sofosbuvir is not a substrate for the mitochondrial

1 RNA polymerase relative to its natural substrate in
2 the context of this assay. The other agent's
3 active triphosphate is incorporated almost as well
4 as this corresponding endogenous molecule. And
5 this may explain some of the differences in
6 cytotoxicity we observed across different cell
7 types.

8 DR. TAY: Chin Tay, Gilead Sciences. We
9 have completed a comprehensive toxicology program
10 with sofosbuvir. So while we did not specifically
11 look for mitochondrial toxicity in our toxicology
12 studies, we did not see any evidence of cardiac
13 tissue or muscle tissue toxicity in our repeat-dose
14 rat and dog studies at exposures 9 and 27 times
15 above the clinical exposure.

16 We have also recently completed our two-year
17 mouse and rat carcinogenicity studies. Those
18 studies have not been reviewed by the agency, but
19 in both studies, we also did not see any cardiac or
20 skeletal muscle tissue toxicity in the mouse at
21 exposures 30 times and the rat 15 times above the
22 clinical exposure.

1 DR. BRAINARD: The safety data in the
2 VALENCE study were consistent with the safety data
3 from the other phase 3 studies and with the
4 sofosbuvir program in general. There was no
5 evidence for sofosbuvir-related cardiotoxicity in
6 the VALENCE study or in any of the other clinical
7 development studies.

8 This table lists the cardiac adverse events
9 in the VALENCE study. These events were infrequent
10 and similar to what was reported in the phase 3
11 studies. They were all mild to moderate in
12 severity, with the exception of one patient with a
13 grade 3 arrhythmia, which was also an SAE.

14 This was a female patient with a family
15 history of Wolff Parkinson White syndrome who had
16 previously been exonerate for Wolff Parkinson White
17 syndrome, but had a medical history of palpitations
18 and frequent visits to the emergency room for these
19 symptoms.

20 She was seen by her physician for
21 palpitations, a feeling of an irregular heartbeat,
22 and a lump in her throat, and was referred to the

1 emergency room.

2 Her EKG was consistent with her baseline and
3 showed extrasystolic beats occasionally. She was
4 observed overnight and given a beta blocker and a
5 sleeping aid, and was discharged the following day.

6 This event was assessed as unrelated to
7 sofosbuvir and ribavirin. She missed one dose of
8 ribavirin the evening she was in the hospital, but
9 otherwise had no change to her study drugs and
10 completed treatment per protocol.

11 DR. MCHUTCHISON: Thank you. So those were
12 the two of the three things that we were asked this
13 morning. The third thing was just our comments
14 about the modeling in genotype 1 treatment-
15 experienced patients. And I'm going to ask
16 Dr. Symonds again to talk about one simple
17 explanation that we have come up with as well,
18 because it is complicated, and I've had difficulty
19 grasping the concept, actually, but I think I have
20 now.

21 But there are two key points, I think,
22 before Dr. Symonds starts. And the first is that

1 within any population of hepatitis C patients who
2 haven't been treated, there's a group of non-
3 responders to a particular therapy. And that
4 therapy could be interferon and ribavirin. It
5 could be interferon, and ribavirin, and something
6 else.

7 Then the second concept that's very
8 important, I think, is that it really doesn't
9 matter what that prior therapy is because it seems
10 like the FDA's analysis can predict that from other
11 baseline factors. And that's a very important and
12 new observation. If you take people who are
13 genetically unfavorable with high viral load with
14 advanced fibrosis, you'd come up with a sustained
15 response rate for a difficult-to-treat group of
16 naive patients that's very similar to null
17 responders. And they are key concepts that help me
18 understand how these exploratory modeling exercise
19 is undertaken.

20 So we have done three separate models
21 independently of what you've heard from the FDA.
22 Dr. Symonds will describe the first, then I'll very

1 briefly describe the other two models.

2 DR. SYMONDS: Bill Symonds, Gilead Sciences.
3 As Dr. McHutchison pointed out, our key assumption
4 here is that within any population of patients, if
5 you start with 100 patients, 50 of those patients
6 or half would be destined to be peg and riba
7 non-responders. And we've seen this across a
8 number of studies that have been conducted over the
9 past decade. You see about a 50 percent response
10 rate at best. Those patients are represented here
11 by the green bar.

12 That leaves the other 50 patients, who would
13 be peg and riba non-responders. So among those
14 patients, it includes partial responders, null
15 responders, and patients who discontinue the
16 therapies.

17 We know from our NEUTRINO trial that
18 11 percent of the patients failed to respond to
19 that triple combination therapy. We would assume
20 that these patients probably have some of the most
21 difficult characteristics of the patients in the
22 orange bar. Therefore, we would assume that that

1 11 percent of patients would all belong within the
2 orange bar, much as the FDA analysis has shown.
3 And you basically see that, that leaves you 39 of
4 the 50 patients or 78 percent of patients who would
5 be predicted to respond to a sofosbuvir plus
6 pegylated interferon and ribavirin regimen.

7 There's some sensitivity analysis over on
8 the right-hand side, where if the peg-riba response
9 rate was lower in a given population, you would
10 expect more patients to respond to the triple
11 combination therapy. And then vice versa; if they
12 were higher, you would expect the response rate to
13 be lower because the easier-to-treat patients would
14 have been taken care of, and you would have a
15 smaller proportion who could then respond.

16 So that's a rather simplistic view on my
17 part, but we have a couple other more complicated
18 methods, which Dr. McHutchison is going to briefly
19 summarize.

20 DR. MCHUTCHISON: Very briefly. So we took
21 data from protease and other treatment groups, the
22 treatment-naive and treatment-experienced groups of

1 patients, and we took the difference in response
2 rates. For example, telaprevir, peg-riba-naive
3 patients, telaprevir, peg-riba non-responder
4 patients, and there's a difference in absolute
5 response rates between those two groups of
6 patients.

7 If we apply that absolute difference and
8 assume that that difference is the same difference
9 we would see in NEUTRINO with sofosbuvir, not
10 telaprevir, you come up with 79 percent. And you
11 can put a confidence interval around that, et
12 cetera.

13 Then we also did it by a log odds estimate
14 as well, which came up with something higher that
15 was 84 percent, so three different methods based on
16 different technologies or methodologies, '78, '79,
17 and '84, which is consistent with what you'd heard
18 prior to lunch. Thank you.

19 DR. MURATA: Thank you to the sponsor for
20 the clarifications. Now, I would like to open up
21 further questioning in terms of clarifying
22 questions by the committee members to either the

1 agents or the sponsor. And Dr. Van Dyke, you had a
2 question.

3 Dr. Connick?

4 DR. CONNICK: The FDA had some resistance
5 analyses that were different than the sponsor's.
6 Specifically, they seemed to uncover some more
7 resistance than the sponsor had. And I was curious
8 what the sponsor thought of that analysis by the
9 FDA.

10 DR. MCHUTCHISON: So I'll ask
11 Dr. Svarovskaia from our clinical virology group to
12 address the other polymorphisms, particularly the
13 L159 that was discussed in the 320, and just in
14 general how we're viewing all of this.

15 DR. SVAROVSKAIA: Jenny Svarovskaia, Gilead
16 Sciences. To look for resistance with performed
17 comprehensive resistance test and across all of our
18 studies, we performed very sensitive deep
19 sequencing across all patients in our phase 2 and
20 phase 3 studies to look for the known resistance
21 mutation for sofosbuvir. And we did not find this
22 mutation among anybody except for 1 patient who

1 received monotherapy.

2 Based on this observation, we looked for
3 phenotypic changes across all the patients. And
4 this slide represents a phase 3 study of phenotypic
5 results. And we phenotyped all patients who
6 experienced biologic relapse at baseline, as well
7 as of post baseline time points. We did not
8 observe any shift in phenotypic between these two
9 sets of samples.

10 We observed a whole set of other mutations
11 besides S282T and NS5B. There was 63 mutations
12 observed in our phase 3 studies, and those
13 mutations were observed in more than 2 patients
14 across multiple studies.

15 We looked for these mutations and have found
16 that none of those mutations confer phenotypic
17 shift to sofosbuvir. None of them were located in
18 the active site. And some of them were located in
19 polymorphic sites and some were at the sites, which
20 were conserved at some of the genotypes but not all
21 of them.

22 These mutations included previously

1 mentioned variance. V321A was not detected at
2 baseline across all studies. It was observed in
3 four genotype 3 patients at relapse, based on our
4 observation.

5 What do we know about this mutation? It was
6 not selected in vitro with sofosbuvir, and we
7 performed a phenotypic test of this mutation. And
8 we found that this mutation does not confer
9 resistance to sofosbuvir, as tested as a
10 site-directed mutant or one of the patient
11 isolates.

12 Therefore, we agree with the agency that
13 this is a treatment-emergent mutation, but it does
14 not appear to confer resistance to sofosbuvir.

15 We also looked at the next mutations, which
16 were described in one of the patients in the pre-
17 transplantation study. This patient experienced
18 suboptimal response to sofosbuvir and ribavirin.
19 And we observed, at very low levels, S282R and
20 L320F mutation post-treatment.

21 We looked using a deep-sequencing analysis,
22 and we found that these mutations did not appear on

1 the same genomes and were allocated on the separate
2 genomes. We introduced S282 as a site-directed
3 mutant in the replicon system, and we found that
4 this mutant does not replicate.

5 L320F was previously observed with other
6 nucleoside inhibitors and was of interest for us.
7 We performed extensive phenotypic testing with this
8 mutation and also found that L320F does not confer
9 resistance to sofosbuvir.

10 The next mutation I would like to discuss is
11 L159F. L159F was also observed previously as a
12 9 mutation, and we paid very close attention to it.
13 It was present in four patients in our phase 3
14 studies at baseline.

15 We also observed in 6 patients of genotype
16 3A at relapse and we also looked for it in in vitro
17 selection. And this mutation was not selected with
18 sofosbuvir in vitro selections.

19 We performed phenotypic analysis using
20 site-directed mutants or patient isolates
21 containing this mutation, and we found that even
22 though this mutation appeared to be treatment-

1 emergent, it does not confer resistance to
2 sofosbuvir.

3 Therefore, taking these observations
4 together, we agree with the agency that we do
5 observe this mutation to be treatment emergent.
6 However, we don't see any resistance conferred by
7 these mutations.

8 DR. CONNICK: Just to follow up, why do you
9 think the mutation is emerging, then?

10 DR. SVAROVSKAIA: This is a very interesting
11 question. We are going to be looking out for these
12 mutations and try to understand what is the
13 mechanism, and whether the presence of this
14 mutation would in any way affect the sofosbuvir
15 treatment.

16 DR. MURATA: Dr. Honegger?

17 DR. HONEGGER: I had the same question.

18 DR. MURATA: Dr. Korman?

19 DR. KORMAN: Louis Korman. I'd like to get
20 back to the modeling question, both from the FDA
21 standpoint and sponsor standpoint, because it
22 relates to the question I asked yesterday.

1 Guidance to the clinician who has to make a
2 decision is a balance between whether you
3 procrastinate with a patient or you don't
4 procrastinate with the patient, in the sense of
5 sequestering them from therapy, waiting for the
6 90 percent or a 95 percent response.

7 So there ought to be some guidance for this.
8 And from what I can tell -- and I'm not an expert
9 in this field -- the only two things that I've seen
10 are whether they have cirrhosis or what their
11 genotype is. Genotype 3 don't do as well as
12 genotype 2 and, if that's cirrhosis, now, cirrhosis
13 is not cirrhosis.

14 If you use the Child Turcotte Pugh score and
15 near 5 or 6, it's very different than their 4, and
16 they both of cirrhosis. You've added platelet
17 count in this. Can you divine any information or
18 can the FDA from its large data set divine any
19 information that can provide guidance both about
20 the response rate, because I want 90 percent unless
21 that patient has a one-year survival that's less
22 than the time that the next drug comes out, that

1 I'm going to treat with, that gives me 100 percent,
2 or 95 percent.

3 Really, if I were a patient, I wouldn't want
4 to be treated with something that was really toxic
5 or risky if I could wait another year, or two, or
6 three. And you're right. This thing is changing
7 quickly. So guidelines that existed two years ago,
8 when we sat through these presentations, are no
9 longer valid, I think.

10 DR. MURATA: Does the agency have a response
11 to that question?

12 DR. MISHRA: Before we address this one, can
13 our virology colleagues comment on something about
14 resistance?

15 DR. MURATA: Sure, to facilitate matters.
16 Dr. Naeger?

17 DR. NAEGER: Hi. I'm Lisa Naeger from FDA.
18 If I could have backup slide 21? And this is to
19 address why we're seeing so much relapse but not
20 necessarily resistance.

21 We don't really have data to tell us what's
22 happening, whether we have wild-type virus, which

1 is not cleared; whether there's two virus
2 populations, a mutant and a wild type, and then
3 once drug is removed, the wild type outgrows the
4 mutant because it's not fit; or whether there is a
5 mutant virus, but it's so unfit that it reverts.

6 Reversion of NS5B. So because of those
7 three possibilities, that's why, once she brings
8 the slide up -- I have reversion in quotes.

9 So we only have two examples to show how
10 long the substitutions might hang around. The
11 S282T that arose in the genotype 2b sofosbuvir
12 monotherapy subject was present at week 4, but no
13 longer detected at week 12 post-treatment. So
14 something happened to it over that eight-week
15 course.

16 Then one breakthrough subject -- and this
17 was the subject from the pre-transplant
18 study -- the L159 was present at a frequency of
19 9.5 percent at post-transplant week 1. And this
20 dropped to 1.2 percent by post-transplant week 2.
21 So it appears that these substitutions are not
22 present for very long. They may be transient. So

1 we may not be able to detect them if our samples
2 are not collected early.

3 But this also supports that we don't have
4 data yet on whether retreatment with sofosbuvir may
5 also be a treatment option, but that data should be
6 coming.

7 DR. MURATA: Thank you. Dr. McHutchison?

8 DR. MCHUTCHISON: Yes. So we have
9 considered this as well. And the NIAID
10 collaborative study and SPARE looked at earlier
11 time points after relapse, week 1 and week 2,
12 rather than just the week 4 time point, hopefully
13 trying to get to this issue. And unfortunately,
14 the viral levels in those that relapse -- and you
15 can detect relapsed virus at week 1 or week
16 2 -- are less than the cut-off that we can do this
17 sort of sequencing and this sort of analysis.

18 We also, in that collaborative study, looked
19 at end of treatment liver biopsies, even though all
20 patients were undetectable at the end of treatment,
21 to see if we could find a small amount of residual
22 virus that harbored one of these variants in those

1 that relapsed. And we were unable, probably due to
2 the technology, to detect any virus in those liver
3 biopsy samples at the end of treatment.

4 We do not have data about retreatment with
5 sofosbuvir-containing regimens, as was said -- you
6 saw the one case that we retreated this
7 morning -- but we do have some other interesting
8 dynamics of what's happening early on retreat. And
9 I'm going to ask Dr. Symonds to talk about what
10 initiatives we've got going, but we have little
11 data, as was stated.

12 Then, Dr. Symonds, after that, if you could,
13 address Dr. Korman's question about SVR rates in
14 cirrhotics with low platelet counts, portal
15 hypertension as well from our trials.

16 DR. SYMONDS: In terms of the retreatment of
17 patients who have failed to achieve an SVR in
18 sofosbuvir, we have a number of different things
19 underway, one being we can glean some information
20 from the transplant study, which we've been talking
21 about today, in the patients who stopped after
22 24 weeks and then restarted.

1 I have here the viral kinetics of those
2 patients the first and second time that they were
3 retreated. It's only I think 7 or 8 patients here,
4 but you can see from the plots that the viral decay
5 the second time after the patient relapsed looks
6 the same as it was the first time. And the viral
7 suppression is very rapid in these patients. And
8 we're able to get them down and keep them down a
9 second time, after an interruption and a period of
10 therapy.

11 We've also got data from the QUANTUM study,
12 which was a study run a couple of years ago now,
13 which we actually had to amend because the other
14 drug had to be stopped within the trial. It
15 originally was a 9-arm trial, but 3 of the arms
16 survived, 2 of them being 12 versus 24 of
17 sofosbuvir and ribavirin in genotype 1 through 6,
18 but essentially it was genotype 1 through 4.

19 But then there was also a retreatment arm,
20 where genotype 1, 4, and 6 patients were retreated
21 for 24 weeks. These were patients who were exposed
22 to sofosbuvir plus or minus another nucleotide,

1 plus or minus ribavirin from anywhere from 1 to
2 9 weeks. They did not have resistance, but they
3 were previously exposed.

4 This data was actually presented at EASL
5 this past year, and 66 percent of those who
6 received 24 weeks of retreatment with sofosbuvir
7 and ribavirin achieved an SVR, a similar rate to
8 what we see in the SPARE trial at the NIAID, where
9 24 weeks of sofosbuvir plus ribavirin had a
10 68 percent response. So it really corroborates the
11 results which we saw there.

12 Then, in terms of the question on platelets,
13 we've actually looked at the SVR rates across
14 genotypes and across studies in some instances
15 using other measures of gauging someone's cirrhosis
16 status. A good one is actually platelets. Were
17 they above or below 125,000?

18 Here, we have data from the NEUTRINO trial,
19 and you basically see the overall result was
20 89 percent. So if your platelet count is less than
21 125,000, 81 percent, small numbers there, only 16
22 of those patients, but if they were over 125,000,

1 90 percent. And we see a similar pattern across
2 the other genotypes as well.

3 Can I have the slides on portal
4 hypertension, please? We've also looked at this by
5 physician report of portal hypertension existing in
6 a patient at baseline. Here, we have the
7 genotype 2 patients, small numbers with portal
8 hypertension in the trials, but you see a slightly
9 lower rate, albeit a small cohort there with only
10 10 patients, compared to a similar rate, 94 percent
11 in those without portal hypertension.

12 DR. MCHUTCHISON: So we added a small group
13 of patients in the trials because we let people in
14 with low platelet counts that had a history of
15 varices or intraabdominal varices on a CT scan,
16 et cetera. So that's the information we have.

17 DR. MURATA: Thank you. Dr. Alcendor?

18 DR. ALCENDOR: Yes. So this is a drug
19 that's a monophosphate prodrug. So in my mind,
20 whole cell kinases will do the other
21 phosphorylation events for you. And so the
22 triphosphate then becomes available to other cell

1 types through gap junctions that allows a bystander
2 effect.

3 Now, can this drug be a problem in people
4 that are being treated with kinase inhibitors?
5 That's one question. The other question is, have
6 you evaluated the extent of the bystander effect of
7 this drug in neighboring cells from the initial
8 cells that might be harboring the virus?

9 In the drug-drug interaction studies that I
10 saw you did, I noticed there were no drugs of abuse
11 included in that list, and I was wondering why.
12 And the other thing is resistant profiles in vitro.
13 Have you seen any changes in resistance profiles in
14 vitro under conditions of long-term cultivation in
15 the presence of high doses of this drug?

16 Because I notice in the cell types that you
17 look at, you had a mixture of transformed cell
18 lines along with embryonic fibroblasts and other
19 cell types. And so can you comment on that?

20 DR. MURATA: That's for the sponsor, I
21 imagine.

22 DR. MCHUTCHISON: Yes. I apologize. So I

1 missed the drug class you were asking about, your
2 third question. I couldn't hear it, so you asked
3 about kinase, bystander cells in terms of
4 reservoirs, I presume.

5 DR. ALCENDOR: Right, right.

6 DR. MCHUTCHISON: Then the third one was --

7 DR. ALCENDOR: Resistance profiles in vitro
8 in cell types that are exposed to high levels of
9 this drug over time, through cultivation.

10 DR. MCHUTCHISON: So I'll ask Dr. Kearney to
11 talk about the class of kinase inhibitors in
12 terms -- sorry. Dr. Tay. Dr. Ray. I'm sorry.
13 And then I'll ask Dr. Svarovskaia to talk about
14 long-term resistance.

15 Dr. Ray, I'd like you to also talk about
16 reservoirs and drug distribution as well.

17 DR. RAY: Adrian Ray, Gilead Sciences.
18 Sofosbuvir a nucleotide prodrug that is subject to
19 significant hepatic extraction and intracellular
20 metabolism. Sofosbuvir, the first intracellular
21 step of activation, is cleavage by
22 carboxylesterase 1 or cathepsin A, two enzymes that

1 take off one of the esters. Then there's multiple
2 sequential steps leading to the nucleoside
3 monophosphate being released, and then subsequent
4 phosphorylation steps to the pharmacologically
5 active triphosphate.

6 We've looked for potential compounds that
7 could inhibit these kinases, and we have not
8 identified any of them. For example, we've done
9 synergy studies with HIV nucleoside reverse
10 transcriptase inhibitors, some of which use some of
11 these same kinases for their activation, and we
12 have not seen any antagonism in our in vitro
13 studies.

14 Related to possible reservoirs for HCV
15 infection, the liver is clearly far and away the
16 established site of the infection. There have been
17 reports of detection of HCV RNA and other tissues,
18 lymphoid tissues, or the brain. Many of these
19 reports have not been corroborated by other
20 reports. I think that this is still a putative
21 site of infection.

22 So sofosbuvir's distribution around the body

1 is fairly broad. It certainly preferentially goes
2 to the liver. One possible site of infection
3 that's been proposed is the brain. Sofosbuvir
4 poorly crosses the blood-brain barrier. So it kind
5 of gives you a sense of, if HCV were to be
6 replicating anywhere else, how the drug distributes
7 throughout the body.

8 DR. SVAROVSKAIA: In regards to the in vitro
9 selection with sofosbuvir, we performed in vitro
10 selection using replicons in multiple genotypes.
11 We initiated our selections with around EC50 of
12 sofosbuvir and increase it to about a tenth or a
13 little bit higher micromolar range of sofosbuvir.

14 Across all different genotypes, we
15 consistently observed S282T. That was the only
16 consistent mutation which conferred resistance to
17 sofosbuvir. No other mutations which confer
18 resistance to sofosbuvir were observed in in vitro
19 selections.

20 DR. MURATA: Thank you.

21 Any additional questions or clarifying
22 questions to the sponsor or to the agency?

1 Ms. Lupole?

2 MS. LUPOLE: Thank you. Patricia Lupole. I
3 read studies on autopsied patients with HCV disease
4 where active virus was found in the blood and
5 spinal columns, in the heart cells, and in the
6 peripheral blood. So the liver is an active site,
7 but there are other areas that probably need looked
8 into. And I just wanted to make that comment to
9 you.

10 DR. MCHUTCHISON: Thank you.

11 DR. MURATA: Any other questions to the
12 sponsor or to the agency?

13 (No response.)

14 DR. MURATA: So to facilitate discussion and
15 voting, I propose that we take a 15-minute break
16 now and then reconvene at 2:30. Again, committee
17 members, please refrain from further discussion.
18 Upon our return, we will proceed with the remainder
19 of the voting and the discussion.

20 (Whereupon, a recess was taken.)

21 **Questions to Committee and Discussion**

22 DR. MURATA: So we'll now proceed with the

1 questions to the committee and then the panel
2 discussions. I would like to remind public
3 observers that while this meeting is open for
4 public observation, public attendees may not
5 participate except at the specific request of the
6 panel.

7 So we have two voting questions followed by
8 three discussion questions. So I will read the
9 paragraph as required for the electronic voting
10 system.

11 So we will be using an electronic voting
12 system for this meeting. Once we begin the vote,
13 the buttons will start flashing and will continue
14 to flash even after you have entered your vote.
15 Please press the button firmly that corresponds to
16 your vote.

17 If you are unsure of your vote or you wish
18 to change your vote, you may press the
19 corresponding button until the vote is closed.
20 After everyone has completed their vote, the vote
21 will be locked in. The vote will then be displayed
22 on the screen. The designated federal official

1 will read the vote from the screen into the record.

2 Next, we will go around the room, and each
3 individual who voted will state their name and vote
4 into the record. You can also state the reason why
5 you voted as you did if you want to. We will
6 continue in the same manner until all questions
7 have been answered or discussed.

8 So the first question is a voting one.
9 "Considering potential risks and benefits, does the
10 available data support approval for sofosbuvir in
11 combination with ribavirin for treatment of chronic
12 hepatitis C in adult patients with genotype 2 and 3
13 infection?"

14 I would like to open up to our committee
15 colleagues about questions regarding the wording of
16 this question. Mr. Raymond?

17 MR. RAYMOND: Thank you. Daniel Raymond.
18 So this is a clarifying question. The way that I
19 read the wording of this question is more
20 restrictive or more narrow than the sponsor's
21 proposed indication language, as it specifies
22 sofosbuvir in combination with ribavirin.

1 My question is, a vote for yes, is that
2 tantamount to a vote both for this question
3 number 2 for genotype 1 and 4, for a narrow or
4 specific indication than what has been proposed by
5 the sponsor, or are we simply voting on the
6 strength of the evidence for sofosbuvir for these
7 two genotypes?

8 DR. MURATA: Dr. Murray?

9 DR. MURRAY: It's the latter. And I think
10 exactly how the indication is crafted, we'll work
11 that out with Gilead after the committee. I mean,
12 we've heard the concerns about the type of
13 indication that might be best as far as maybe
14 reimbursement later, of people being able to use
15 these drugs.

16 So this is just kind of the approval for the
17 general indication, so whether we have a broad
18 indication and some limitations in the usage
19 statement, or the indication is more directive in
20 the first indication statement, I think we'll
21 probably be working that out later with taking into
22 account all the comments that we've heard at the

1 meeting.

2 DR. MURATA: Dr. Ghany?

3 DR. GHANY: My question was along the same
4 lines. So here we're voting for the drug or the
5 regimen?

6 DR. MURRAY: It is both, so it is approval
7 of this drug as was studied with this regimen for
8 genotype 2 and 3, and then later for genotype 1.

9 Does that help?

10 DR. MURATA: Any questions about the
11 wording? Ms. Lupole?

12 MS. LUPOLE: Is that for 12 or 16 weeks?

13 DR. BIRNKRANT: It's 12 for genotype 2 and
14 24 for genotype 3.

15 DR. MURRAY: Then that information would be
16 in the dosage administration section, the weeks.
17 But yes, it would be 12 and 24 for 2 and 3,
18 respectively.

19 DR. MURATA: If there are no questions or
20 comments concerning the wording of the question, we
21 will now open the question to discussion prior to
22 opening up for a vote. Any other discussion

1 points? Mr. Raymond?

2 MR. RAYMOND: I have a feeling I know what
3 the vote is going to look like, and that might
4 suggest why there's not a lot of discussion. But I
5 just want to note that this is a historic moment.
6 This is the first vote for an interferon-free
7 regimen to treat hepatitis C. And I'm very proud
8 to be here at this occasion, and I think that this
9 is going to be a very important move forward.

10 DR. MURATA: Any other discussions?

11 (No response.)

12 DR. MURATA: If there is no further
13 discussion on this question, we will now begin the
14 voting process. Please press the button on your
15 microphone that corresponds to your vote. You will
16 have approximately 20 seconds to vote. Please
17 press the button firmly.

18 After you have made your selection, the
19 light may continue to flash. If you are unsure of
20 your vote or you wish to change your vote, please
21 press the corresponding button again before the
22 vote is closed.

1 (Vote taken.)

2 DR. MURATA: Everyone has voted. The voting
3 is now complete.

4 CMDR ABRAHAM-BURRELL: We have 15 votes for
5 yes, zero votes for no, and zero votes for
6 abstaining.

7 DR. MURATA: Now that the vote is complete,
8 we will go around the table and have everyone who
9 voted state their name, vote, and if you want to,
10 you can state the reason why you voted as you did
11 into the record. We'll start with Dr. Daskalakis.

12 DR. DASKALAKIS: Demetre Daskalakis from
13 Mount Sinai. Truly a historic moment. I can't
14 wait to get this drug in the clinic. So I think
15 we're all very excited to free people from the
16 barriers for treating this really important
17 disease.

18 MR. RAYMOND: Daniel Raymond. I voted yes.
19 Somebody earlier described this as a magic drug. I
20 don't know that I'd quite go that far, but it seems
21 they've pulled off the hat trick of superior
22 efficacy, great safety, and a very convenient

1 profile that doesn't generate concerns around
2 resistance or drug-drug interactions that are
3 unmanageable.

4 DR. CONNICK: Liz Connick. I voted yes.
5 This is a tremendous advance for patients, and I
6 think both the sponsor and the FDA should be
7 applauded for having gotten us here.

8 DR. CORBETT: Amanda Corbett. I voted yes
9 as well, and I can say the practitioners and
10 patients in our clinic will be very excited that
11 this medication will hopefully be soon approved.

12 DR. GIORDANO: Tom Giordano. I voted yes,
13 and I'll just second Mr. Raymond's comments.

14 DR. MURATA: Yoshi Murata. I voted yes. I
15 believe that the data, including the risks and the
16 benefits, do support my vote for yes for this
17 statement.

18 DR. HAGEDORN: I'm Curt Hagedorn, and I
19 voted yes. Our patients have been waiting for this
20 for a long time.

21 DR. VAN DYKE: Russell Van Dyke. I voted
22 yes for the reasons stated. I was pleased to hear

1 that there was a pediatric development plan in
2 progress so that children could share in this
3 advance. And I hope that includes a palatable
4 pediatric formulation.

5 DR. ALCENDOR: Donald Alcendor. I voted
6 yes. In part, this drug seems to be efficacious.
7 And listening to the speakers today, their personal
8 experiences with this drug, I think is very
9 important and compelling. And again, the idea of
10 making this drug available to the people in need is
11 going to be very important.

12 DR. FOLLMANN: This is Dean Follmann. I
13 voted yes. I thought the evidence was
14 overwhelming, and I thought the sponsor did a very
15 thorough and thoughtful drug development with a lot
16 of important experiments that answered interesting
17 questions for us.

18 DR. GHANY: This is Marc Ghany. First, I
19 wanted to congratulate both the sponsor and the FDA
20 for getting us here. I voted yes because, quite
21 simply, this is a game-changer.

22 DR. HONEGGER: Jonathan Honegger. I also

1 voted yes. I agree that the data were
2 overwhelming.

3 DR. KORMAN: Louie Korman. I voted yes. I,
4 again, would like to congratulate both the sponsor
5 and the FDA, particularly the FDA for a willingness
6 to move away from the trials that were difficult,
7 as Dr. Jacobson pointed out. And I don't have to
8 procrastinate as much, which would make my mother
9 happy.

10 DR. FRIEDMAN: Lawrence Friedman. I had the
11 privilege of voting for ribavirin as well as
12 telaprevir and boceprevir, and this is my favorite
13 vote.

14 (Laughter.)

15 DR. FRIEDMAN: I voted yes, and it's a great
16 step forward.

17 MS. LUPOLE: Patricia Lupole. This is truly
18 a victory for HCV patients today. Thank you all.

19 DR. MURATA: Thank you very much. So that
20 is the vote for question 1.

21 We will now move to the second voting
22 question as written. It states, "Considering

1 potential risks and benefits, does the available
2 data support approval of sofosbuvir in combination
3 with pegylated interferon and ribavirin for the
4 treatment of chronic hepatitis C in treatment-naïve
5 adults, patients with genotype 1 and 4 infection?"

6 I would like to ask if there are any issues
7 or questions about the wording of the question.

8 Dr. Giordano?

9 DR. GIORDANO: So I just want to be clear.
10 What we're asked to vote on here is specifically
11 genotypes 1 and 4 and in treatment-naïve
12 populations. And so the discussion about the
13 treatment-experienced patients is off the table at
14 the present time. Is that correct?

15 DR. MURATA: Dr. Birnkrant?

16 DR. BIRNKRANT: I'm sorry. If you're asking
17 about the treatment-experienced genotype 1
18 patients, that's part of discussion point 3.

19 DR. GIORDANO: Thank you.

20 DR. MURATA: Thank you for the
21 clarification. I just have a clarification that's
22 requested by the administrative staff. Ms. Lupole,

1 did you state your vote as a yes?

2 MS. LUPOLE: Yes. Yes, yes, yes.

3 (Laughter.)

4 DR. MURATA: I apologize for the confusion,
5 but that's what the request is.

6 MS. LUPOLE: I'm sorry.

7 DR. MURATA: Thank you. Any other questions
8 regarding the wording of question 2?

9 (No response.)

10 DR. MURATA: Then if there are no questions
11 or comments concerning the wording of the question,
12 we will now open the question to discussion.

13 No hands go up.

14 So then if there is no further discussion on
15 this question, we will now begin the voting
16 process. Again, please press the button next to
17 your microphone that corresponds to your vote and
18 you will have approximately 20 seconds to vote.

19 Press the button firmly after you have made
20 your selection. The light may continue to flash.
21 If you're unsure of your vote or you wish to change
22 your vote, please press the corresponding button

1 again before the vote is closed.

2 (Vote taken.)

3 DR. MURATA: Everyone has voted, and the
4 vote is now complete.

5 CMDR ABRAHAM-BURRELL: Fifteen votes for
6 yes, zero votes for no, zero abstain.

7 DR. MURATA: Now that the vote is complete,
8 we will again go around the table and have everyone
9 who voted state their name, vote, and if you want
10 to, you can state the reasons why you voted as you
11 did into the record. And again, Dr. Daskalakis?

12 DR. DASKALAKIS: Demetre Daskalakis. I
13 voted yes, and it's just ditto to everything that
14 we said for the last round.

15 MR. RAYMOND: Daniel Raymond. I voted yes
16 for similar reasons. And I also wanted to
17 acknowledge the work of the sponsors in developing
18 strategies to enrich enrollment of black patients
19 as well as patients on opioid substitution therapy,
20 as well as the agency for working with the sponsors
21 in thinking through the use of historical controls.

22 Then again, I would like to iterate that the

1 broader the labeling -- the patients that I talk to
2 today, they look ahead, and they are not
3 thinking -- if they have genotype 1, they're not
4 thinking of using this with interferon. They're
5 thinking of either the spare regimen with ribavirin
6 or the COSMOS regimen. And it would be very
7 frustrating if they were not able to pursue their
8 hopes of a cure with this powerful drug. Thank
9 you.

10 DR. CONNICK: Liz Connick. I voted yes for
11 the same reasons previously stated.

12 DR. CORBETT: Amanda Corbett. I voted yes
13 as well and for the same reasons as others have
14 already mentioned.

15 DR. GIORDANO: Tom Giordano, and I voted
16 yes. I also want to congratulate the sponsor for
17 enrolling a sufficient proportion of
18 underrepresented population in showing that it can
19 be done and that you can actually get good results
20 in that population. So I hope that that is a
21 message that gets heard beyond the confines of this
22 room.

1 I again really echo all of Mr. Raymond's
2 comments. And I do have to say that I did pause
3 about voting because this was, in my opinion, still
4 one study in this genotype. And though it was a
5 very convincing study and a very convincing body of
6 data, I did teeter with my vote a little bit, I
7 have to admit.

8 DR. MURATA: : Yoshi Murata. I voted yes
9 due to the, in my opinion, favorable risk-benefit
10 profile.

11 DR. HAGEDORN: Curt Hagedorn. I voted yes
12 for the reasons that have already been outlined.

13 DR. VAN DYKE: Russell Van Dyke. I voted
14 yes. I was particularly impressed with the very
15 favorable resistance data. I think we have a lot
16 more to learn about resistance with this drug. I
17 hope it stays as is.

18 DR. ALCENDOR: Donald Alcendor. I voted yes
19 for the same reasons.

20 DR. FOLLMANN: Dean Follmann. I voted yes.
21 I too had to think a little bit about this because
22 I'm hesitant to give approval for a one-arm study.

1 I thought the arguments for the one-arm study here
2 that it would be difficult to have a comparison
3 group that is an argument. Sometimes, it's more
4 compelling than the others. And I think, in the
5 guidance that the FDA talk about, they talk about a
6 one-arm study being an acceptable path for it, I
7 guess, if you have a blockbuster treatment or the
8 potential for a blockbuster treatment.

9 For me, the more important point here was
10 the 90 percent success rate. I think, if the
11 success rate were lower, these other arguments
12 against a one-arm study like, "We can't recruit,"
13 or, "This could have been a great drug, but in
14 fact, it wasn't," those wouldn't be so strong
15 arguments in my mind for a one-arm study.

16 So the 90 percent success rates are really
17 what made me comfortable with this vote yes.

18 DR. GHANY: I'm Marc Ghany, and I voted yes
19 for the reasons I previously stated.

20 DR. HONEGGER: Jonathan Honegger. I also
21 voted yes for the reasons we've already stated.

22 DR. KORMAN: Louie Korman. I voted yes

1 because, now, I actually can encourage patients to
2 consider therapy with 90 percent response. But now
3 I'll have to worry about the 10 percent who are
4 non-responders and figure out what to do with them,
5 so it never ends.

6 DR. FRIEDMAN: Lawrence Friedman. I voted
7 yes. This is my second favorite vote of all time.

8 (Laughter.)

9 DR. FRIEDMAN: I think it's no small feat
10 that we now have a three-month regimen that
11 includes interferon. I think that's a great
12 accomplishment. I want to thank Mr. Raymond for
13 his comments throughout. I think they've been
14 right on the mark.

15 I want to just amplify on Dr. Van Dyke's
16 comments because, if I stay on this panel for
17 another 15 years, I just have a feeling we'll be
18 talking a lot about resistance in multiresistant
19 organisms. I fear that. So we have to be very
20 careful about that.

21 MS. LUPOLE: Patricia Lupole. And I voted
22 yes for the same reasons. Thank you.

1 DR. MURATA: Thank you very much. So that
2 concludes the discussion and the voting of question
3 number 2. So the next is question number 3. This
4 is the first of three for discussion.

5 It states, "Please comment on the strength
6 of evidence for use of sofosbuvir in combination
7 with pegylated interferon and ribavirin for
8 treatment of chronic hepatitis C in patients with
9 genotype 1 infection who are non-responders to a
10 prior course of pegylated interferon and ribavirin.
11 Please comment if additional data are needed in
12 this population."

13 So before we open this up for discussion,
14 are there any issues of questions about the wording
15 of this question?

16 (No response.)

17 DR. MURATA: If there are no questions, now
18 we'll open it up for discussion by the committee
19 members. Dr. Follmann?

20 DR. FOLLMANN: Yes. I thought about this
21 some. I think, basically, I'm okay extrapolating
22 to this group. The FDA did different calculations

1 as did the sponsor, and they showed a success rate
2 between 70 and 80 percent for this group.

3 The assumption that you basically need to
4 make to do the calculations work is that the act of
5 identifying a P/R responder, by going through the
6 therapy and failing, won't affect their ultimate
7 outcome on sofosbuvir. And I don't know if that's
8 really true or not, but I'm willing to make that
9 assumption, I guess, for this population.

10 I think the kinds of studies I would like to
11 see, really, would be related to the duration of
12 therapy. Maybe a FUSION-type study where you
13 compare 12 to 16 or 12 to 24 weeks of therapy might
14 be an appealing study for this group. Those
15 extrapolations, like I said, give you a success
16 rate of maybe 70 or 80 percent. Maybe it's lower
17 and maybe the extended therapy would be beneficial.

18 So we're making a kind of a leap here in
19 this comment, and it would be nice to get more
20 information.

21 I guess, like I said earlier, I don't like
22 to make leaps of faith in a way, but I think here

1 it's different when you have what seems to be a
2 very promising, successful drug, and you're sort of
3 thinking about how to optimize therapy. And so
4 that's a different kind of milieu, and I'm more
5 willing to make leaps about how to tweak therapy
6 and so on

7 DR. MURATA: Dr. Friedman?

8 DR. FRIEDMAN: Lawrence Friedman. I agree
9 with Dr. Follmann. I was skeptical at first
10 because I was raised to believe that you had to do
11 a randomized controlled study of the population for
12 which a drug was intended to confirm its efficacy.

13 But I was quite intrigued by the FDA's
14 presentation of the data and the correlation
15 between hard-to-treat patients and null responders.
16 I think that's worthy of publishing this so the
17 data can be examined more critically.

18 I also appreciate the agency's advocacy for
19 extending effective treatments as much as possible
20 to patients in need. I really think that's noble
21 and was echoed by some of our community advocates
22 today.

1 So I've been convinced and I would be in
2 favor of this indication.

3 DR. MURATA: Dr. Ghany?

4 DR. GHANY: Marc Ghany. Yes. I think I
5 would agree with the previous two speakers,
6 Dr. Follmann and Dr. Friedman. It is a bit of a
7 leap of faith, but it's somewhat comforting on the
8 data that we have already.

9 I would encourage the sponsor to actually do
10 studies in this population, but I think moving
11 forward, it's how do we deal with this because,
12 obviously, the problem is going to come up. We
13 can't obviously test new drugs in every single
14 population, and how do we handle this moving
15 forward?

16 Perhaps the agency has a strategy for doing
17 this. Maybe they are willing to share with us
18 maybe what that is. But we're going to also have
19 the problem of combined drugs from different
20 classes and different groups of patients.

21 I think it's very challenging moving
22 forward, how to deal with this. So I think we need

1 better models, better predictive models. And I
2 don't know if the agency can make these databases
3 open to other investigators to analyze or whether
4 it's prohibitive or not, but I just wanted to get
5 some feedback.

6 DR. MURATA: Dr. Daskalakis?

7 DR. DASKALAKIS: I want to echo the
8 sentiment that the data, at least the modeling,
9 seems appropriate to approve the drug for this
10 indication. I think that we've learned some
11 lessons from the HIV story. And I think that,
12 historically, it was said that providers are always
13 ahead of the approval process. And I think that
14 this time the approval process is in sync with the
15 providers and the patients.

16 So I commend both the FDA as well as the
17 sponsor for acknowledging that the docs and
18 patients are smart, and you can figure out an
19 approach that makes sense for them based on that.

20 So with that said, also I think that
21 reviewing all of the data on the drug, one of the
22 most shocking things about it is just how well

1 tolerated it is. So if there was an issue with
2 tolerability, I would be less likely to say that
3 this is okay. But it's so clean from the side
4 effect perspective, that the benefit is so high for
5 people who are living with hepatitis C who may have
6 failed a regimen, that it just seems to be a leap
7 of faith, but the faith is well-founded.

8 DR. MURATA: Dr. Giordano?

9 DR. GIORDANO: With all due respect to my
10 colleagues on the panel here, I have to disagree.
11 I think you're probably right. And I think if I
12 were faced with the decision to treat a patient who
13 was experienced, I would probably opt to use this
14 drug.

15 However, that's not what our charge is. Our
16 charge is to evaluate the evidence, and does the
17 evidence support use in people who are P/R-
18 experienced? And the fact of the matter is, there
19 is no evidence. It's a very compelling hypothesis.
20 I will grant you that. But it's a hypothesis at
21 this point.

22 So my advice or my thought is that we need

1 some data. It doesn't have to be a randomized,
2 controlled clinical trial, phase 3 quality, but we
3 need something to hang our hat on. And I will
4 leave it to the agency to decide what that
5 something is, but I think there has to be
6 something.

7 That being said, clinicians are savvy and
8 are going to do what they need to do to take the
9 best care of their patients. But the agency's
10 responsibility is at a different level?

11 DR. MURATA: Dr. Korman?

12 DR. KORMAN: Louie Korman. So I asked
13 myself the why-not question. Why wouldn't I do
14 this? And the answer, to me, was pegylated
15 interferon. And I would use that only if I thought
16 that the benefit was worth that risk, both the
17 quality of life risk, the complication risk. And
18 the model doesn't give me enough data. It just
19 says, "Yeah, you'll get 17 percent."

20 Will I get 75 percent in a cirrhotic with
21 low platelets? Will I get 75 percent with 1b or
22 1a? Will I get 75 percent in an African-American?

1 Will I get 50 percent? So I need a little bit more
2 guidance. And I think that the physician and the
3 patient can make that decision in the confines of
4 the consultative office and in that discussion.

5 I don't want to shock you, but I have used
6 drugs off-label.

7 (Laughter.)

8 DR. FRIEDMAN: And I think that decision-
9 making at this point probably should reside with
10 the patient and their physician.

11 DR. MURATA: Mr. Raymond?

12 MR. RAYMOND: Thanks. I found myself
13 reflecting, listening to Dr. Giordano, that I came
14 out of a treatment activist culture around HIV and
15 hepatitis C, where we always wanted the sponsors to
16 do all of the studies in all of the populations.

17 A lot of that was based on two assumptions.
18 One is that we couldn't allow some subpopulations
19 to wait until postmarketing commitments, which
20 might take a long time to be fulfilled if they ever
21 quite materialized.

22 The second is that whatever we had at the

1 end of the day when a drug or a regimen was
2 approved, that would be what people would be living
3 with for the next three to five years. And I think
4 that I find myself in a position that feels like a
5 bit of a reversal for my younger self, that I'm
6 okay with this. I am okay with the development
7 program.

8 I think that this is a decent bridge regimen
9 for a subpopulation of genotype 1 non-responders
10 for whom an interferon-based regimen is appropriate
11 and acceptable. I say this is a bridge regimen
12 because I would anticipate that it will probably
13 fall out of use in a couple of years. But in the
14 meantime, I think it would be helpful to have a
15 label that provides the best thinking about what we
16 would anticipate were this drug to be prescribed,
17 even in the lack of actual clinical data.

18 So that's why I do feel supportive of this.
19 I think certainly it would be helpful to have a
20 better understanding of whether 12 weeks is the
21 optimal duration, but I also think that with the
22 pace that other combinations are coming along, it

1 is a viable expectation that for people with less
2 interferon responsiveness in genotype 1, ideally,
3 optimization will probably require a second DAA.

4 So in the meantime, I do support this
5 treatment experience for this particular regimen.

6 DR. MURATA: Thank you. Dr. Ghany?

7 DR. GHANY: Marc Ghany. I thought I'd share
8 how I thought about this. If you treat no one, the
9 response is zero. And what are the current options
10 for individuals who are non-responders? The
11 guidelines recommend it's still a peg ribavirin
12 backbone with a PI. And we've heard over the last
13 couple of days what the downsides to that regimen
14 are.

15 The way I see it, this regimen has to be at
16 least as effective as a PI peg plus riba backbone.
17 I can't see it being worse. And if the modeling is
18 correct and we can get three-quarters of
19 individuals to respond, I see that as a significant
20 improvement for a non-responder, a peg ribavirin
21 non-responder population.

22 DR. MURATA: Dr. Hagedorn?

1 DR. HAGEDORN: I'd just like to say that to
2 not allow patients who are non-responders to
3 receive this treatment I think would be a serious
4 error. We have so many patients that are
5 progressing rapidly towards liver transplant and
6 developing hepatoma.

7 I can tell you, in clinic, where we had a
8 lot of veterans with hepatitis C, the incidence of
9 hepatoma was crazy. It was unbelievable. And to
10 deny these patients this, I think would be a
11 mistake. Can the agency monitor this subset of
12 patients regarding response or something like that?
13 That's my opinion on that.

14 DR. MURATA: Dr. Birnkrant?

15 DR. BIRNKRANT: I just want to say that as
16 we reviewed this application, we realized how
17 important a drug this was. And we also realized
18 that not every patient population was represented.
19 So even though we are regulators, and we're very
20 proud of that, we are also patient advocates and
21 we're really proud of that.

22 So we tried to figure out a way that we

1 could look at the data in a somewhat different
2 fashion to be able to come up with a recommendation
3 for groups who may not have been studied as
4 thoroughly as other groups. And that's how we came
5 up with the modeling approach.

6 In addition, as I mentioned multiple times,
7 we're fortunate to have these databases in house.
8 And again, we thank the pharmaceutical sponsors for
9 sharing all of that data with us.

10 In addition, as I also mentioned, we'll be
11 working with a TARGET group in a real-life
12 situation, where they will be using these drugs in
13 the community. And it's not necessarily that
14 there's a specific protocol for use of the drugs.
15 There are protocols to collect the types of data
16 that we're interested in. But we'll get to see
17 off-label use. We can't shut our eyes to that. We
18 know what happens.

19 So that's why we have to be able to provide
20 as much information as possible to practitioners
21 and patients, so that they understand as much as
22 they can about the drugs.

1 I think we'll learn a lot from TARGET. I
2 think we'll learn a lot over the years from the
3 companies as they submit more and more trials. In
4 addition, I believe Gilead has some data that's
5 maturing in some of these groups that we're
6 interested in. So that data will also populate the
7 database that we have at work, and we'll continue
8 to do our analyses to help provide information to
9 the community.

10 DR. MURATA: Thank you for the
11 clarification.

12 Any other discussion points regarding this
13 question number 3?

14 (No response.)

15 DR. MURATA: Okay. Then let me summarize
16 the viewpoints that were raised.

17 It appears that there is a spectrum of
18 responses to this question, on one hand, whether it
19 represents extrapolation versus, as some of our
20 colleagues have mentioned, leap of faith, based on
21 some assumptions of modeling versus this maybe
22 perhaps insufficient data versus a hypothesis that

1 really requires validation by some level of
2 clinical trials.

3 But in principle, there appears to be also a
4 practical and pragmatic aspect of answering this
5 question, considering the available treatment
6 options, as stated by someone with colleagues in
7 terms of the current available guidance and need
8 for a potentially effective regimen.

9 Also, the tolerability profile as reviewed
10 by the agency and as provided by the sponsor seems
11 to favor use in this population.

12 So some of the comments that our colleagues
13 have mentioned for additional studies include
14 potentially examining the duration of therapy,
15 whether it's 12 versus 24 weeks, whether there are
16 one or more regimens to be added to this proposed
17 regimen as combination therapy or better predictive
18 models.

19 Finally, Dr. Birnkrant mentioned the
20 agency's clarification on its role as a regulatory
21 agency as well as efforts to advocate for the
22 benefit of the patients, the efforts by the agency

1 as well as the sponsors to collectively
2 provide -- to generate a large database that can
3 then be tested on target groups. She emphasized
4 the effort on the agency and the division's part to
5 provide as much as possible in with respect to
6 available data and its practical use in this
7 particular patient population.

8 We move on to the second of three discussion
9 questions, question number 4, "Please comment on
10 the strength of evidence for use of sofosbuvir in
11 combination with ribavirin in HCC patients meeting
12 the Milan criteria awaiting liver transplantation.

13 Are the available data sufficient for dosing
14 recommendations? If not, what additional studies
15 are recommended?"

16 In the fine print, the Milan criteria is
17 reviewed and I'll just read it out for the
18 audience's sake or others who can't read it. "The
19 Milan criteria were defined as 'the presence of a
20 tumor 5 centimeters or less in diameter in subjects
21 with single hepatocellular carcinoma and no more
22 than three tumors nodules, each three centimeters

1 or less in diameter in subjects with multiple
2 tumors.

3 "Now, there should be no extra hepatic
4 manifestations of the cancer and no evidence of
5 vascular invasion of tumor."

6 Given that, are there any questions or
7 comments about the wording of the question?

8 (No response.)

9 DR. MURATA: If there are none, then we'll
10 open it up for discussion. Dr. Hagedorn?

11 DR. HAGEDORN: I've had the opportunity to
12 work in three different liver transplant programs,
13 and this is a huge problem. A hundred percent of
14 these patients who are going to transplant with
15 hepatitis C get reinfected. The disease really
16 accelerates post-transplant for reasons that we
17 don't completely understand, but partly, probably
18 because of immunosuppression.

19 So this is one of these huge areas of needs.
20 Patients are dying on lists because there aren't
21 enough livers. And then you give a liver to a
22 patient with hepatitis C, and they've lost it in

1 two years. It's a tragedy. It's crazy.

2 So this is a huge area of need. My only
3 concern is the MELD score on these patients was
4 low. I think I heard 14 is the highest MELD score.
5 So I would advocate that I think this is an
6 important area to allow patients to be treated.
7 But what is the agency's recommendation -- what
8 would your recommendations be regarding MELD score
9 or severity of illness?

10 DR. MISHRA: So as far as I know, sponsor is
11 doing a separate trial in decompensated patients
12 because, as you pointed out, the MELD score, the
13 highest MELD score in this study was not the
14 typical MELD score which will be used for a patient
15 to be transplanted besides HCC meeting Milan
16 criteria.

17 So they are doing a trial and, hopefully,
18 that trial will address some of the questions you
19 raised. We have not reviewed the data, and I am
20 not sure how many patients have been enrolled in
21 that trial so far.

22 DR. MURATA: Dr. Korman?

1 DR. KORMAN: I want to second Dr. Hagedorn's
2 comments. The number of patients with
3 hepatocellular carcinoma and the tragedy of them
4 getting reinfected is just absolutely critical.
5 The difficulty is that I think all of these are
6 compensated cirrhotics -- or most of them are
7 generally compensated cirrhotics, where the tumor
8 is discovered incidentally and part of the
9 screening program.

10 I think the critical issue will be how
11 tolerable this drug will be with some of the other
12 agents that are necessary to support these patients
13 and whether we can do harm in patients who are
14 waiting for transplantation, what the regimens will
15 be.

16 I don't know how applicable registries would
17 be to the development of a better understanding of
18 the way this gets done because, once it's out, it's
19 going to be used in a variety of concoctions by
20 various centers. And tracking that information in
21 a very limited set, in a small number of centers,
22 it would be much more amenable to tracking if the

1 resources are available than it would be if they're
2 used in large communities through the UNOS
3 organizations or some of the structures that
4 already are in place for the management of
5 transplantation.

6 DR. MURATA: Dr. Ghany?

7 DR. GHANY: Marc Ghany. I do have some
8 concerns about this combination in transplant
9 patients. It may have to do with -- the data is
10 not very clean. It's a little muddy. I would have
11 expected more patients to be negative, but it may
12 have to do with the duration of therapy.

13 Clearly, we need more work here. And I
14 really would like to stress if the sponsor can
15 collect more data, particularly in individuals with
16 higher MELD scores, because right now this is
17 really a very small proportion of individuals who
18 are going to receive a transplantation.

19 As I've stated before, I think the
20 critical -- if we can get people HCV RNA-negative
21 going into the transplant, their outcome is going
22 to be substantially better.

1 So again, just to reemphasize, if the
2 sponsor can start collecting data of the use of
3 this drug in patients with more advanced liver
4 disease, I think that's critical.

5 DR. MURATA: Thank you. Dr. Friedman?

6 DR. FRIEDMAN: Lawrence Friedman. Yes. I
7 agree with what's been said. I think this is a
8 growing problem. We're seeing more and more
9 hepatocellular carcinoma, and it's occurring in our
10 hepatitis C patients. And it's rather alarming.

11 Here we have a drug that's relatively free
12 of side effects, that doesn't interact with the
13 drugs we worry that other drugs interact with, and
14 I think we ought to be using it in this setting.
15 And I think we ought to be studying how to push the
16 boundaries on that for people with higher MELD
17 scores.

18 I agree with Dr. Ghany's concern about the
19 duration of treatment because the data has seemed
20 to show that you have to give it for at least
21 30 days before transplantation to hope to clear the
22 virus. So that needs to be studied, and then

1 people prescribing the drug in this setting need to
2 be advised about that fact.

3 DR. MURATA: Dr. Alcendor, did you have a
4 comment?

5 DR. ALCENDOR: I think this is a very
6 special patient. This is not normal in terms
7 of -- you're talking about continual
8 immunosuppression for an allograft transplant in a
9 patient that requires that immunosuppression long
10 term. You're talking about a virus that can
11 possibly establish latent reservoirs in that
12 patient. And over time, you're just looking at the
13 practicality of just organ shortages. And when
14 you're lucky enough to get an organ, you want to
15 try to keep it.

16 You look at all of those things. This is
17 going to be a wait-and-see approach in those
18 patients. It's a work in progress, but it's work
19 that has to be done.

20 DR. MURATA: Thank you. Dr. Follmann?

21 DR. FOLLMANN: So to me, these are patients
22 who would be eligible for treatment, so why not

1 treat them, is what I was thinking. So I was
2 comfortable with the idea of the 48-week treatment
3 duration, which was, as my understanding, the
4 current study, which is ongoing.

5 I think the current study that's ongoing is
6 also -- I think it's ongoing -- very interesting
7 because you basically have the livers becoming
8 available at sort of a random time relative to when
9 the patients initiated therapy. So I believe it's
10 as if you're randomizing duration of therapy prior
11 to transplantation, and you can analyze that data
12 that way. It's kind of a powerful method.

13 I would say the sponsor didn't really do
14 that in their analysis on CC-74, which was days
15 from being undetectable to transplant. That time
16 can depend on how quickly you respond and so on.
17 So it's not quite the same as looking at days of
18 duration of therapy prior to transplant, which
19 would be the analysis that I think is more cleaner,
20 more like a randomized trial.

21 But I thought it made sense to make the drug
22 available to patients like this, and you have this

1 natural experiment going on, which will help I
2 think refine the duration question if we just
3 collect the data that's going to be available
4 anyway and make decisions based on that.

5 DR. MURATA: Does the sponsor have a comment
6 about that?

7 DR. MCHUTCHISON: Thank you. The
8 decompensated study is fully enrolled. We have a
9 separate study with an all-oral regimen in 350
10 pre-transplant patients. And Dr. Symonds will
11 address the duration of treatment as compared to
12 the duration of target not detected, to answer your
13 question.

14 DR. SYMONDS: We've looked at the duration
15 of treatment in these patients, the duration of
16 time below the lower limit of quantification as
17 well as the TND values.

18 In these patients, actually, our first and
19 most simple attempt was of course to just look at
20 the number of days of therapy a patient was on
21 before transplantation. And when we first started
22 looking at the data, it appeared that it didn't

1 matter how long someone had been on therapy without
2 taking the virus into account. But it changes
3 things a bit when you start to look down deep at
4 the TND values.

5 Here we go. This is the same slide that I
6 showed earlier in the presentation. The dark bars
7 are all the same, as I showed earlier. The dark
8 green are those without recurrence, and the red
9 ones are those with recurrence. The lighter color,
10 the shaded part, are the days on therapy.

11 So you'll see three different patterns here.
12 The patients at the top that are all red and the
13 shaded red, those patients were on therapy
14 sometimes as long as 200 days, but did not have any
15 consecutive days below target not detected at the
16 time of their transplantation.

17 The patients in the middle part of the bars
18 got durations of therapy, and many of them had
19 fairly normal-looking viral kinetics and became TND
20 within a month of going on therapy. Those are the
21 patients that have the small gap between the end of
22 the line and when the dark part starts.

1 Then there's patients at the bottom who
2 completed their 24 weeks of therapy, and then were
3 followed off therapy. Those patients were probably
4 SVRs, irrespective of the transplant, and went into
5 the transplant TND without remaining on drug.

6 So what we really noticed here was,
7 basically, there are some patients who can take
8 therapy for quite a long time and don't get TND.
9 Those patients are congregated at the top, of
10 course. But if you draw the line at about 30 days,
11 which I had on the other slide, it's right around
12 the last of the middle red bars, towards the top,
13 once you get to those patients, everybody had a
14 duration of therapy.

15 They also had a normal-looking TND profile
16 where they got down within a month or two, and then
17 went to transplant while they were TND. And those
18 are the patients most likely to not recur. So I
19 hope that sheds a little bit more light

20 DR. MURATA: Dr. Ghany?

21 DR. GHANY: So Dr. Symonds, do you actually
22 have an idea of how long you have to be TND before

1 transplant to remain negative post-transplant?

2 That's the key.

3 DR. SYMONDS: Yes. So here's the original
4 slide. So of the patients who were TND for greater
5 than 30 days, only 1 of them recurred. Of the
6 patients who were greater than or who were TND less
7 than 30 days, only 3 of them out of that group -- I
8 think it's about 10 there -- did not recur.

9 So it looks there's probably some time
10 period in there. It may be 30 days. It may not,
11 whereas, if you had that critical period -- and
12 again, these people were -- to be classified on
13 this slide as TND, you had to be TND at the time of
14 transplantation. If you were TND early and then
15 came back up above TND, you came off this analysis.
16 And those are who some of the people at the top
17 are. So it's the ones who stayed TND all the way
18 to transplant.

19 DR. MURATA: Dr. Giordano?

20 DR. GIORDANO: Tom Giordano. Just to follow
21 up on that point, the slide which shows the
22 treatment duration, you have a lot of patients who

1 got treatment for a prolonged period of time and
2 did not suppress, basically.

3 I know it's small numbers, but can you look
4 at those patients clinically and see are they
5 different in some way? Is there some baseline
6 characteristics or other factors that are different
7 in those patients compared to the ones who did
8 respond?

9 DR. SYMONDS: Yes. So this is a rather
10 basic analysis, but the recurrences are on the
11 left-hand column and no-recurrence is on the right
12 hand. And one thing you'll see is that most of
13 them are genotype 1, but most of the patients in
14 the study were genotype 1. You see Childs A versus
15 B. It doesn't seem like the Bs are overrepresented
16 in that group, so it doesn't appear to be an issue
17 of liver status.

18 Platelet counts are similar, or a higher
19 proportion, anyway. A quarter of the patients were
20 treatment-experienced in the no-recurrence arm, and
21 only one arm is treatment-naive. And then only one
22 of the patients in the recurrence arm was

1 treatment-naive. So the majority of the treatment-
2 naive are treatment-experienced and a lesser
3 proportion in the other group.

4 So we've also done a multivariate analysis,
5 and it's early-day still. But in this study,
6 amongst the 1b patients, for the 1b patients who
7 recurred were at the same site. So we're still
8 investigating is there something unique? And some
9 of the viruses even look fairly similar. It's not
10 the same virus, but they do look similar.

11 So we're exploring still with surgical
12 practices at that site and many other things, and
13 it's a very delicate balance of how you pursue
14 that, of course.

15 DR. MCHUTCHISON: So it's a work in
16 progress, and Bill has actually done all of this in
17 the last 10 days or 14 days with our group, so
18 we'll continue.

19 DR. MURATA: Thank you. Dr. Korman?

20 DR. KORMAN: I have a question. Peg is
21 contraindicated in transplant patients, or
22 cirrhotics, advanced cirrhotics?

1 DR. MURRAY: Not in cirrhotics, in Child B
2 and C.

3 DR. KORMAN: Child B.

4 DR. MURRAY: Yes, and C.

5 DR. KORMAN: But not in Child A --

6 DR. MURRAY: No.

7 DR. KORMAN: -- which many of these patients
8 are.

9 DR. MURRAY: Right.

10 DR. MURATA: Any other comments?

11 Dr. Hagedorn?

12 DR. HAGEDORN: I would just like to comment
13 that a lot of us who take care of these patients
14 pre-transplant were fearful that the development
15 companies would not test these drugs in this
16 population and wait some time. So I want to thank
17 you for testing it in this group because this is a
18 challenging group of patients.

19 Our fear was that this is one of the
20 toughest groups to treat and it would be the last
21 group to get any approval to use the drugs in. So
22 I wanted to make that clear.

1 DR. MURATA: Thank you. Mr. Raymond?

2 MR. RAYMOND: Yes. I had wanted to say the
3 same thing. I think the commitment that the
4 sponsor has made to this population in critical
5 need were really -- I mean, I think I also want to
6 acknowledge from the public comment period the
7 gentleman from Nigeria, who gave a very vivid
8 portrait of the consequences of not having any
9 available options to prevent recurrence.

10 I'll be happy to defer to my more clinical
11 colleagues on the specificities of this, but I
12 think that a breakthrough like this for an area of
13 such significant need makes me more tolerant of
14 some fuzziness in some of the specifics around the
15 data and the dosing.

16 DR. MURATA: Any additional comments?

17 (No response.)

18 DR. MURATA: So to summarize the points that
19 were discussed, clearly, there appeared to be a
20 consensus on the need to treat that patient
21 population in terms of burden of disease in
22 post-transplant patients with hepatitis C

1 recurrence, the incidence of hepatocellular
2 carcinoma.

3 The data that were presented earlier in the
4 day by the sponsor included relatively low MELD
5 scores that were probably deemed to be reflective
6 of the generally compensated cirrhotics. There
7 were some concerns raised about the applicability
8 of such data to real-life situations in terms of
9 whether or not the available data are as crisp and
10 clear-cut as they should be.

11 The duration of therapy prior to the
12 transplant was, as presented initially, not well
13 defined and also may reflect the availability of
14 the transplanted organ as a main indicator of when
15 such therapy was initiated.

16 One of the comments by one of the
17 hepatologists in the group commented about the
18 correlation of hepatitis C virologically
19 undetectable before transplant is likely a
20 favorable outcome post-transplant. And then in
21 response, the sponsor did present their recent data
22 analysis on the ongoing decompensated patient

1 population study.

2 In their limited analysis, they had
3 discussed the time to non-detectability or TND for
4 those on one hand, patients achieving a functional
5 SVR versus never achieving TND. And somewhere
6 around the middle, in a limited ongoing analysis,
7 30 days appear to be a working cut-off.

8 There are some nuanced points about some
9 ongoing multivariate studies, patient population,
10 other viral genotypes, but they appear to be
11 preliminary at that time.

12 But again, the lingering echoing sentiment
13 among the panel members, essentially, it's a very
14 challenging patient population in which there is
15 really a burden of disease and unmet medical need
16 that should be addressed.

17 We move on to the last of the three
18 discussion questions. As stated, it reads, "Please
19 comment on postmarketing studies/trials that are
20 needed to further define the optimal use of
21 sofosbuvir."

22 Before we open it up for discussion, are

1 there any questions on the wording at the moment?

2 (No response.)

3 DR. MURATA: Dr. Ghany?

4 DR. GHANY: Are we confined to just
5 discussing the use of sofosbuvir with the currently
6 presented regimens, so ribavirin, or peg plus
7 ribavirin, or other drugs in development?

8 DR. MURATA: Could I ask the agency to
9 clarify at that point?

10 DR. BIRNKRANT: I think you're not confined.
11 So you can go ahead and ask whatever you would
12 like.

13 (Laughter.)

14 DR. BIRNKRANT: That doesn't happen too
15 often.

16 DR. MURATA: I'm glad I asked for that
17 clarification.

18 Any other points on the wording before we
19 open it up? So now, this discussion point is open
20 for discussion. Ms. Lupole?

21 MS. LUPOLE: One of the things we face are
22 what happens to the patient after taking interferon

1 and ribavirin, the lasting effects, the cognitive
2 function. There's a lot of issues that patients
3 still face, whether they cleared the virus or not.
4 And I would encourage the FDA to continue looking
5 into aftercare for these patients because their
6 quality of life has truly been decreased. And if
7 we're going to continue to use these drugs, which I
8 really don't see any option at this point in time,
9 this may be an issue that needs looked into. Thank
10 you.

11 DR. MURATA: Dr. Ghany?

12 DR. GHANY: Marc Ghany. I think some of the
13 studies that should be done, we've touched upon
14 already, more studies in patients with more
15 advanced MELD scores and other populations, so I
16 don't want to reiterate those. What I wanted to
17 emphasize, and hopefully the sponsor will support
18 such studies, are clearly where the field is moving
19 as towards interferon and perhaps even ribavirin-
20 free regimens.

21 So I'd like to encourage the sponsor to
22 continue to support studies with sofosbuvir and

1 other agents that are in phase 3 development
2 trials, or even phase 2, that look promising, and
3 to make the drug available to other pharmaceutical
4 companies that have these compounds so that both
5 patients and their physicians can have access to
6 these drugs to treat them. As we've seen from
7 emerging data that's coming out and some that will
8 be presented at a liver meeting, the results look
9 very encouraging.

10 DR. MURATA: Dr. Alcendor?

11 DR. ALCENDOR: Yes. I wanted to talk about
12 marketing to underserved communities. And I think,
13 when you look at the people that would need these
14 drugs, many of them will come from underserved
15 communities. And I think there should be some
16 consideration there.

17 I think the trend for the people that would
18 need this drug, particularly geriatric patients and
19 many of the baby boomers that are just finding out
20 they have hepatitis but it's been with them for
21 25 years, are likely to be cirrhotics down the road
22 to be considered.

1 Finally, the cell cytotoxic studies that
2 have been done, I think cell lines are fine, but I
3 think you should include primary cells in your
4 cytotoxic studies that would include
5 cardiomyocytes, brain microvascular endothelial
6 cells, other cell types that are important as
7 potential reservoirs through this virus in some of
8 these patients long term.

9 DR. MURATA: Dr. Van Dyke?

10 DR. VAN DYKE: Yes. Russell Van Dyke. As
11 we talked about before, I think there really is a
12 need to do ongoing surveillance for viral
13 resistance because I think there's still a lot of
14 questions, and I think there's a potential for
15 increasing viral resistance on therapy that needs
16 to be really anticipated.

17 In addition, I mean, I'm not an expert in
18 this, but it sounds like there's a need for long-
19 term follow-up to find out the outcomes of
20 treatment on liver disease. What happens to the
21 fibrosis? Does it recur? Their cirrhosis. Does
22 it get better. Is it stable? And does treatment

1 really prevent hepatocellular carcinoma?

2 I don't know that we know that data. It
3 would be interesting to look.

4 DR. MURATA: Mr. Raymond?

5 MR. RAYMOND: Thank you. Daniel Raymond. I
6 would suggest along the lines of what Dr. Ghany
7 said, that there's a need to look at how to
8 optimize treatment strategies using sofosbuvir-
9 containing regimens to maximize the outcomes
10 specifically for some of the genotype 1 patients
11 who might also be interferon-unwilling, unable for
12 the pre-imposed transplant. I know that there's
13 coinfection studies underway. I think it will be
14 important to see the results of those.

15 Then I think there was a question that's
16 come up in the context of lingering uncertainties
17 about resistance about retreatment of people who
18 did not achieve an SVR on a previous sofosbuvir
19 regimen.

20 DR. MURATA: Dr. Daskalakis?

21 DR. DASKALAKIS: Just a really quick tag
22 onto that is, since there is a growing population

1 of individuals who have not succeeded on a
2 protease-based regimen salvage trial, looking at
3 folks who failed protease inhibitor-based regimens
4 would be useful as well.

5 DR. MURATA: Any additional comments?

6 (No response.)

7 DR. MURATA: So to summarize the points that
8 were raised for this particular question, there are
9 a number of different areas that the panel has
10 commented upon, including long-term effects
11 following the interferon and ribavirin-containing
12 regimen with sofosbuvir in terms of varying side
13 effects and long-term effects.

14 Again, as mentioned by the hepatologists in
15 the group, additional studies on patients bearing
16 higher MELD scores than what was previously
17 presented in the sponsor's presentations.

18 Sofosbuvir is a component of interferon,
19 ribavirin-free regimens. Unreached populations
20 beyond what was covered in these clinical studies,
21 including the geriatrics or those on the "baby
22 boomer" populations that are being tested at an

1 increased frequency.

2 There are some virological and cell
3 biological cytotox assay comments, including
4 suggestions about testing the cytotoxicin, primary
5 cells including cardiac and brain cells; the
6 continuing focus on additional data regarding viral
7 resistance; long-term clinical follow-up on
8 pertinent parameters, including fibrosis,
9 cirrhosis, and incidence of hepatocellular
10 carcinoma, again an emphasis on pre- and post-
11 transplant population, HIV, hep C coinfectd
12 patients; and really more management questions in
13 more complex patients, including retreatment in
14 patients who initially received a sofosbuvir-
15 containing regimen and did not achieve sustained
16 virologic response, or previously treated hep C
17 patients who had a clinical virological failure
18 with a protease inhibitor.

19 **Adjournment**

20 DR. MURATA: So now that we've just voted
21 and discussed, I want to thank the sponsor and the
22 agency for arranging this meeting, and we will now

1 adjourn. Panel members, please remember to drop
2 off your name badge at the registration table on
3 your way out so that they may recycle. Thank you.

4 (Whereupon, at 3:36 p.m., the meeting was
5 adjourned.)
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