

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM
DRUGS ADVISORY COMMITTEE

Date: May 24, 2012

Time: 8:30 AM - 4:30 PM

Location: Food and Drug Administration
White Oak Campus
Building 31, The Great Room
Silver Spring, Maryland

Capital Reporting Company
Peripheral and Central Nervous System Drugs Advisory Committee 05-24-2012

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1 MEETING ROSTER

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1 MEETING ROSER (CONT'D)

2 Ronald Farkas, M.D., Ph.D., Clinical Team Leader, DNP,
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1 P R O C E E D I N G S

2 DR. JOHNSON: Good morning. I would like to
3 first remind you all to please silence your cell
4 phones, your BlackBerrys, and other devices if you have
5 not done so already.

6 I would like to identify the FDA press
7 secretary, Sandy Walsh. Please stand if you're in the
8 room.

9 DR. FOUNTAIN: Good morning. Welcome to the
10 advisory committee meeting. Before we begin, why don't
11 we go around the table and have introduction of the
12 committee members and consultants? And why don't we
13 start at this end?

14 DR. UNGER: I'm Ellis Unger. I'm acting
15 director of the Office of Drug Evaluation I, FDA.

16 DR. KATZ: Russ Katz, director of the
17 Division of Neurology Products, FDA.

18 DR. FARKAS: Ron Farkas, the clinical team
19 leader in the Division of Neurology Products, FDA.

20 DR. JILLAPALLI: Devanand Jillapalli, medical
21 officer, Division of Neurology Products, FDA.

22 DR. LUAN: Julia Luan, statistician.

1 DR. ENSRUD: Erik Ensrud from the Boston VA
2 Medical Center in Brigham Women's Hospital.

3 DR. ROSENBERG: Paul Rosenberg from Johns
4 Hopkins University.

5 DR. GOOCH: Clifton Gooch, the University of
6 South Florida.

7 DR. LOGIGIAN: Eric Logigian, University of
8 Rochester Medical Center.

9 DR. MIELKE: Michelle Mielke, Mayo Clinic.

10 DR. CLANCY: Robert Clancy, Children's
11 Hospital, Philadelphia, University of Pennsylvania.

12 DR. FOUNTAIN: Nathan Fountain, University of
13 Virginia.

14 DR. JOHNSON: Glendolynn Johnson, DFO, PCNS.

15 DR. FRANK: Sam Frank, Boston University, and
16 I am the consumer representative.

17 MS. HOUSE: Tiffany House, patient
18 representative.

19 DR. MARDER: Ellen Marder, neurologist, UT
20 Southwestern and VA Medical Center.

21 DR. BAGIELLA: Emilia Bagiella, Mount Sinai
22 School of Medicine.

1 DR. OAKLANDER: I am Anne Louise Oaklander
2 from the Department of Neurology at Massachusetts
3 General Hospital.

4 DR. VERMA: Ashok Verma, University of Miami.

5 DR. PRESTON: David Preston, Case Western
6 Reserve University, Cleveland, Ohio.

7 DR. SHEFNER: Jeremy Shefner, Upstate Medical
8 University in Syracuse, New York.

9 DR. COHEN: Jeffery Cohen, Dartmouth Medical
10 School.

11 DR. KRAMER: Lynn Kramer, industry
12 representative.

13 DR. FOUNTAIN: Thank you. For topics such as
14 those being discussed at today's meeting, there are
15 often a variety of opinions, some of which are quite
16 strongly held.

17 Our goal is that today's meeting will be a
18 fair and open forum for discussion of these issues and
19 that individuals can express their views without
20 interruption. Thus, as a gentle reminder, individuals
21 will be allowed to speak into the record only if
22 recognized by the chair. We look forward to a

1 productive meeting.

2 In the spirit of the Federal Advisory
3 Committee Act and the Government in the Sunshine Act,
4 we ask that the advisory committee members take care
5 that their conversations about the topic at hand take
6 place in the open forum of the meeting.

7 We are aware that members of the media are
8 anxious to speak with the FDA about these proceedings.
9 However, FDA will refrain from discussing the details
10 of this meeting with the media until its conclusion.
11 Also, the committee is reminded to please refrain from
12 discussing the meeting topic during breaks or during
13 lunch. Thank you.

14 Now, I'll pass it to Lieutenant Commander
15 Glendolynn Johnson, who will read the conflict of
16 interest statement.

17 DR. JOHNSON: The Food and Drug
18 Administration is convening today's meeting of the
19 Peripheral and Central Nervous System Drugs Advisory
20 Committee under the authority of the Federal Advisory
21 Committee Act of 1972. With the exception of the
22 industry representative, all members and temporary

1 members of the committee are special government
2 employees or regular federal employees from other
3 agencies and are subject to federal conflict of
4 interest laws and regulations.

5 The following information on the status of
6 this committee's compliance with federal ethics and
7 conflict of interest laws, covered by but not limited
8 to those found at 18 U.S.C., Section 208 and Section
9 712 of the Food, Drug, and Cosmetic Act, is being
10 provided to participants in today's meeting and to the
11 public.

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

22 Under Section 712 of the FD&C Act, Congress

1 has authorized FDA to grant waivers to special
2 government employees and regular federal employees with
3 potential financial conflicts when necessary to afford
4 the committee essential expertise.

5 Related to the discussion of today's meeting,
6 members and temporary members of this committee have
7 been screened for potential financial conflicts of
8 interest of their own, as well as those imputed to
9 them, including those of their spouses or minor
10 children, and, for purposes of 18 U.S.C. Section 208,
11 their employers. These interests may include
12 investments, consulting, expert witness testimonies,
13 contracts, grants, CRADAs, teaching, speaking, writing,
14 patents and royalties, and primary employment.

15 At today's meeting, the committee will
16 discuss the safety and efficacy of new drug application
17 202737, proposed trade name, Vyndaqel, tafamidis
18 capsules, submitted by FoldRX Pharmaceuticals, a
19 subsidiary of Pfizer. The proposed indication is for
20 the treatment of transthyretin familial amyloid
21 polyneuropathy.

22 This is a particular matters meeting, during

1 which specific matters related to FoldRX and Pfizer's
2 Vyndaqel will be discussed. Based on the agenda and
3 all financial interests reported by the committee
4 members and temporary members, no conflict of interest
5 waivers have been issued in connection with this
6 session. To ensure transparency, we encourage all
7 standing committee members and temporary voting members
8 to disclose any public statements that they have made
9 concerning the product at issue.

10 With respect to the FDA's invited industry
11 representative, we would like to disclose that Dr. Lynn
12 Kramer is participating in this meeting as a non-voting
13 industry representative, acting on behalf of regulated
14 industry. Dr. Kramer's role in this meeting is to
15 represent industry in general and not any particular
16 company. Dr. Kramer is employed with Eisai.

17 Dr. Kramer would like to disclose that Eisai
18 and Pfizer currently have a co-promotion agreement for
19 Aricept, an unrelated product.

20 We would like to remind members and temporary
21 members that, if the discussion involve any other
22 products or firms not already on the agenda for which

1 an FDA participant has a personal or imputed financial
2 interest, the participants need to exclude themselves
3 from such involvement and their exclusion will be noted
4 for the record. FDA encourages all other participants
5 to advise the committee of any financial relationships
6 they may have with the firm at issue. Thank you.

7 DR. FOUNTAIN: All right. We'll now proceed
8 with Dr. Katz's introductory remarks.

9 Both the FDA and the public believe in a
10 transparent process for information gathering and
11 decision making. To ensure such transparency at the
12 advisory committee meeting, FDA believes it is
13 important to understand the context of an individual's
14 presentation.

15 For this reason, FDA encourages all
16 participants, including the sponsor's non-employee
17 presenters, to advise the committee of any financial
18 relationships that they may have with the firm at
19 issue, such as consulting fees, travel expenses,
20 honoraria, and interest in the sponsor, including
21 equity interests and those based upon the outcome of
22 the meeting. Likewise, FDA encourages you, at the

1 beginning of your presentation, to advise the committee
2 if you do not have any such financial relationships.

3 If you choose not to address this issue of
4 financial relationships at the beginning of your
5 presentation, it will not preclude you from speaking,
6 though.

7 Dr. Katz?

8 DR. KATZ: Thank you, Dr. Fountain.

9 First, let me welcome the committee members,
10 the already-appointed standing committee members. We
11 have a number of members who I guess are awaiting final
12 sign-off to be official committee members, but I
13 appreciate very much your agreeing to be members and
14 for coming this morning. I also would like to thank
15 our patient representative.

16 I'd also like to thank the folks who signed
17 up to speak in the open public hearing. Your comments
18 are very important to the process, and I appreciate
19 very much your making the effort to come today.

20 So as you know and as we've heard, of course,
21 we're here to discuss NDA 202737, submitted by Pfizer,
22 Incorporated for the use of tafamidis meglumine,

1 proposed name Vyndaqel, in the treatment of patients
2 with familial amyloid polyneuropathy, which I'll refer
3 to as FAP.

4 FAP is caused by one of numerous mutations in
5 the gene that codes with transthyretin or TTR. TTR
6 occurs normally as a tetramer, and it's a transporter
7 of thyroxine and the retinal binding protein retinal
8 complex. In a normal case, it exists as a tetrameric in
9 equilibrium with its component monomers. In patients
10 with FAP, though, the mutation causes the tetramer to
11 dissociate into abnormal monomers that misfold, form
12 toxic intermediates, ultimately resulting in the
13 formation of amyloid, which deposits in numerous
14 tissues.

15 There are numerous phenotypes. In FAP, the
16 primary, though certainly not the sole, organ of injury
17 is the peripheral nerve. Patients with FAP develop
18 signs of a severe progressive sensory motor and
19 autonomic neuropathy. Symptoms can begin in the third,
20 fourth, or fifth decade and death usually ensues, on
21 average, within 10 or so years after the onset of
22 symptoms.

1 Other mutations can result in other primary
2 organs of toxicity, especially the heart, resulting in
3 a condition called familial amyloid cardiomyopathy or
4 FAC. The most common mutation causing FAP results in a
5 substitution of valine by methionine at position 30,
6 and this is the so-called V30M mutation.

7 There are no specific current treatments for
8 FAP, other than liver transplant. Because the abnormal
9 tetramer is produced in the liver, a liver transplant
10 is helpful. Of course, not everyone can get a liver
11 transplant.

12 This is an orphan disease, meaning, by law,
13 it has a prevalence of less than 200,000 patients in
14 the United States. And in fact, the prevalence of FAP
15 in the U.S. is somewhere around 2500, maybe less, and
16 the worldwide prevalence is somewhere between 5,000 and
17 10,000, presumably. And patients are clustered
18 geographically, and there are larger clusters in
19 Portugal, Sweden, and Japan.

20 Tafamidis, which is the drug under discussion
21 today, binds to the two thyroxin binding sites of the
22 tetramer and presumably stabilizes the tetramer, so

1 presumably fewer toxic monomers are produced, hence,
2 less amyloid is formed and deposited in tissues. And
3 the sponsor asserts that it is this action of tafamidis
4 that can slow the progression of the disease.

5 In support of this claim, the sponsor has
6 submitted the results of a single, adequate, and well-
7 controlled study, so-called Study 005, which was
8 performed in patients only with the V30M mutation.

9 In addition, the sponsors performed Study
10 006, which is a follow-on open-label study to 005 in
11 which patients who had received placebo in 005 were
12 switched to treatment with tafamidis, and patients who
13 had been randomized to tafamidis in 005 continued to
14 receive tafamidis for another 12 months.

15 Although Study 006 was open label, the
16 patients and investigators were blinded to their
17 original treatment in Study 005. And in addition, the
18 sponsors performed several other and submitted the
19 results of several other open-label, uncontrolled
20 studies, which enrolled patients both with the V30
21 mutation and with other mutations.

22 So my goal here this morning in my brief

1 remarks is twofold. One, I want to just give an
2 overview of the issues that we are concerned about in
3 the data that was submitted. Dr. Farkas will present
4 later this morning a much more detailed presentation of
5 the issues that we are concerned about and why we're
6 concerned about them, but I just want to touch on them
7 briefly. But the other purpose of my remarks is to
8 give you a background into the relevant regulatory
9 pathways to potential approval for any drug, really. I
10 think it's important for the committee and other folks
11 to understand what regulatory pathways are available
12 for drug approval. So let me start with that.

13 The sine qua non for drug approval in the
14 United States is a demonstration of what's known as
15 substantial evidence of effectiveness. And since 1962,
16 the law has required this sort of evidence to be
17 provided before a drug can be approved for marketing.

18 Substantial evidence of effectiveness was
19 defined in the law -- it's still defined -- as evidence
20 from what are called adequate and well-controlled
21 clinical investigations that establish that the drug
22 has the effect claimed for it in product labeling. And

1 it's important to note that the language of the law is
2 in clinical investigations, plural. And typically, in
3 practice and traditionally, this standard has been
4 considered to have been met if at least two adequately
5 designed and conducted clinical trials demonstrate
6 statistically significant between-treatment contrasts
7 on prospectively defined, clinically relevant outcome
8 measures. And this incorporates the standard
9 scientific requirement for independent replication of
10 any finding.

11 Traditionally, statistical significance has
12 been defined as a two-tailed p value of less than 5
13 percent for the between-treatment contrast. That's a
14 definition you all know of statistical significance
15 that is deeply embedded in the culture of clinical
16 trials and drug approval. It's the standard from which
17 we rarely waver. And when we do, we do so with some
18 trepidation.

19 In 1997, the law was amended to include an
20 additional definition of substantial evidence of
21 effectiveness. The new definition stated that
22 substantial evidence can consist of the results of a

1 single, adequate and well-controlled trial with
2 something called confirmatory evidence.

3 The law didn't specify under what
4 circumstances this new standard might apply, nor did it
5 define what it meant by confirmatory evidence.
6 Nonetheless, the agency, in 1998, issued a guidance
7 document that described the aspects of a single study
8 that might make it meet the new single-study standard.
9 Among these characteristics -- these are not all of
10 them -- but among the characteristics are a very low p
11 value, a p value considerably lower than the standard
12 two-tailed .05, on the primary outcome or outcomes;
13 multiple secondary outcomes reaching a dependent
14 statistical significance, or very nearly so, especially
15 on outcomes that were not just highly correlated with
16 each other, but which assessed significantly different
17 clinical domains; multiple subgroups of patients all
18 showing similar effects, in other words, mildly
19 impaired patients, severely impaired patients, that
20 sort of thing; multiple study sites showing effects;
21 and no one particular study site providing all the
22 persuasive evidence.

1 So in other words, this one study would
2 presumably provide the sort of, I guess you could say,
3 internal replication that two studies would provide
4 under the usual standard. And it would be considered
5 to provide, in a sense, the same amount of evidence of
6 effectiveness as two typical studies.

7 Depending upon the robustness of the single
8 study, the confirmatory evidence required by the law
9 could be provided by that single study itself or
10 confirmatory evidence could come from a source external
11 to that study. It's also worth noting that the
12 standard still that is most commonly applied is the
13 two-study standard.

14 I need to discuss another relevant regulatory
15 pathway before we move on. Since 1992, the agency has
16 had the authority to approve a treatment on the basis
17 of an effect on what I would call an unvalidated
18 surrogate marker. This approach you probably have
19 heard of as accelerated approval or subpart H approval,
20 subpart H being the section in the regulations that
21 describes this approach.

22 So briefly, you undoubtedly all know a

1 surrogate marker is typically a lab test that has no
2 immediate direct bearing on how the patient feels or
3 functions, something like blood pressure or an imaging
4 marker, but that serves as the primary measure of drug
5 effect for purposes of drug approval. And less
6 commonly, actually, a clinical outcome can serve as a
7 surrogate if it's not the clinical outcome ultimately
8 that you really care about, but an effect on which
9 might predict the ultimate clinical outcome. An
10 ultimate clinical outcome of interest might be
11 something like mortality.

12 The agency, of course, has long approved
13 drugs based on their effects on surrogates when data
14 has established that an effect on that surrogate, a
15 drug-induced effect on that surrogate, is known to
16 produce -- there's evidence that it will produce,
17 usually out in time -- an effect on the clinical
18 outcome of interest. So blood pressure drugs are
19 approved on the effect of some blood pressure because
20 it's known that that predicts fewer strokes, fewer
21 heart attacks in the future.

22 These surrogates are called validated

1 surrogates because we know, based on evidence, that
2 when you affect a surrogate, you will affect the
3 clinical outcome of interest down the road. But in
4 contrast to validated surrogates, there are surrogates
5 for which drug-induced effects are predicted to result
6 in a beneficial clinical effect, but we don't really
7 know yet that they do predict that clinical benefit.
8 And these are what I would call unvalidated surrogates.
9 And again, the agency has the authority to approve a
10 drug based on its effects on such a surrogate if we
11 find that the effect on the surrogate is reasonably
12 likely to predict the clinical benefit we care about.
13 And that's language of the law, reasonably likely to
14 predict a clinical benefit.

15 It's very important, I think, to understand
16 that concluding that an effect on an unvalidated
17 surrogate will be reasonably likely to predict a
18 clinical benefit will typically depend upon a detailed
19 understanding of the effects, both positive and
20 negative, of the drug under study as well as a detailed
21 understanding of the path of biological pathways of the
22 disease that lead to clinical symptoms. This is

1 information that we typically don't have. We typically
2 don't know all the effects, good and bad, of a drug.
3 And we certainly typically don't know all the
4 pathophysiology pathways that lead to disease in any
5 given case.

6 Although there is often a clear correlation
7 between a proposed surrogate and disease progression in
8 the untreated state, it may very well be the case that
9 under treatment conditions, this relationship no longer
10 exists.

11 There are numerous examples in medicine in
12 which an expected beneficial effect on the proposed
13 surrogate did not translate into a clinical benefit.
14 And because approval based on an effect on an
15 unvalidated surrogate, accelerated approval, subpart H
16 approval, involves considerable uncertainty about the
17 clinical benefit to be obtained, the regulations
18 require that sponsors perform studies in the post-
19 marketing period to actually document that the drug in
20 fact does have the effect of the clinical benefit
21 predicted. And if these studies aren't done in a
22 timely manner or if the studies are done and they

1 actually show that there is no clinical benefit, these
2 drugs can be removed expeditiously from the market.

3 At this point, I have to make something clear
4 to bring together these sorts of regulatory approaches,
5 and it's something that I think is commonly
6 misunderstood. In order for us to approve a drug on the
7 basis of an effect on such an unvalidated surrogate --
8 again, accelerated approval -- we have to find that
9 there is substantial evidence of effectiveness for the
10 effect on the surrogate.

11 So as I noted earlier, the sine qua non for
12 approval is the finding of substantial evidence of
13 effectiveness. And if we're contemplating utilizing
14 the accelerated approval route, we still have to have
15 substantial evidence of effectiveness for the
16 surrogate.

17 As I just discussed, there are really only
18 two ways to obtain substantial evidence of
19 effectiveness, either with two adequate and well-
20 controlled trials or one trial and confirmatory
21 evidence. One of these standards has to be met for the
22 effect on the surrogate for us to approve a drug under

1 subpart H or accelerated approval.

2 The reasonably likely standard applies to the
3 question of whether or not that effect on the surrogate
4 will result in a clinical benefit down the road, but
5 the effect on the surrogate has to be supported by
6 substantial evidence of effectiveness as the law
7 defines it.

8 So as I said, FAP is an orphan disease. It's
9 a relatively small orphan disease. And it's important
10 for you to know, though, that the law actually makes no
11 distinction between the evidence required to approve a
12 drug for an orphan disease and the evidence required to
13 approve a non-orphan disease. Specifically, we have to
14 find that there is substantial evidence of
15 effectiveness to support the orphan claim, just like we
16 do for any other type of claim.

17 But having said this, it should also be said
18 that there is considerable flexibility in how the
19 standards are applied in any given case, both orphan or
20 not orphan for that matter, and we are undoubtedly
21 going to be discussing the sorts of flexibility built
22 into the system a great deal today.

1 We are committed to applying as much
2 flexibility as we can, but this has to be done within
3 the requirements of the law. The law standards are
4 designed to ensure, as much as possible, that only
5 drugs that have been found to have the effects claimed
6 for them are approved for marketing. The law
7 presupposes, and I think appropriately so, that
8 approving drugs that have not been shown to be
9 effective is inappropriate. And I think that's a
10 widely accepted premise.

11 I should note that it's possible under
12 certain circumstances to make a drug more or less
13 widely available, at least for some patients, before a
14 drug is approved but while studies designed to
15 demonstrate its effectiveness are ongoing; and we will
16 be discussing these sorts of approaches later. But
17 approval for marketing has to be based on a finding of
18 substantial evidence of effectiveness.

19 With this background, I'll just turn to some
20 of the issues, then, that we would like the committee
21 to consider and are incorporated in our documents and
22 in the question list that we sent you. Dr. Farkas will

1 be presenting later, and he will go into these issues
2 in far more detail, but I just want to lay them out for
3 you at the beginning.

4 Probably, perhaps, of primary concern for us
5 is the finding that neither of the two outcomes
6 prospectively designated in the protocol as primary
7 yielded between-treatment contrasts that were
8 statistically significant by the usual standard.

9 Specifically, the p value for the contrast on
10 the NIS-LL, which is a measure of peripheral nerve
11 function -- and the primary outcome was based on a
12 responder analysis defined in a certain way -- that p
13 value was .07. And the p value for the TQOL, which is
14 a quality of life sort of global measurement, was 0.12.

15 Now, the sponsor notes that there were
16 considerably more dropouts from this study than they
17 planned on, and these dropouts or discontinuations were
18 largely related to patients who received liver
19 transplants. Most of these patients were on the
20 transplant list well before the study started,
21 presumably. And these transplants occurred when their
22 names came up, and they are presumably unrelated to the

1 patient's treatment assignment or perhaps how they were
2 doing in the study. And according to the sponsor,
3 analyses accounting for these discontinuations yielded
4 what we'd call nominally significant results of around
5 .04 to .05.

6 These secondary analyses were prospectively
7 described in the protocol, but strict adherence to
8 standard statistical practice would suggest that when
9 the primary outcomes don't reach statistical
10 significance, which these didn't, it's usually
11 inappropriate to perform subsequent analyses. And
12 again, strictly speaking, if those subsequent analyses
13 are performed, it's difficult, if not impossible, to
14 really understand what the p values mean. A p value of
15 .05 done after the primary outcomes were negative
16 doesn't have the same meaning as a p value of .05 for
17 the primary outcomes.

18 So in addition to the protocol-specified
19 primary outcome of the NIS-LL, which was again a
20 responder rate, the sponsor analyzed the change from
21 baseline in the NIS- LL as a continuous variable, and
22 there they also obtained a nominal p value of .03. Our

1 statistician, Dr. Luan, also performed a similar
2 analysis of the NIS-LL as a continuous variable, but
3 she excluded two placebo patients who were clearly
4 outliers. And when that analysis was done, the result
5 lost even nominal statistical significance.

6 In addition to Study 005, multiple secondary
7 outcomes were assessed. These were all in the
8 protocol, but there was no prospective statistical plan
9 as far as we know to analyze these outcomes in any
10 particular order. And for some of these between-
11 treatment contrasts, for some of these outcomes, the
12 between- treatment contrast was again nominally less
13 than 5 percent. And the sponsor describes these
14 analyses as being prospectively designated.

15 It's true. They were prospectively
16 designated, but again, there was no formal statistical
17 plan in place for analyzing these outcomes in a
18 particular order. And as I noted, given the fact that
19 there was no attempt to correct for multiple
20 comparisons, no prospectively designated order in which
21 these were to be treated, and given the fact that the
22 primary outcomes were negative, it's very difficult to

1 understand what those p values mean.

2 I should also make clear that even if several
3 outcomes are seen to be nominally statistically
4 significant, whatever that means, the ones in the study
5 are likely to have been fairly highly correlated with
6 each other. So for this reason, the results of
7 numerous analyses, which appear possibly to be
8 significant on the face, although again they're
9 nominal, cannot be considered to be analyses of
10 entirely independent outcomes. And therefore, any
11 attempt to consider these multiple allegedly nominally
12 significant findings as providing independent
13 replication of the sort we talked about earlier is very
14 problematic.

15 There are several other issues of concern. We
16 found that there is evidence of important differences
17 at baseline between the two treatment groups. And in
18 particular, several lines of evidence suggest that
19 patients randomized to tafamidis were less impaired at
20 baseline than those randomized to placebo. That just
21 happened by chance. But we also found out that the
22 ultimate responder status was actually dependent on the

1 baseline status. And when Dr. Luan performed an
2 analysis accounting for these baseline differences, for
3 the NIS- LL, I believe the responder rate, the p value
4 increased from the .07, which was seen on the
5 prospective primary outcome, to a .16.

6 The sponsor also examined the effects of
7 baseline differences and found no effect of differences
8 on the outcome. However, we believe Dr. Luan has shown
9 that those analyses are highly dependent upon how
10 patients were categorized at baseline. And these were
11 categorizations, as far as we can tell, that were not
12 described prospectively in the protocol, they were
13 performed after the trial was done, and the results
14 were known. Various other categorizations did not give
15 consistent results.

16 Another concern arises from the fact that
17 almost 60 percent of the patients were enrolled at a
18 single center. Recall one of the criteria for the
19 substantial evidence deriving from a single study, that
20 the guidance document describes, is that no one single
21 center provide all the positive results.

22 All of the apparent effect of the treatment

1 study-wide arose from this center, where it again needs
2 to be noted that there appeared to be important
3 baseline differences between the two treatment groups.
4 In the other centers, which contained 40 percent of the
5 patients in this study, no effect of the treatment was
6 seen.

7 So as you know, the sponsor also performed
8 Study 006. We don't believe this can be considered an
9 adequate and well-controlled trial, but the sponsor
10 does offer it as providing supportive evidence of
11 effectiveness.

12 Again, although some of the contrast
13 performed by the sponsor did reach nominal statistical
14 significance, these results need to be considered in
15 light of the fact that treatment was unblinded for all
16 patients. There appeared to be no prospective plan for
17 analyzing particular outcomes in particular orders. And
18 the patients entered into 006 represented a non-
19 randomized subset of patients enrolled in 005. And
20 even so, the results don't appear to uniformly support
21 an effect of tafamidis. So we're certainly interested
22 in what the committee thinks about that.

1 So given these data and concerns, we're
2 asking the committee if any of the standards for
3 approval described earlier can be considered to apply
4 in this case. Specifically and of paramount
5 importance, we need to know if the committee can
6 conclude that the sponsor has submitted substantial
7 evidence of effectiveness for tafamidis as a treatment
8 for FAP or to slow the progression of FAP.

9 Recall the two definitions of substantial
10 evidence. we don't believe that the sponsor has
11 submitted two adequate and well-controlled studies. So
12 therefore, we're asking the committee if you believe
13 that the sponsor has submitted a single, adequate, and
14 well- controlled study plus confirmatory evidence that
15 establishes effectiveness.

16 In this regard, recall that in a typical case
17 that relies on a single study, that single study is
18 typically robust with low p values, many different
19 outcome measures and analyses yielding statistical
20 significance and findings that do not arise from a
21 single center. That's typically, anyway.

22 For such a standard to apply, a highly robust

1 single study could itself provide the necessary
2 confirmatory evidence. Or the latter, again, could
3 come from another source, in this case, perhaps Study
4 006, although as we've seen, we have concerns about the
5 findings in that study.

6 Importantly, if you can't conclude that the
7 one- study standard has been met for a clinical
8 outcome, we need to know if you can conclude that this
9 standard has been met for a surrogate that is
10 reasonably likely to predict a clinical benefit. And
11 as noted earlier, such a surrogate is typically a lab
12 test, but it can be, as I said, a clinical outcome.

13 It's possible that one could consider some of
14 the clinical outcomes assessed as serving as potential
15 surrogates for purposes of accelerated approval, for
16 example, the large fiber function outcome, the small
17 fiber function, or the NIS-LL itself.

18 Again, it's important to remember that,
19 first, the sponsor must submit substantial evidence of
20 effectiveness for the effect on the surrogate. And so
21 in this regard, the committee must find that
22 substantial evidence of effectiveness has been

1 demonstrated for one or some of these outcomes before
2 it can even be considered as the basis for approval
3 under subpart H. And if the committee would consider
4 this approach, we would need to know what ultimate
5 clinical outcome you think the effect on those earlier
6 outcomes would predict and what the evidence is for
7 claiming that it would predict it.

8 Regarding other potential surrogates, it is
9 worth pointing out that there seems to be an
10 overwhelmingly clear effect of tafamidis on TTR
11 stabilization, not only in Study 005, but in other
12 open- label studies which enrolled patients who did not
13 have the V30M mutation. They had other mutations.

14 Regardless of the mutations studied, the
15 sponsor reports that almost all patients treated
16 achieved stabilization of TTR. So a few words of
17 clarification with regard to that finding are in order,
18 I think.

19 As I noted earlier, TTR is in equilibrium
20 with its monomers. The assay the sponsor used
21 assesses, in effect, the speed of dissociation of the
22 tetramer into the monomers. By stabilization of TTR,

1 as assessed by this test, the sponsor means that the
2 rate of stabilization has been slowed compared to the
3 baseline rate. It does not mean that the TTR has been
4 completely stabilized. And the data from Study 005
5 suggests that the average slowing of the rate of
6 dissociation is about two-and-a-half-fold slower than
7 at baseline.

8 So when the sponsor reports that essentially
9 all patients receiving tafamidis achieve stabilization,
10 that's the average degree of slowing or dissociation
11 that they achieved. And of course, that represents a
12 distribution.

13 But as Dr. Farkas will go into in more
14 detail, we have concerns both about the specific assay
15 used to document the stabilization of TTR. For
16 example, does it really represent -- given the
17 conditions of the assay, does it actually represent
18 stabilization of the tetramer in vivo?

19 But also, we have questions about whether an
20 effect on this measure is, in fact, reasonably likely
21 to predict a beneficial clinical effect. Recall that
22 approving a drug under subpart H requires numerous

1 assumptions about the effects, good and bad, of the
2 treatment and the pathophysiology of the disease. For
3 example, whether this degree of stabilization will have
4 any effect on the ultimate disability in patients with
5 FAP or any effect at all on the formation and
6 deposition of amyloid, which presumably is the ultimate
7 cause of the patient's symptoms, isn't known.

8 We're of course very interested in knowing,
9 then, if the committee believes the sponsor has
10 submitted substantial evidence of effectiveness for a
11 surrogate marker that is reasonably likely to predict a
12 meaningful clinical benefit. And Dr. Farkas again will
13 go into some more detail about the use of surrogates in
14 this case.

15 If the committee cannot conclude that the
16 sponsor has submitted substantial evidence of
17 effectiveness for either clinical outcome or a
18 surrogate marker that's reasonably likely to predict a
19 clinical benefit, we need to know if the committee can
20 conclude that Study 005 could serve as one adequate and
21 well- controlled study that could contribute to a
22 finding of substantial evidence of effectiveness if

1 combined with an additional study that might be
2 performed in the future.

3 Finally, Dr. Farkas will describe what we
4 believe are several potentially acceptable designs for
5 additional clinical studies that the sponsor might be
6 able to perform if we find that that is necessary.
7 These designs would be capable, in our view, of
8 efficiently answering the question of effectiveness of
9 tafamidis while minimizing, to the extent possible,
10 patients' exposures to an ineffective treatment.

11 One final word. As I wrote in my briefing
12 memo, agency policy requires primary reviewers to make
13 a recommendation about what action the agency should
14 take on any new drug applications. And as you know,
15 we've included several agency reviews with
16 recommendations. I just, again, want to assure the
17 committee that we have not made any final decision on
18 this application. Clearly, we are coming to you today
19 because we believe that we cannot make a final decision
20 without your input and advice.

21 So with that introduction, I'd like to thank
22 you for the work that you have done in preparation for

1 the meeting. Thank you in advance for the work you
2 will be doing today. I'd also say that we gave you a
3 question list. Of course, we are interested -- if
4 there's something that is not on that list that you
5 think is relevant, that we haven't brought up, we of
6 course want to know what you think about that, too.

7 With that, I will hand the floor back to Dr.
8 Fountain. Thank you.

9 DR. FOUNTAIN: Thank you. Dr. Chaudhry
10 joined us.

11 Could I ask you to introduce yourself? We
12 introduced ourselves earlier.

13 DR. CHAUDHRY: I apologize for coming late.
14 I'm Vinay Chaudhry. I'm a professor at Johns Hopkins
15 University School of Medicine, and I'm a peripheral
16 nerve expert in neuromuscular diseases and see some
17 patients with amyloid and other peripheral
18 neuropathies.

19 DR. FOUNTAIN: Thank you.

20 We'll now proceed with the sponsor's
21 presentation. Dr. Kahn?

22 MS. KAHN: Good morning, Mr. Chairman,

1 members of the committee, Dr. Katz, FDA, ladies and
2 gentlemen. I'm Clare Kahn, vice president for worldwide
3 regulatory strategy for specialty care at Pfizer. And
4 on behalf of Pfizer, we thank you for the opportunity
5 to discuss tafamidis today.

6 Pfizer recognizes the burden that rare
7 diseases impose on patients in society and we are
8 committed to finding innovative new treatments for
9 patients with orphan and genetic diseases. So before I
10 begin, I'd like to thank all the investigators and the
11 patients who have participated in the tafamidis
12 program.

13 The indications sought for tafamidis, trade
14 name Vyndaqel, is for the treatment of transthyretin
15 amyloidosis in adult patients with symptomatic
16 polyneuropathy to delay neurologic impairment.

17 Transthyretin is a tetrameric protein
18 synthesized in the liver that derives its name from its
19 function as a tertiary transport protein for thyroxine
20 and retinal binding complex. And transthyretin
21 familial amyloid polyneuropathy, or TTR-FAP, is one of
22 two major phenotypes of familial amyloidosis. The

1 other is cardiomyopathy, which is also known as TTR-
2 FAP, and that's the subject of a separate development
3 program.

4 So TTR-FAP is a very rare and fatal genetic
5 disease caused by a mutation in the TTR gene, which
6 renders the tetramer protein unstable. And it's this
7 instability that's the rate-limited step in the amyloid
8 cascade which develops into an irreversible and
9 relentlessly progressive neurodegenerative disease.
10 There's no pharmacological treatment available in the
11 United States and the only option is liver
12 transplantation to remove the source of the unstable
13 protein.

14 Now, tafamidis is a small molecule
15 specifically designed to bind the thyroxin binding site
16 of TTR and serve as a selective stabilizer to block
17 that rate- limiting step in the amyloid cascade, and
18 slow the progression of disease. Stabilization of the
19 tetramer is a biologically plausible biomarker for
20 efficacy of tafamidis across our clinical program.

21 Meeting the unmet need in TTR-FAP is a story
22 of bench-to-bedside drug development. You're going to

1 hear how a clinical observation of naturally protective
2 genetic variance led to the elucidation of the
3 molecular pathophysiology and a rational drug design
4 focused on tetramer stabilization.

5 The clinical program tested the effectiveness
6 of this approach based upon a single placebo-controlled
7 trial with confirmatory evidence from supportive trials
8 to seek approval and access for patients in the U.S.
9 It's this program that supported approval last year in
10 Europe under a provision called exceptional
11 circumstances, which bears a commitment to obtain
12 additional data in the more rare V30M non-V30M, I
13 should say, variance using the THAOS registry in the
14 post- approval setting.

15 THAOS is the only prospective disease
16 registry for all patients with TTR amyloidosis, and
17 it's been in effect since 2007, allowing us to study
18 patients with all variants at all stages of disease,
19 including pre- and post-transplant and those receiving
20 tafamidis. And at this time, over 1,200 patients are
21 participating globally, including in the U.S.

22

1 So there are no present trials for such a
2 rare disease, so we engage in a thoughtful process of
3 selecting endpoints validated in diabetic neuropathy,
4 adding additional endpoints relevant to TTR-FAP.
5 Clinical outcomes such as ambulation or mortality are
6 less feasible, given the years it would take to study
7 and the intervention of transplantation. And it's
8 these outcomes that will also be addressed in the THAOS
9 database.

10 So to support our indication, we used an
11 array of mechanistic and clear clinical measures which
12 sought to demonstrate replication of effect on very
13 different dimensions of disease progression. And two
14 co-primary endpoints taken together were to demonstrate
15 the clinical benefit of how a patient feels or
16 functions. Then a range of neurological and
17 neurophysiological function measures were used to
18 document disease progression and serve as clinical
19 markers, which are reasonably likely to predict
20 clinical benefit.

21 In this disease, where wasting is a key
22 feature, the modified body mass index is not just a

1 nutritional measure, but has been shown to have
2 prognostic value for outcome. And so if viewed
3 together with all of the other measures, serves as an
4 additional clinical marker. And of course, all of the
5 effects were anticipated from the necessary
6 stabilization of TTR, which underscores the program
7 across the program and provides a biologically
8 plausible marker by interruption of that first step in
9 the amyloid cascade.

10 As I mentioned, the core to the program is a
11 single double-blinded placebo-controlled trial, Study
12 005, conducted in patients with a common genetic
13 variant, V30M. We acknowledge that the primary
14 endpoint did not meet the pre-specified statistical
15 criteria for the intent-to-treat population. However,
16 as you will hear throughout the presentation, if
17 permitted to examine the totality of the data, the
18 weight of evidence across a variety of endpoints
19 provides a strong support for the efficacy of tafamidis
20 through stabilization of TTR.

21 Confirmatory evidence is derived from Study
22 006, which affords a second look at that same array of

1 endpoints, comparing patients continuing on tafamidis
2 with those switched from placebo to tafamidis.

3 Generalizability of effect is supported by
4 Study 201 in the non-V30M patients, the durability of
5 effect, examined over two and a half years in this NDA,
6 across Studies 005 and 006, and continuing in the
7 ongoing study, 303, which captures all patients and
8 some of whom who have exceeded five years now in
9 treatment.

10 The tafamidis program is the first
11 prospective drug development for TTR-FAP and has 187
12 patient years in 127 unique patients. The totality of
13 the data from a single pivotal and supportive trial
14 using clinical endpoints and biomarkers, together with
15 an uncomplicated safety profile, provides convincing
16 evidence of a positive benefit-risk that justifies
17 making this medicine available to patients as soon as
18 possible.

19 FDA has afforded fast-track and priority
20 review, which is befitting of a serious orphan disease
21 with unmet medical need, and this brings us to the
22 committee today. For traditional approval, you would

1 need to consider the two co-primary endpoints, which is
2 essentially the basis of question 2A. An accelerated
3 approval is based on endpoints that are reasonably
4 likely to predict clinical benefit, which is
5 essentially the basis of question 2B.

6 Regardless of the approval pathway, Pfizer is
7 committed to continuing the study of tafamidis in TTR-
8 FAP. If accelerated approval is granted on the
9 condition that clinical benefit is to be confirmed
10 post-approval, Pfizer commits to conduct a feasible
11 confirmatory efficacy trial. This would allow pts in
12 the United States with this progressive condition to
13 receive tafamidis treatment now without waiting for the
14 completion of a new confirmatory trial.

15 Now, before we begin our presentation, I'd
16 like to note that Dr. David Lewis from Tufts
17 University, who's an expert on liver transplant, is
18 here with us today.

19 Now, to our agenda. It's my pleasure to
20 introduce Dr. Steven Zeldenrust from the Mayo Clinic,
21 who will provide his clinical experience with TTR-FAP
22 and its devastating effect on patients.

1 DR. ZELDENRUST: Thank you, Dr. Kahn.

2 Good morning. I'm Steve Zeldenrust, an
3 assistant professor of medicine and a consultant in the
4 division of hematology at the Mayo Clinic. I'd like to
5 disclose that I am a paid consultant to the sponsor,
6 but I have no financial interest in the outcome of
7 today's meeting.

8 You may be wondering why a hematologist is
9 here to talk to you this morning about a neurologic
10 disease. My Ph.D. thesis focused on transthyretin
11 amyloid, and I'm currently attending physician at Mayo
12 Clinic, where we have a specialized treatment center
13 for the treatment of amyloid within the division of
14 hematology. And as a clinician primarily responsible
15 for TTR-FAP patients, I see roughly 30 patients a year.

16 This hopefully gives you some idea of the
17 extreme rarity of this disease, since we are considered
18 one of the primary referral centers for this disease in
19 the United States.

20 My reason for being here today is really
21 quite simple. I hope to put a face on TTR-FAP. Most
22 of you have likely never heard of this disease before

1 today and never seen a patient with it. So as a
2 physician who cares for these patients, I hope to leave
3 you with some idea of the problems they face and the
4 limited treatment options that are available for them.

5 So what is TTR-FAP? It's the most common
6 hereditary form of the rare, fatal, protein-deposition
7 diseases we call amyloidosis. And you'll hear more
8 about the pathogenesis of the disease from Dr. Kelly,
9 but it's important to know that it's an autosomal-
10 dominant disease with variable penetrants. And that
11 means that 50 percent of the children of an affected
12 patient can inherit the gene, but may not develop the
13 clinical disease.

14 It's a highly diverse disease with over 100
15 different point mutations identified in a protein that
16 only contains 127 amino acids. But despite that
17 genetic diversity, the pathogenesis of the disease
18 remains the same regardless of the mutation.

19 TTR-FAP is an extremely rare disease, with a
20 U.S. prevalence estimated at fewer than 2500 patients.
21 Given its rarity, it's frequently misdiagnosed. And as
22 a result, as few as 350 people in total are currently

1 identified as having this disease in the United States.
2 Worldwide prevalence is roughly two to four times that
3 seen in the United States.

4 TTR-FAP occurs both endemically and
5 sporadically throughout the world. And on the map you
6 see here are clusters of patients that have been
7 reported in various regions of the world. Three large
8 circles represent endemic foci of the disease in
9 Portugal, Sweden, and Japan. And these patients all
10 share the most common V30M mutation, which is present
11 in about 40 percent of U.S.

12 patients. As you'll hear, much of what we
13 know about this disease comes from studies of these
14 patients.

15 The smaller circles represent sporadic foci,
16 found in the rest of the world, including the U.S. And
17 these can either be large families that share a common
18 mutation or often single families with a novel one.

19 TTR-FAP patients frequently develop symptoms
20 in their 30s and 40s, in the prime of their lives, with
21 irreversible progression, leading ultimately to death
22 within 10 or 15 years from onset.

1 So what does TTR-FAP look like? As you might
2 have gathered from its name, TTR familial amyloid
3 polyneuropathy, the predominant feature of this disease
4 and the one that's most relevant to today's discussion,
5 is that of a degenerative peripheral neuropathy. Nerve
6 function is affected in a link-dependent fashion,
7 starting with the longest nerves in the body, typically
8 those in the lower extremities. Initial symptoms are
9 often fairly innocuous, some mild discomfort or
10 numbness, usually in the toes. But this is followed by
11 relentless progression involving the feet, then the
12 legs, and ultimately the upper extremities. By the
13 time patients have sensory involvement below their
14 ankle, they begin to experience motor symptoms and
15 weakness as well.

16 The process can take years, but progressively
17 affects patients' ability to perform simple tasks like
18 dressing, eating, and taking care of themselves. Within
19 a few years from onset, the symptoms reach the knee, at
20 which point patients are no longer able to walk on
21 their own.

22 By this time, they have complete loss of

1 sensation in their feet, often suffering injuries they
2 are oblivious to. They can no longer drive or work.
3 They become totally dependent on others to care for
4 them. They ultimately progress to become bedridden or
5 wheelchair bound, where they're at risk for infections,
6 pneumonia, and malnutrition, leading to death.

7 Patients frequently suffer from autonomic
8 dysfunction as well. Autonomic neuropathy causes
9 erectile dysfunction, which can be very distressing to
10 a 30-year-old man. Orthostatic hypotension and syncope
11 lead to difficulty standing and frequent falls.

12 GI involvement shows up as alternating
13 diarrhea and constipation, which can be disabling, as
14 patients can have up to 20 stools in a day. Many
15 become incontinent and are afraid to leave their home
16 as a result. Urinary retention leads to increased
17 infections and requires self-catheterization, which can
18 be extremely difficult when you can't feel your
19 fingers.

20 Although we've been talking about the
21 neurologic features of this disease, we can't lose
22 sight of the fact that TTR-FAP is a systemic disease

1 and can involve other organs as well. And while not
2 common in the V30M population, significant cardiac
3 involvement is critical and can range from mild
4 arrhythmias to cardiomyopathy and outright heart
5 failure. The kidneys, eyes, even the central nervous
6 system, can be involved in many patients, depending on
7 the mutation that they carry.

8 Weight loss is another common feature that's
9 often overlooked in the course of this disease. And
10 while we don't know the exact etiology of the severe
11 and progressive weight loss, autonomic dysfunction
12 undoubtedly plays a major role as patients battle
13 incontinence, gastroparesis, and impaired motility.
14 Cachexia inevitably ensues and is a common cause of
15 death.

16 These pictures were of one of my patients,
17 shown in the two pictures on the left, prior to the
18 development of symptomatic amyloidosis at a time when
19 he was actually trying out as a lineman for the
20 Minnesota Vikings football team.

21 The picture of him seated on the right was
22 taken just before he underwent liver transplant, a

1 point at which he had unintentionally lost over 150
2 pounds. By this time, he had also developed profound
3 sensory and motor symptoms as well.

4 So what can we do to help? The only
5 available treatment option at present is liver
6 transplantation. The vast majority of circulating TTR
7 is produced by the liver. By replacing the patient's
8 liver with one from a healthy donor, we can effectively
9 remove the source of the amyloid.

10 Most of what we know about liver transplant
11 comes from studying V30M patients, in which 80 percent
12 of patients benefit, including a clear, long-term
13 survival advantage. However, it's hardly a benign
14 procedure. It has a 10 percent mortality risk in the
15 first year and an overall 23 percent mortality risk by
16 five years. Patients with non-V30M mutations do even
17 worse, with a 44 percent mortality risk at five years,
18 and can often develop progressive symptoms following
19 transplant.

20 In addition to the risks of the surgery
21 itself, patients need to be on lifelong
22 immunosuppression, leading to increased infectious

1 complications. And as you can imagine, this is a
2 daunting prospect for a 30- or 40-year-old to consider.
3 And for patients that may have watched a sibling or
4 relative die as a result of their transplant, you can
5 see the fear on their face when they hear that this is
6 the only treatment option available to them.

7 Of course, due to limited donor availability,
8 not all patients accepting of the procedure actually
9 undergo a transplant. Depending on the transplant
10 center and the patient's blood type, the wait time may
11 be a year or more. Those with cardiac involvement
12 often need a combined heart-liver transplant, which
13 adds significantly to both the risk and the wait time.

14 Even more worrisome than the surgery itself
15 is the fact that not all patients benefit. It's clear
16 from both the literature and from my own practice that
17 some patients will continue to progress after a liver
18 transplant, particularly those with cardiac
19 involvement. It's been well-documented that continued
20 production of wild-type TTR by the donor liver can
21 participate in new amyloid deposits following liver
22 transplant.

1 What about those who are waiting or are
2 ineligible for liver transplant? Treatment for these
3 patients is purely palliative. And while that's
4 important for managing symptoms, none of these
5 treatments alter the natural history of the disease or
6 slow its progress.

7 So where does tafamidis come in? Despite the
8 success of liver transplant, it's clear not everyone is
9 eligible for transplant or benefits from it. We
10 desperately need more treatment options for these
11 patients, other than just palliative care.

12 You'll see some data today that suggests
13 tafamidis may be helpful in filling that need, but some
14 important questions remain to be answered.

15 What about patients with advanced symptoms?
16 Is there a point of no return? Does tafamidis have a
17 beneficial effect in cardiac involvement? And given
18 the significant number of U.S. patients with cardiac
19 involvement at the time of diagnosis, is a combined
20 heart-liver transplant the only option for these
21 patients? Is there a role for patients that progress
22 after a liver transplant?

1 I think it's worth noting that TTR
2 stabilization is really a novel paradigm in the
3 treatment of this disease. Liver transplant simply
4 substitutes wild type TTR for the mutant, but tafamidis
5 and other TTR stabilizers have the ability to stabilize
6 the wild type protein as well as the mutant. Clearly,
7 more studies are needed to answer these questions.

8 So in summary, TTR-FAP remains a rare,
9 relentless, and variable fatal disease which is
10 challenging to both diagnose and treat.

11 The only currently available treatment option
12 is liver transplant, which is an invasive procedure
13 associated with significant morbidity and mortality and
14 not an option for all patients. For those ineligible
15 for transplant, palliative treatment is the only
16 option.

17 TTR-FAP patients and the physicians who treat
18 them, like myself, desperately and urgently need more
19 effective treatments like the one being discussed
20 today. And while there are still some unanswered
21 questions regarding how tafamidis will fit into the
22 treatment of TTR-FAP patients in the U.S., the fact is

1 patients continue to suffer and die while we wait for
2 better treatments to become available.

3 Thank you.

4 Now it's my pleasure to pass the podium to
5 Dr. Jeff Kelly, the inventor of tafamidis.

6 DR. KELLY: Good morning. I am Jeff Kelly.
7 I'm chairman of molecular medicine and professor of
8 chemistry at the Scripps Research Institute. I had the
9 privilege of discovering tafamidis and starting FoldRX
10 Pharmaceuticals. Thus, I would receive financial
11 benefit from approval.

12 My role this morning is to tell you how, by
13 uncovering the mechanism of aggregation of
14 transthyretin, we were able to conceive of the kinetic
15 stabilizer strategy and the molecule tafamidis, which
16 is a kinetic stabilizer, which you'll see from the
17 clinical data today slows familial amyloid
18 polyneuropathy.

19 So I'd like to provide an introduction to the
20 transthyretin amyloidosis briefly from the perspective
21 of structural biology, and then talk about the kinetic
22 stabilization strategy, and then some of the

1 experiments upon which the 20-milligram once-daily dose
2 was selected.

3 So the liver biosynthesizes and secretes 95
4 percent of transthyretin that's in the plasma as a
5 tetramer, which I'll have more to say about in a few
6 minutes. The tetramer has to dissociate to a monomer,
7 and the monomer has to misfold in order to self-
8 assemble into a variety of structures, including
9 amyloid fibrils. And there's compelling genetic and
10 pharmacologic evidence that the process of
11 amyloidogenesis causes these diseases. And as you
12 heard from Steve, some of the mutants lead to a primary
13 autonomic or peripheral neuropathy. And that will be
14 the focus today. And other sequences of transthyretin
15 lead to cardiomyopathy.

16 If you focus your attention on the left-hand
17 side of this slide, 60 percent of the protein that's in
18 your plasma is unliganded transthyretin comprised of
19 four beta-sheet-rich subunits, as you can see. The
20 remaining 40 or so percent is shown on the right-hand
21 slide. This is transthyretin in complex with retinal
22 binding protein, bound to vitamin A.

1 Thyroid-binding globulin and albumin carry
2 the vast majority of thyroid hormone in our plasma. In
3 fact, if you immunoprecipitate transthyretin and induce
4 sophisticated LCMS analysis, in most patients you
5 cannot detect thyroid hormone in transthyretin. So
6 we're going to take advantage of the idea that these
7 sites are unoccupied to kinetically stabilize the
8 protein.

9 So in the next slide, this represents about
10 25 years' worth of mechanistic work. And I'd like to
11 draw your attention to the second entry from the left.
12 That is the naked tetramer, which is the most
13 amyloidogenic form of transthyretin. But only after it
14 dissociates first to a dimer, which rapidly falls apart
15 to a folded monomer, it's only when the folded monomer
16 changes its confirmation do you enter the
17 neuropathological paradigm on the bottom, where the
18 aggregation of the misfolded monomer into numerous
19 structures, including amyloid fibrils, leads to
20 pathology.

21 Now, we were very fortunate in our
22 experiments showed that the weak link in this tetramer

1 is actually the dimer-dimer interface that comprises
2 the small molecule binding sites. So you could
3 imagine, if you created a small molecule that was
4 neither a thyroid agonist or an antagonist, but bound
5 in a very high affinity to that site, then you could
6 stabilize the protein and lock it in its functional
7 form, and preclude it from getting into the
8 neuropathological mechanism.

9 Now, you're going to hear quite a bit about
10 different mutations today, but really, for the purpose
11 of today's discussion, this is very simple. They all
12 destabilize the tetramer. As a consequence, they
13 increase the concentration of the amyloidogenic
14 monomer.

15 Remember, aggregation reactions are
16 concentration-dependent. The higher the concentration,
17 the faster the aggregation reaction. And of course,
18 the faster the aggregation reaction, generally
19 speaking, the earlier the onset of pathology.

20 So while we were busy using structure-based
21 drug design to ultimately come up with tafamidis, Dr.
22 Teresa Coelho, who you'll hear more from later, who has

1 the most experience with tafamidis and familial amyloid
2 polyneuropathy from a clinical perspective, wearing her
3 other hat as a medical geneticist, discovered three
4 families in Portugal that are highly relevant to
5 today's discussion.

6 So these individuals have the Val30Met
7 polyneuropathy-associated mutation on one allele. On
8 the other allele, they have a 3119Met mutation.
9 Remember, this protein is a tetramer. So in these
10 individuals, the tetramer is comprised statistically of
11 Val30Met and 3119Met subunits.

12 So using E. coli, we were able to make the
13 various tetramers shown here, comprised of both
14 Val30Met and 3119Met subunits. And as you can see, as
15 you increase the stoichiometry of the 3119Met subunits
16 relative to Val30Met, both the rate of tetramer
17 dissociation and the rate of amyloidogenesis plummets.

18 Now, Dr. Katz made a very interesting point
19 in his introductory remarks today. Most proteins are
20 in equilibrium and, thus, they exchange very quickly.
21 The fact that we were able to isolate these different
22 tetramers tells you that transthyretin is special. It

1 has a very high kinetic barrier for dissociation to
2 begin with. And that point will become relevant again
3 in a few minutes.

4 So if you focus your attention on the upper
5 left-hand side of this slide, what you see is, as you
6 increase the number of 3119Met subunits, you increase
7 the barrier for tetramer dissociation. Effectively,
8 the reason these individuals don't develop amyloidosis
9 is that their tetramer is locked in a functional form
10 because that barrier is insurmountable under
11 physiologic conditions.

12 Now, if you focus your attention on the right
13 side, the way tafamidis works is that it binds to and
14 stabilizes the ground state of the tetramer, increasing
15 the activation energy. So if you have a compound that
16 binds with a dissociation constant like tafamidis,
17 around two nanomolar, that makes that barrier
18 insurmountable under physiologic conditions.

19 So you heard Dr. Katz mention a rate constant
20 that was two or three times slower. That's in 5-molar
21 urea. If you study this protein under physiologic
22 conditions with tafamidis bound, it takes months to

1 dissociate. Okay? Again, it's a special protein, very
2 high kinetic barriers.

3 So as I mentioned, we had the privilege of
4 using structure-based drug design. In fact, structure-
5 based drug design was invented with transthyretin. So
6 we came up with tafamidis, which as you can see looks
7 nothing like thyroid hormone. In fact, it doesn't
8 displace thyroid hormone from the thyroid receptor.

9 So how did we select the 20-milligram dose?
10 We selected the 20-milligram dose using an ascending or
11 a dose escalation study where we monitored
12 transthyretin's stability as a function of the
13 tafamidis-to-TTR plasma ratio, as you see on the X
14 axis.

15 So at 20 milligrams, the minimum
16 concentration or the trough concentration occupies 1.2
17 of the two binding sites. That is sufficient to lock
18 the protein in a tetrameric form kinetically. At Cmax,
19 two binding sites are occupied. So again, this
20 experiment is done by adding 4.8-molar urea to plasma
21 so that you can monitor dissociation on a reasonable
22 experimental time scale. It was never meant to use it

1 to extrapolate the rate constant to any kind of
2 physiologic condition. If we want to do that, we have
3 specific assays for that, which we can talk about in
4 Q&A.

5 So if you now look at amyloidogenesis of the
6 most important mutants of transthyretin -- Val30Met,
7 you've heard of, polyneuropathy, V120II, cardiomyopathy
8 -- you can see in the concentration range, from Cmin to
9 Cmax, this small molecule effectively blocks
10 amyloidogenesis over a 72-hour time period. That's
11 highly relevant because this protein only lives in our
12 plasma about 24 hours.

13 So let me conclude. TTR tetramer
14 destabilization leads to amyloid fibrils and many other
15 aggregates. Perhaps the most important conclusion from
16 my remarks today are that tafamidis and the genetic
17 mutation that Teresa Coelho discovered act in the same
18 way. They kinetically lock the protein in a functional
19 form and they don't let it enter the amyloidogenic
20 cascade. And I told you about the experiments that we
21 use to select the dose, and I also told you about the
22 stabilization assay that we can talk more about later

1 if you'd like.

2 It simply remains for me to introduce Roy
3 Freeman, professor of neurology at Harvard, who's going
4 to tell you about the clinical metrics today.

5 DR. FREEMAN: Good morning. Thank you, Dr.
6 Kelly. I am Roy Freeman. I am a professor of
7 neurology at Harvard Medical School, and I direct the
8 Center for Autonomic and Peripheral Nerve Disorders. I
9 am a paid consultant to Pfizer, but have no financial
10 interest in the outcome of this meeting. The goal of
11 my presentation is to introduce the endpoints used in
12 the tafamidis FAP program.

13 A few moments ago, you heard Dr. Kelly very
14 eloquently describe the rational molecular pharmacology
15 that underlies the clinical development of tafamidis.
16 For me, as a clinical translational neuroscientist
17 who's spent decades studying disease modification
18 therapies for peripheral neuropathy, it is hard to
19 imagine anything more exciting than this.

20 However, the introduction of tafamidis into
21 the clinical arena imposed a set of challenges,
22 specifically, how to quantify the neuropathy with

1 reproducibility and sensitivity with a disease-
2 modifying intervention. Up until this point, there had
3 been no prospective multi- center interventional
4 trials, no validated clinical assessment tools, and no
5 validated endpoints.

6 It was decided to draw on the instruments
7 used in disease-modifying trials to treat diabetic
8 peripheral neuropathy. Diabetic peripheral neuropathy,
9 like FAP, is a length-dependent axonal neuropathy with
10 sensory, autonomic, and motor features. The most
11 widely used, best-validated, and most robust of the
12 instruments used in diabetic peripheral neuropathy
13 trials is the NIS, and specifically the NIS-LL, the
14 Neuropathy Impairment Score of the Lower Limbs.

15 The NIS-LL is a validated structural
16 neurological assessment tool. It is a subcomponent of
17 the NIS specifically directed at the evaluation of the
18 lower limbs, where the deficits in FAP occur initially.
19 There is assessment of muscle strength, sensation, and
20 reflexes. The lower limb score of the NIS-LL is from 0
21 to 88, where 88 is the greatest impairment. In
22 individuals with diabetic peripheral neuropathy, the

1 NIS- LL increases by 0.9 points a year.

2 You will later hear from Dr. Donna Grogan
3 that in FAP, there's a deterioration in the NIS-LL by
4 .35 points a month, essentially a rate of change almost
5 five times faster than seen in diabetic polyneuropathy.
6 A consensus statement by the Peripheral Nerve Society
7 proposed that a change of two points in the NIS-LL is
8 clinically detectable and clinically meaningful.

9 With respect to the subcomponents of the NIS-
10 LL, of greatest clinical and functional
11 significance is muscle power testing. And with this
12 instrument, all of the major muscle groups within the
13 lower limbs are assessed. In brief, with progression
14 proximally of the neuropathy, as ankle, knee, and hip
15 weakness ensue, there will be substantial functional
16 disability: ankle weakness, walking difficulties, knee
17 weakness, instability even while standing, and hip
18 weakness, resulting in wheelchair dependence.

19 Other subcomponents of the NIS-LL are the
20 reflexes, which provide a general overview of nervous
21 system function. And in addition, sensation is tested:
22 pinprick, light touch, vibration, and

1 position sense. From a functional standpoint, vibration
2 and position sense, the proprioception functions, are
3 intimately involved with balance. Impaired
4 proprioception will contribute to the walking
5 difficulties.

6 The NIS-LL is corroborated by more objective
7 neurophysiological measures, the nerve conduction
8 studies, the standard neurophysiological assessment of
9 the lower limbs: quantitative sensory testing,
10 vibration perception threshold, code perception, and
11 heat pain, and autonomic testing, heart rate
12 variability, a robust measure of cardiac vagal
13 parasympathetic function.

14 The results of these neurophysiological
15 assessments are integrated into two composite scores,
16 sigma 7 or the sum of 7, which you see on the left,
17 which is a predominantly large fiber assessment, and
18 sigma 3, seen on the right, a predominantly small fiber
19 assessment.

20 Now, when used in disease-modifying trials
21 for diabetic peripheral neuropathy, the NIS-LL has been
22 used in three different ways. It's been used as a

1 continuous variable, addressing the total range of
2 changes that occur with this assessment tool. It's
3 also been used as a categorical variable, typically a
4 responder defined as a change less than 2 points in the
5 NIS-LL, as was done in clinical trial 005. And
6 finally, it has been used as a composite score,
7 combining both the NIS-LL itself with the more
8 objective corroborating neurophysiological assessments.

9 In addition, a quality of life measure was
10 used, the Norfolk Quality of Life, which is a widely-
11 used and well-validated instrument in diabetic
12 peripheral neuropathy. This is five domains, including
13 large fiber, small fiber, and autonomic domains.

14 The modified body mass index was another
15 endpoint in the clinical trial. This is the standard
16 body mass index, corrected for serial albumin. You may
17 recall there is malnutrition in familial amyloid
18 polyneuropathy, in part due to amyloid deposition in
19 the gastrointestinal tract, in part due to the
20 autonomic neuropathy, causing diarrhea, resulting in
21 malabsorption, diminished albumin, consequent edema,
22 and the modified body mass index accounts for the

1 presence of edema. This correlates with disease
2 severity, progression, and mortality in familial
3 amyloid polyneuropathy and is a well-validated
4 prognostic factor for predicting survival post-liver
5 transplant.

6 I now want to introduce the clinimetric
7 study. This study examines the question how applicable
8 are these measures drawn from diabetic peripheral
9 neuropathy to familial amyloid polyneuropathy, what is
10 their diagnostic discriminatory ability across the
11 disease stages of familial amyloid polyneuropathy.

12 The study was an observational, single-
13 center, cross-section, non-interventional study, which
14 looked at healthy volunteers and patients with various
15 stages of familial amyloid polyneuropathy. The
16 Coutinho staging system was used, which, in brief,
17 cardinal features address ambulatory abilities. In
18 stage 1, no assistance is required for walking; stage
19 2, assistance is required, and stage 3, wheelchair-
20 boundedness occurred. All other neurological measures
21 move in the same direction. The endpoints in the
22 clinical trial were all assessed.

1 Looking at the primary efficacy endpoint, the
2 overview of the structured neurological examination,
3 the NIS-LL, as you see, differentiates with
4 significance between healthy volunteers in stage 1,
5 stage 1 and stage 2, and stage 2 and stage 3.

6 Now approaching the study from the standpoint
7 of the progression of the peripheral neuropathy, as
8 anticipated in the earlier stages, even the subclinical
9 stages, neurophysiological abnormalities would occur.
10 And here we see the neurophysiological tests, the
11 composites, a score of 7, large fiber, a composite
12 score of 3, small fiber differentiates between stage 1
13 and stage 2. And as anticipated, at the later stages
14 of the disease, when the nerves are fairly severely
15 damaged, you would not expect neurophysiology to
16 differentiate between those stages.

17 Similarly, sensation involved earliest in the
18 course of the disease, you see differentiation between
19 healthy volunteers in stage 1, stage 1 and stage 2.
20 With progression of the disease, reflexes will become
21 involved, differentiation between stage 1 and stage 2,
22 and ultimately, as muscle strength becomes impaired,

1 differentiation between stage 1 and stage 2, and stage
2 2 and stage 3.

3 Looking at this with a little more
4 granularity, early in the course of the disease there
5 will be toe weakness. And here, you see the instrument
6 differentiates between stages 1 and stage 2. But with
7 progression -- ankle weakness, knee weakness, and
8 ultimately hip weakness -- the differentiation is
9 strongest between the latter stages of the disease, hip
10 weakness, stage 2 and stage 3; just what one would
11 expect with a distal to proximal progressing axonal
12 neuropathy.

13 Thus, in conclusion, these differences and
14 patterns of deficits detected by the NIS-LL, the NIS-LL
15 subscales, and neurophysiology discriminate among the
16 disease stages with biological plausibility and are
17 consistent with the clinical course of the disease.
18 Although not shown, the total quality of life and the
19 modified body mass index show similar diagnostic
20 discriminatory abilities. Thus, these proposed
21 endpoints are sensitive indicators of disease severity
22 and are appropriate to measure disease-modifying

1 therapies in familial amyloid polyneuropathy.

2 I would now like to invite Dr. Donna Grogan
3 to the podium to discuss the clinical development
4 program for tafamidis.

5 DR. GROGAN: Thank you, Dr. Freeman. Good
6 morning. My name is Donna Grogan and I am a physician
7 consultant to Pfizer. As the former chief medical
8 officer at FoldRX, I was responsible for the clinical
9 development of tafamidis, and I would receive a
10 financial benefit from its approval.

11 It is a real honor to be presenting the
12 results of the years of research in this unprecedented
13 program in this very rare disease. To address the
14 questions posed to you today, I will be reviewing the
15 tafamidis development program, including the efficacy
16 and safety data from the pivotal trial, FX005, as well
17 as data from the supportive studies.

18 Through the course of my presentation, I will
19 be addressing many of the concerns raised in the FDA
20 briefing document. Of note, we conducted a full
21 clinical pharmacology program, the results of which are
22 described in your briefing document.

1 As with many rare diseases, the tafamidis
2 development program includes a single, well-controlled
3 pivotal trial in patients with TTR-FAP. And this is
4 due to the V30M mutation. The study represents the
5 first prospective trial completed with a novel,
6 investigational agent in this patient population. The
7 pivotal trial was followed by a 12-month, open-label,
8 single-treatment, extension study that provided us with
9 additional and longer-term efficacy and safety data and
10 also efficacy data in another group of patients, those
11 previously on placebo.

12 In order to provide supporting data on the
13 efficacy and safety of tafamidis in TTR patients with
14 mutations other than V30M, we also conducted a 12-month
15 open-label study in that population. And finally, we
16 continue to monitor the safety and efficacy from the
17 patients in our earlier trials through our ongoing
18 label extension study 303.

19 Now, for a more detailed discussion of each
20 of these studies, 005 was a standard double-blind
21 design in which patients were randomized to tafamidis,
22 20 milligrams once daily or matching placebo for 18

1 months. This study was designed to enroll patients for
2 whom a disease-modifying approach like tafamidis would
3 be likely to show clinical benefit, that is, those
4 patients who still maintain a relatively high degree of
5 neurologic function to be preserved.

6 In addition, we enrolled patients with the
7 V30M mutation because they represent approximately 85
8 percent of the worldwide population of patients with
9 this disease and approximately 40 percent of the
10 patients in the U.S. Although limited to the V30M
11 mutation, we do believe the results are generalizable
12 due to the similarities in neuropathic disease
13 progression across mutations in TTR-

14 FAP.

15 The clinical endpoints in this study were
16 those that measured different dimensions of this
17 disease and are sensitive indicators of disease
18 severity, as just described by Dr. Freeman. The first
19 co-primary endpoint was the NIS-LL. For this endpoint,
20 a categorical analysis was utilized, defining the NIS-
21 LL responder as that patient with a less than 2 point
22 increase at 18 months, based on a precedent trial in

1 diabetic polyneuropathy.

2 Importantly, patients who discontinued
3 earlier to undergo liver transplant were categorized as
4 non- responders. We believe this represents a
5 conservative analysis, as unlike patients with chronic
6 liver disease, TTR-FAP patients undergo liver
7 transplant when an organ becomes available and not as
8 salvaged therapy.

9 The second co-primary endpoint was the
10 patient- reported outcome measure, the Norfolk Quality
11 of Life. In addition to the categorical analysis of the
12 NIS-LL, this continuous variable was analyzed as a
13 continuous variable and as the pre-specified key
14 secondary endpoint.

15 So in addition to the NIS-LL subscales, the
16 Norfolk domains, other secondary endpoints assessed
17 more objective measures of both small and predominantly
18 large neurofunction and analyzed as submitted scores.
19 The modified body mass index, this measure of overall
20 disease severity, was also assessed. And finally, we
21 assessed the effect of tafamidis on tetramer
22 stabilization and the maintenance of this effect over

1 time.

2 These endpoints represent both clinical and
3 biomarker assessments. No multiplicity adjustment was
4 applied, as the co-primary endpoints were analyzed
5 independently and a single key secondary endpoint was
6 identified. This is not uncommon in the setting of
7 this rare disease with the limited patient population.
8 We specified two analysis populations, as described on
9 this slide, the intent to treat and the efficacy
10 evaluable.

11 Of the 128 patients randomized, 125
12 constitute the intent-to-treat population, with 87
13 making up the efficacy evaluable population. There was
14 a low rate of discontinuation for adverse events, and
15 the most common reason for discontinuation as liver
16 transplantation.

17 The 20 percent dropout rate was evenly
18 distributed between the treatment groups and was higher
19 than the 5 to 10 percent expected rate of
20 discontinuation assumed in the study design. But
21 again, it's important to note that the majority of
22 patients were on the liver transplant list at the time

1 of enrollment. And that liver transplant was performed
2 not as salvage therapy, but when an organ became
3 available. In fact, 73 percent of the patients who
4 underwent liver transplant did so prior to the 12-month
5 assessment.

6 So for any trials in rare disease, you have
7 to go to where the patients are, and that is what we
8 did in this trial. The enrollment proportions across
9 sites, shown here in the middle column, matches the
10 proportion of TTR-FAP patients who undergo liver
11 transplant, as reported by the FAP World Transplant
12 Registry on the far right column.

13 So although a single center provided slightly
14 over 50 percent of the patients enrolled in this trial,
15 this reflects real-world treatment of TTR-FAP and was
16 thus by necessity. The Porto site represents the
17 largest population of patients with this disease in the
18 world and sees over 700 patients annually.

19 Now, baseline demographics demonstrated that
20 patients were evenly divided between males and females,
21 with an average age of 38 to 40 years. Placebo
22 patients reported a mean disease duration of

1 approximately 12 months less than those on tafamidis.
2 This mean difference appears related to a few outliers
3 in a tafamidis group, with the median disease durations
4 more similar between the groups.

5 But it's also important to understand that
6 disease duration is a somewhat imprecise estimate and
7 it is based on patient-retrospective recall of dates of
8 symptom onset. In fact, over 50 percent of patients'
9 start dates, either month or year, were not available
10 for at least one TTR-related event. Therefore,
11 definitive conclusions about the disease duration in
12 either group are difficult.

13 The baseline disease characteristics
14 demonstrate the relatively early stage of disease, with
15 all patients fully ambulatory at the time of enrollment
16 except for two patients, one in each treatment group.
17 Thus, the endpoints used in this trial will show assay
18 sensitivity in these early-stage patients, based on the
19 data just shown by Dr. Freeman.

20 Although there were no statistically
21 significant differences in disease characteristics,
22 there were numerically higher NIS-LL scores in the

1 placebo group. In subsequent slides, you will see
2 analyses that account for these numerical differences
3 and why we do not believe these differences impact the
4 overall interpretation of the study.

5 Now, for the primary endpoint results. Forty-
6 five percent of tafamidis-treated patients were NIS-LL
7 responders, compared with 29.5 percent of placebo
8 patients, with a p value of 0.068. So while tafamidis
9 showed a benefit, it did not achieve statistical
10 significance. But it's important to remember that, in
11 this analysis, patients undergoing liver transplant
12 were categorized as non-responders. So the higher-
13 than- anticipated dropout rate may have adversely
14 affected our ability to demonstrate a statistically
15 significant difference between the two treatment groups
16 in this analysis.

17 Placebo patients experienced a non-
18 significant worsening in mean total quality of life
19 score at 18 months compared with tafamidis. It is
20 important to remember that, as a disease-modifying
21 treatment, tafamidis does not afford symptomatic
22 benefit, and so we don't anticipate improvement in

1 symptoms or signs, but rather stabilization.

2 Now, when these same endpoints are evaluated
3 in the efficacy evaluable population, those patients
4 completing the full 18 months of treatment per
5 protocol, there are significantly more NIS-LL
6 responders in the tafamidis group compared with
7 placebo, 60 percent versus 38 percent, with a p value
8 of 0.041. And in this population, patients on placebo
9 demonstrated significant worsening in total quality of
10 life score compared with tafamidis patients, who had
11 virtually no change in this score.

12 Now, in order to evaluate the potential
13 impact of the baseline differences between the
14 treatment groups, the responder analysis was assessed
15 using different categories of NIS-LL. We performed
16 this analysis in the efficacy evaluable population, as
17 demonstrated on the slide, with the baseline categories
18 of less than 4, 4 to 8, and greater than 8. In this
19 analysis, the effect of tafamidis was evident in those
20 patients who are more impaired at baseline.

21 Now, the FDA, in their briefing document,
22 performed additional analyses using different

1 categories. These figures represent the data provided
2 by the FDA statistical reviewer briefing document
3 figures 10 through 12, formatted to show the percent
4 response by treatment group, by NIS-LL severity
5 baseline category.

6 The bottom left is the below and above median
7 of baseline NIS-LL scores. The upper right is the
8 below quartile, between lower and upper quartile, and
9 above upper quartile. And the bottom right is within
10 each quartile. But regardless of the method of
11 categorizing baseline NIS-LL, we see a higher rate of
12 NIS-LL responders in tafamidis-treated patients
13 compared with placebo in the more moderate to more
14 severe categories of patients enrolled in this study.

15 These results suggest that, for this
16 categorical analysis of the NIS-LL, the baseline
17 imbalance did not adversely affect the overall
18 interpretation of the results, which is that more
19 patients on tafamidis were NIS-LL responders than those
20 on placebo.

21 Now, when the NIS-LL, this continuous
22 variable, is analyzed as a continuous variable, we see

1 statistical significance between the treatment groups.
2 The pre- specified key secondary, using a repeated
3 measures analysis, demonstrates that tafamidis patients
4 had significantly less worsening in NIS-LL at month 18
5 compared with placebo patients. This difference
6 represents approximately 50 percent less decline in
7 neurologic function in those patients treated with
8 tafamidis.

9 This figure on the right is a post hoc
10 analysis that incorporates baseline NIS-LL disease
11 severity scores in the model. And as you can see,
12 statistical significance is maintained.

13 The FDA noted that there were two outliers in
14 the placebo group. And when these two patients were
15 excluded from the ITT population, statistical
16 significance in this analysis was lost.

17 The data from these two patients, as in all
18 patients in our trial, were confirmed with the site as
19 valid data and truly and accurately representing the
20 progression of these patients. So although they were
21 more rapidly progressing, it accurately reflected their
22 course.

1 So to preserve the information provided by
2 these two patients, we would argue that an alternative
3 method might be preferable. In this method, their
4 values were not excluded, but rather replaced with the
5 values from a patient who had the next highest values
6 in the dataset. The results, which are demonstrated on
7 the right-hand panel, remain statistically significant
8 and are similar to what we observed in the key
9 secondary analysis, reproduced on the left.

10 So in summary, the NIS-LL change from
11 baseline remains statistically significant across
12 analyses and methodologies. First is the pre-specified
13 key secondary analysis, using the MMRM method. Second
14 is the same analysis, but with an adjustment for
15 baseline NIS-LL severity. Third is the alternative
16 method of dealing with the two placebo outlier
17 patients. And last, although the data not graphically
18 displayed, is the method using a multiple imputation
19 method of dealing with missing data. Two of these
20 analyses, the second and the fourth, were performed
21 based on requests from the European authorities.

22 As you can see, across all of these analyses,

1 tafamidis patients had significantly less worsening of
2 NIS-LL compared with placebo patients.

3 Now, let's delve into the NIS-LL in a little
4 more detail. When we look at the components of this
5 score, we see numerical advantages across the subscales
6 in the tafamidis group. However, placebo patients
7 experienced significantly more muscle weakness compared
8 with tafamidis. And of course, worsening motor
9 function would be expected to put the patients at a
10 higher risk for development of ambulation abnormalities
11 over time.

12 An even more detailed review of the motor
13 subscale reveals that the tafamidis group demonstrated
14 stability in muscle strength across the four major
15 muscle groups of the lower limb, but in contrast, the
16 muscle weakness in the placebo group occurred in this
17 distal to proximal fashion, as would be expected for a
18 length- dependent neuropathy. These results provide
19 compelling evidence of the positive treatment effect of
20 tafamidis and is supportive of the differences observed
21 between the treatment groups in the NIS-LL responder
22 analysis.

1 So finally, what about the influence of the
2 high-enrolling site, Porto, on the analysis of the NIS-
3 LL? We explored this question using the continuous
4 change analysis of the NIS-LL across sites, in contrast
5 to the analysis performed in the briefing document by
6 the FDA, in which pooling was performed across the
7 sites other than Porto in evaluating the responder
8 analysis.

9 First to note is that there was a lower
10 dropout rate due to liver transplant in the Porto site,
11 12.5 percent, compared with all other sites combined,
12 32 percent. This probably reflects the longer wait
13 time on the liver transplant list due to the large
14 volume of patients in Porto, but it also demonstrates
15 that there is less missing data from this site,
16 supporting the strength of the data results.

17 This bi-site analysis suggests that, except
18 for two sites, Brazil and to a lesser extent Argentina,
19 the results favored tafamidis in those sites with
20 sufficient data at 18 months.

21 Now, similar findings were also observed in
22 this bi-site analysis in the more objective measure of

1 large fiber function, the summated 7 score, again
2 favoring tafamidis across the majority of sites. And
3 similar findings were also found with the modified body
4 mass index and the summated 3 scores, so these analyses
5 further support the overall interpretation of the
6 effect of tafamidis, regardless of geographic location
7 or site.

8 Now, for the neurophysiologic measures. We
9 see similar treatment effects to what was observed with
10 the NIS-LL. In these analyses, tafamidis-treated
11 patients demonstrated approximately 50 percent
12 preservation of large fiber function compared with
13 placebo, and this is consistent with the 50 percent
14 preservation observed with the NIS-LL. For the small
15 fiber function, treatment with tafamidis was associated
16 with approximately 80 percent less deterioration,
17 compared with placebo.

18 Tafamidis treatment was also associated with
19 significant improvement in the modified body mass
20 index, compared with worsening seen in the placebo
21 patients. This assessment of overall disease severity
22 suggests an overall greater disease progression in the

1 placebo patients.

2 Now, you will recall Dr. Kelly's hypothesis
3 that a clinical benefit could be achieved through TTR
4 stabilization by inhibiting amyloid fibril formation.
5 Greater than 97 percent of patients on tafamidis
6 exhibited TTR stabilization throughout the course of
7 the study. And this stabilization translated into the
8 clinical effects just described. These results support
9 the use of TTR stabilization as a biomarker that is
10 reasonably likely to predict clinical benefit.

11 Now, despite the challenges of conducting a
12 prospective trial in this rare, fatal,
13 neurodegenerative disease with limited patients, the
14 pivotal trial, we believe, provides evidence that
15 stabilization of the tetramer by tafamidis translates
16 to beneficial effects across the array of clinical
17 measures that were utilized in the trial.

18 On this slide, we are displaying the point
19 estimates in 95 percent confidence intervals for each
20 endpoint. Across all of these endpoints, which assess
21 again different dimensions of this disease, a
22 beneficial effect of tafamidis is observed. The

1 directional consistency provides internal replication
2 and evidence for the overall benefit of tafamidis in
3 this disease.

4 I would now like to describe the results of
5 the 006 study, the open-label extension trial.
6 Following completion of the double-blind trial,
7 patients were enrolled in this extension study and all
8 received 20 milligrams, tafamidis, once daily. The
9 objectives included the assessment of safety as well as
10 the evaluation of efficacy, using the same endpoints as
11 the previous trial. You can see from this diagram that
12 these trials provide data on 30 months' continuous
13 treatment with tafamidis for those patients on
14 tafamidis in the double-blind trial and 12 months' data
15 for those patients previously on placebo. The blind
16 from the pivotal trial was maintained during the open-
17 label extension for both patients and physicians.

18 Eighty-six of the 91 patients who completed
19 005 continued into this open-label extension with 77
20 completing the 12-month treatment period. Six patients
21 discontinued due to liver transplant, so a much lower
22 rate than what we observed in the double-blind trial.

1 The intent-to-treat population includes 38 patients in
2 the tafamidis-tafamidis group. And that group is those
3 patients who received tafamidis in both the double-
4 blind trial and the open-label extension, and 33
5 patients in the placebo-tafamidis group, those patients
6 who received placebo in the double-blind trial, and
7 then tafamidis in the open-label extension.

8 The baseline demographics for the study were
9 similar between the tafamidis-tafamidis group and
10 placebo-tafamidis group, with median disease durations
11 of approximately 36 months. However, baseline disease
12 characteristics demonstrate that the placebo-tafamidis
13 group has significantly worse NIS-LL, quality of life,
14 and summated 3 score, with numerically worse sum 7 and
15 lower BMI.

16 This is not surprising, given the observed
17 progression in disease which occurred in this group
18 during the previous 12 -- 18 months of placebo
19 treatment. But these patients remained at a stage of
20 disease within the range of endpoint assay sensitivity
21 and remained ambulatory. And many of these analyses
22 that I'll show you is a within-treatment-group

1 analysis.

2 So on this slide, as I mentioned, we
3 performed a within-group analysis of the monthly rate
4 of change during the double-blind trial compared to the
5 open-label extension. And what we can determine from
6 doing that analysis is twofold: one, whether the
7 effects of tafamidis persist during the 12 months of
8 open-label treatment in those patients who were on
9 tafamidis for the full 30 months and whether tafamidis
10 slowed disease progression in those patients previously
11 on placebo.

12 So in the tafamidis-tafamidis group, as
13 expected, the monthly rates of change were similar
14 between the two studies and, again, consistent with the
15 sustained treatment effect of tafamidis. And this is
16 in contrast with the monthly rate of change observed in
17 the placebo-tafamidis patients while they were on
18 placebo in the previous double-blind trial, which is
19 three times that of the tafamidis-tafamidis patients.

20 However, once the placebo patients switched
21 to tafamidis, there was a statistically significant
22 decrease in their NIS-LL rate of changed compared to

1 their rate while on placebo in the previous trial. In
2 fact, this rate of change is now approaching the rate
3 observed in the tafamidis-tafamidis group.

4 This is very supportive data on the impact of
5 tafamidis in slowing disease progression, even for
6 those patients with more severe disease at the time of
7 tafamidis initiation. And in addition, it provides
8 further evidence that the benefits observed in 005 were
9 the results of a tafamidis treatment effect rather than
10 any baseline differences.

11 A similar rate of change analysis was
12 performed for the quality of life score. In the
13 tafamidis- tafamidis group, the total quality of life
14 rate of change from baseline was minimal and similar
15 between the first 18 months of treatment with tafamidis
16 and the following 12 months.

17 However, for the placebo-tafamidis group,
18 there was a statistically significant decrease in their
19 rate of change in quality of life while on tafamidis,
20 compared with their prior treatment with placebo. And
21 this actually resulted in a maintenance in their
22 quality of life in these patients upon initiation of

1 tafamidis.

2 Similar findings are observed in the
3 neurophysiologic measures of large fiber function on
4 the top left and small fiber function on the bottom
5 left, with slowing of rate of progression in these
6 endpoints in the placebo-tafamidis group upon
7 initiation of tafamidis. These data confirm the
8 findings on the NIS-LL shown previously.

9 Although the sum 3 rate of change on the
10 bottom left in the tafamidis-tafamidis group increases
11 slightly, the absolute change observed over the 30
12 months of treatment is still less than that observed in
13 the 005 placebo group after 18 months untreated.

14 Finally, upon initiation of tafamidis, those
15 patients previously on placebo exhibited improvement in
16 their modified body mass index. This is not unexpected
17 and has been reported in patients post-liver
18 transplant.

19 NIS-LL responder status was maintained over
20 time. This slide displays the NIS-LL responder rate
21 over the 18 months of double-blind trial in the first
22 three sets of bars and the 12 months open-label trial

1 in the last two sets of bars. Fifty-five percent of
2 the patients in the tafamidis-tafamidis group remained
3 NIS-LL responders at month 30, again, less than 2 point
4 change in the NIS-LL, further supporting the
5 sustainability of the effect of tafamidis treatment.

6 And in those patients previously on placebo, upon
7 initiation of 12 months of tafamidis treatment, 60
8 percent of those patients had no disease progression.

9 Finally, the high proportion of patients with
10 tetramer stabilization was maintained in the tafamidis-
11 tafamidis group, similar to what was observed in the
12 005 study. And stabilization is now demonstrated in
13 the placebo-tafamidis patients, which, as we've shown,
14 translates to slowing in disease progression across the
15 endpoints just described.

16 So in summary, the treatment benefits with
17 tafamidis were maintained over 30 months, with over 50
18 percent of patients experiencing no disease
19 progression, as assessed by the NIS-LL responder
20 analysis.

21 Patients who had been on placebo had a slower
22 rate of disease progression across the array of

1 endpoints upon initiation of tafamidis treatment. And
2 these data do provide internal replication of the
3 effect and serve as a source of confirmatory evidence
4 of the efficacy of tafamidis.

5 To provide support for the use of tafamidis
6 in patients with mutations other than V30M, an
7 additional 12-month open-label study was performed, 1-
8 A-201. In this study, the primary endpoint was TTR
9 stabilization, with secondary endpoints similar to
10 those in the previous trials.

11 The study was conducted in patients with
12 eight different TTR variants and was intended to
13 evaluate the stabilization of TTR across multiple
14 mutations in order to assess a generalizability of
15 tafamidis treatment effects. Twenty-one patients were
16 enrolled in four countries, including the U.S. Patients
17 were older, had longer disease duration, and had more
18 advanced disease than the patients evaluated in Study
19 FX005.

20 Consistent tetramer stabilization was seen
21 and was demonstrated in all patients across all TTR
22 mutations. The clinical endpoints used in this trial,

1 as I mentioned, were similar to those used in the
2 previous trials. The change from baseline to month 12
3 for the patients enrolled in the 1-A-201 study, these
4 non-V30M patients, are displayed in the second column.
5 For comparison, the 12-month data by treatment group
6 from the FX005 study are displayed in the last two
7 columns.

8 So despite having more severe disease at
9 baseline, changes from baseline on the efficacy
10 endpoints were similar to changes observed in the FX005
11 treatment group and were less than that observed in the
12 placebo group.

13 So in summary, TTR stabilization was
14 demonstrated across all mutations evaluated in this
15 study, and these findings, along with the clinical
16 results, support the generalizability of tafamidis
17 treatment.

18 So to conclude our discussion of efficacy,
19 let me summarize. In the single pivotal trial,
20 although the co-primary endpoints were not met, the
21 totality of evidence and consistency in response across
22 these multiple endpoints that measured different

1 aspects of this disease provide internal replication of
2 the effects of tafamidis in delaying neurologic
3 impairment in patients with TTR-FAP.

4 Tafamidis-treated patients experienced 50 to
5 80 percent preservation of neurologic function, as
6 measured by the NIS-LL in neurophysiologic measures,
7 less overall disease severity, and consistent
8 stabilization of the tetramer.

9 The results from the single pivotal trial are
10 supported by confirmatory evidence of efficacy from the
11 supportive studies, in which we demonstrated
12 maintenance of the effect of tafamidis for over 30
13 months, slowing of disease in those patients previously
14 on placebo, thus replicating the FX005 treatment
15 effect, but in a more severe population, and consistent
16 TTR stabilization across all mutations.

17 Therefore, we conclude that the totality of
18 the data support the original hypothesis that drove
19 this development program, that stabilization of the
20 tetramer by tafamidis does translate to slowing of
21 disease progression in patients with TTR-FAP.

22 We just completed the review of the efficacy

1 data. And now, I will review the clinical safety data,
2 the other side of this benefit-risk question. Please
3 note that we have a full non-clinical safety program
4 that's described in your briefing document.

5 The clinical data are derived from the
6 clinical patient studies just described; 127 unique
7 patients were treated with tafamidis. The accrued
8 exposure is graphed on this slide in six-month
9 increments. The median exposure is 35 months and 30
10 patients have been treated with tafamidis for more than
11 four years. These data represent approximately 351
12 patient years of exposure. For the safety presentation,
13 I will focus on the double-blind trial.

14 Few patients discontinue the study due to
15 AEs, four from the tafamidis group and three from the
16 placebo group. The adverse events that led to
17 discontinuation in individual patients are noted on the
18 right-hand side.

19 The majority of patients in both treatment
20 groups reported at least one adverse event. The
21 majority of adverse events were assessed as mild or
22 moderate in severity. Those AEs reported more

1 frequently greater than or equal to two patients in the
2 tafamidis group are highlighted, with the most common
3 being diarrhea and urinary tract infection.

4 There were few serious adverse events
5 reported. Six tafamidis patients and five placebo
6 patients experienced at least one SAE. In those on
7 tafamidis patients, they were related primarily to
8 infection. All were successfully treated and resolved.

9 In Study 005, there were no deaths that
10 occurred while on treatment. Five deaths were reported
11 post-liver transplant, two of those patients previously
12 on tafamidis and three previously on placebo. No
13 deaths were reported in Studies 006 or 1-A-201. And
14 four deaths occurred in Study 303, but none were
15 considered to be related to treatment.

16 Now, to further assess the observed imbalance
17 in urinary tract infections, we did the following
18 analyses. We found that there was a higher ratio of
19 women in the tafamidis group who had UTIs compared to
20 placebo patients. However, in both groups, the
21 majority of cases were mild to moderate, were
22 successfully treated, and resolved, or were resolving.

1 There were not discontinuations from the study due to
2 UTIs and no association between low white cell counts,
3 neutrophils, lymphocytes, or any association with
4 parameters in these patients who had infections.

5 A look at these additional safety topics
6 revealed no evidence of adverse treatment effects
7 caused by tafamidis, including extensive monitoring of
8 thyroid function, liver function test, blood pressure,
9 and heart rate, and ECGs.

10 Based on the totality of the safety data
11 across the clinical program, it was determined that
12 there are four AEs for which there is a basis to
13 believe there is a causal relationship between their
14 occurrence and the use of tafamidis. These AEs are
15 identified as adverse drug reactions, as noted on this
16 slide, and are proposed to be included in the product
17 label.

18 Now, recognizing that safety data in this
19 application is limited due to the rarity of this
20 disease, we will continue to collect safety data in the
21 post- marketing setting, using the tools as described
22 on this slide.

1 So in closing, tafamidis was generally well
2 tolerated in clinical trials, with a low
3 discontinuation rate due to adverse events. And many
4 of these AEs observed are consistent with disease
5 morbidity. The identified risks are manageable and
6 acceptable in the context of this disease and ongoing
7 safety data are being collected.

8 So I hope I have provided you with an
9 understanding of the scope of the efficacy and safety
10 data included in this application. I now would like to
11 invite Dr. Teresa Coelho, the principal investigator at
12 Porto, who will provide a clinical perspective on TTR-
13 FAP.

14 DR. COELHO: Thank you, Dr. Grogan. Good
15 morning. I am Teresa Coelho. I am a neurologist and a
16 neurophysiologist from Porto, Portugal, where I have
17 treated FAP patients for 25 years. I'm a consultant to
18 the sponsor and I was an investigator in the clinical
19 trials. My institution was paid per protocol, but I
20 have no financial interest in the outcome of this
21 meeting.

22 Porto and my hospital in particular is where

1 the disease was discovered 70 years ago. Portugal is
2 the most important endemic region in the world. In
3 some districts north of Portugal, the prevalence of the
4 disease is higher than 1 patient per 1,000 inhabitants.

5 San Antonio Hospital houses the largest
6 clinic in the world. We follow 700 patients and 300
7 carriers every year, and we diagnose around 80 to 100
8 percent new patients every year. So it's not
9 surprising that half the patients on the world FAP
10 liver transplant registry are from Portugal.

11 In my practice, I have treated more than 70
12 patients with tafamidis. I have 44 patients currently
13 on treatment, including 22 for almost five years and 22
14 for three and a half years. My experience so far has
15 been that the majority of patients are stable. They
16 are all in stage 1 and fully ambulatory. In fact, 41
17 out of the 43 patients were on the liver transplant
18 waiting list. We drew their names from the list
19 voluntarily. The patients and doctors agree that they
20 were stable enough and will continue to be closely
21 monitored.

22 FAP is a heterogenous condition. Even in an

1 endemic area like Portugal, we see heterogeneity. We
2 have diagnosed families with non-Val30Met mutations.
3 The age of onset varies between 20 and 80 years, and we
4 follow a significant group of late onset patients. We
5 have several patients with additional organ involvement
6 beyond neuropathy.

7 Despite this variability, the neuropathy
8 characteristics and the pattern of progression is
9 similar across sites and mutations. The pathogenesis
10 is the same, as you heard from Dr. Kelly. It's always
11 a length- dependent neuropathy with sensory, motor, and
12 autonomic involvement, with a severe progression
13 invariably leading to a fatal outcome. For patients
14 who present with neuropathy, life expectancy is
15 consistent in different foci. That's why I believe
16 tafamidis data may be generalizable to the U.S. patient
17 population.

18 As someone who has treated patients for so
19 many years and saw liver transplant as the first hope,
20 I am excited about an option that does not have the
21 additional complications associated with liver
22 transplant.

1 Thank you for your attention. And now, I
2 would like to invite Dr. Ilise Lombardo to the podium
3 to present the benefit-risk profile of tafamidis.

4 DR. LOMBARDO: Thank you, Dr. Coelho.

5 My name is Dr. Ilise Lombardo, and I'm a
6 physician with Pfizer, and I lead the worldwide medical
7 and clinical efforts to register tafamidis for the
8 treatment of TTR-FAP. At this time, I am going to
9 summarize the data you've heard, which will be the
10 basis for your evaluations of the questions,
11 specifically whether these data provide substantial
12 evidence of the clinical effect of tafamidis.

13 In the spirit of the Orphan Drug Act and per
14 the FDA guidance, it's been noted that the broadest
15 flexibility is afforded in applying the statutory
16 standards for substantial evidence of efficacy in light
17 of the nature and severity of this very rare disease.
18 Of course, the appropriate assurances of both safety
19 and effectiveness must be met. But we believe the
20 totality of data that we have presented today meet that
21 standard for tafamidis.

22 As you've heard, there are two pathways for

1 approval, traditional approval and accelerated or
2 subpart H approval, which differ based on the type of
3 endpoints used to demonstrate substantial efficacy.
4 Traditional approval requires the demonstration of
5 substantial evidence of efficacy on a clinical
6 endpoint. And that's what you're being asked to
7 consider for tafamidis in question 2A.

8 Subpart H or accelerated approval, which we
9 believe is more appropriate for tafamidis, also
10 requires the demonstration of substantial evidence of
11 effect. However, this evidence of effect can be shown
12 by either a clinical endpoint or biomarker that has not
13 been formally validated, but is reasonably likely to
14 predict clinical effect. That's what you're being
15 asked to consider with question 2B. And in this case,
16 confirmation of this clinical effect is then
17 demonstrated in a confirmatory study in the post-
18 approval setting.

19 I'd like to remind you that, as noted by FDA
20 in their briefing document, clinical benefit is
21 determined by tafamidis's effect on the NIS-LL and the
22 TQOL, while the secondary clinical endpoints may all be

1 considered measures of disease progression likely to
2 predict clinical benefit. In addition, TTR
3 stabilization is a biologically plausible marker that's
4 reasonably likely to predict clinical benefit.

5 So the co-primary endpoints, the NIS-LL, and
6 the Norfolk TQOL, when considered together, are
7 appropriate clinical endpoints by which we can assess
8 tafamidis's efficacy as outlined in question 2A. Now,
9 as discussed, the primary analysis of the co-primary
10 endpoints on the left favor tafamidis, but did not meet
11 statistical significance. However, for a disease-
12 modifying approach, observation time is crucial to
13 allow for the natural progression of disease. And due
14 to the large and early dropout from liver transplant,
15 the efficacy evaluable population is a relevant
16 analysis by which to examine the treatment effect for
17 tafamidis. And we did reach clinical statistical
18 significance on each co-primary endpoint in this
19 population.

20 Further, and as Dr. Grogan showed, the
21 statistically significant change from baseline to month
22 18 for the NIS-LL further supports the effect of

1 tafamidis on neurologic function. These data provide
2 evidence for the effect of tafamidis on the clinical
3 endpoints outlined in 2A.

4 The secondary endpoints measured disease
5 progression across multiple aspects of TTR-FAP and
6 these formed the basis for the assessment of evidence
7 in question 2B, to determine substantial evidence for a
8 biomarker endpoint reasonably likely to predict
9 clinical benefit.

10 Given the large number of unknowns as we
11 entered into this program, we intentionally included
12 measures examining different aspects of disease
13 progression. Including this many different measurements
14 was a development risk. If they didn't all line up,
15 the results would have been very difficult to
16 interpret. But when they all point in the same
17 direction, they provide internal consistency and a
18 source of replication of effect.

19 These are measures of disease status over
20 time and, by their very nature, are reasonably likely
21 to predict clinical benefit. And the consistency of
22 findings favoring tafamidis across all of these

1 independent measures provides confidence that these
2 data are in fact reflective of a true clinical benefit
3 for tafamidis in the treatment of TTR-FAP.

4 As we look at these endpoints, especially the
5 sum 3, the muscle strength, and the mBMI, we can say
6 with confidence that the endpoints changed and that
7 these endpoints are reasonably likely to predict
8 clinical benefit. Also, the sum 3, sum 7, and mBMI
9 correlate with the co-primary measures of clinical
10 benefit.

11 In addition, the open-label study 006
12 provides us an opportunity to further examine
13 tafamidis's treatment effect. Here, we see the rate of
14 change analyses that were shown by Dr. Grogan, but for
15 the placebo-tafamidis patients across the different
16 endpoints.

17 Through examination of placebo patients,
18 shown in gray, when crossed over to active treatment,
19 shown in light blue, we see confirmatory evidence of
20 tafamidis's clinical benefits. All measures
21 demonstrated statistical or directional showing of
22 disease progression in this patient group.

1 So in summary, the totality of evidence
2 across secondary endpoints within the 005 study and the
3 006 study demonstrates consistency and replication. And
4 these findings provide substantial evidence of effect
5 on multiple endpoints reasonably likely to predict
6 clinical benefit.

7 The consistency of these findings makes
8 sense, given the mechanism of action of the drug. As
9 you heard from Dr. Kelly, TTR dissociation is the rate-
10 limiting step in the pathophysiology of TTR-FAP. And
11 TTR stabilization, which correlates with amyloid fibril
12 inhibition, is a plausible biomarker reasonably likely
13 to predict clinical benefit. In our program, we
14 demonstrated that tafamidis stabilizes TTR, and then
15 this translates into the clinical effects we've seen in
16 both Study 005 and 006.

17 These data, along with the stabilization of
18 mutations other than V30M, support the generalizability
19 of these results across mutations in this very rare
20 disease, including those seen in the U.S. patient
21 population.

22 Now turning to safety, the development

1 program characterized an acceptable safety profile for
2 tafamidis, especially in light of the irreversible
3 neurodegeneration and ultimate fatality of TTR-FAP. The
4 safety profile was similar across treatment groups with
5 respect to common adverse events and discontinuation
6 rates due to AEs and SAEs. The adverse events seen in
7 the tafamidis-treated patients were generally mild and
8 manageable.

9 We believe the risk of approving tafamidis,
10 given the above safety profile, is low compared to the
11 risk of patients with TTR-FAP of having no approved
12 treatment available. Currently, the only available
13 option is liver transplant. While it is a valuable
14 treatment for some patients, it's an invasive procedure
15 with significant mortality, morbidity, and lifelong
16 immunosuppression.

17 Tafamidis would be the first pharmacologic
18 treatment option and the only option available to
19 patients immediately upon diagnosis. While on
20 tafamidis, patients could continue to be evaluated for
21 progression or assessed for liver transplant according
22 to current standards of practice.

1 As with any rare disease, we recognize there
2 remain unanswered questions. A main source of new data
3 generation will be through the THAOS disease registry,
4 which we established five years ago to collect data on
5 clinical outcomes which require observation periods too
6 long for randomized controlled trials. Participants
7 include patients with TTR-FAP who are untreated,
8 treated patients with tafamidis, and those post-liver
9 transplant. THAOS also collects data on patients in
10 their related disorder, TTR cardiomyopathy, as well as
11 asymptomatic genetic carriers.

12 THAOS is the ideal data source for
13 examination of clinical benefit of long-term, real-
14 world outcomes, and we will routinely make these data
15 available for regulatory review.

16 Now, we note from the FDA's slides that
17 potential expanded access is proposed as a means to
18 make tafamidis available for patients. However,
19 expanded access is not a substitute for product
20 approval. Subpart H approval is the only sustainable
21 model for making tafamidis available for patients as
22 soon as possible. If, after these proceedings, subpart

1 H approval is granted, Pfizer will conduct an
2 additional confirmatory study in the post-approval
3 setting.

4 There are a range of options that we've
5 discussed with FDA for a confirmatory study. These
6 include utilizing the well-established THAOS registry,
7 open-label treatment versus a historic control, the
8 potential of another double-blind placebo-controlled
9 study, or a study in TTR cardiomyopathy. FDA has
10 indicated that a placebo-controlled trial is the
11 preferred option. And while these studies will take
12 time to complete, they are feasible.

13 The tafamidis clinical development program
14 presented today contains the only control data from
15 completed prospective studies in this orphan disease.
16 The primary endpoints provide evidence for clinical
17 effect of tafamidis and the secondary endpoints, which
18 match what we understand of the underlying
19 pathophysiology of TTR-FAP, are reasonably likely to
20 predict clinical benefit.

21 There is convincing evidence to conclude a
22 positive benefit-risk for tafamidis, given the

1 meaningful impact on delaying disease progression and
2 the totality of the efficacy data, along with a
3 manageable safety profile. We believe the benefits of
4 tafamidis outweigh any potential risks.

5 As we conclude our presentation, I want to
6 remind you of the degenerative and progressive nature
7 of this disease that typically affects patients in the
8 prime of their lives. They face catastrophic clinical
9 consequences. They must either undergo liver
10 transplantation or face a protracted course with
11 progressive and substantial disability, ultimately
12 succumbing to the disease, typically dying within 10 to
13 15 years of the first onset of symptoms.

14 TTR-FAP patients in the U.S. desperately need
15 a treatment option. There will be opportunities to
16 collect further data on the clinical effect of
17 tafamidis, but this will take time. We ask that
18 approval for tafamidis be considered based on the
19 benefit-risk profile demonstrated in the current data
20 package to make this treatment fully available for U.S.
21 patients now.

22 Thank you for your consideration and we'll

1 look forward to your questions.

2 DR. FOUNTAIN: Thank you. Now we move to the
3 clarifying questions. Are there any clarifying
4 questions for the sponsor? And again, please remember
5 to state your name before you speak.

6 (No response.)

7 DR. FOUNTAIN: Maybe I'll take the option of
8 asking the first question.

9 Can you comment on whether or not cardiac
10 effects were monitored during this study or if there
11 are other aspects of familial amyloid cardiopathy that
12 were considered during the course of the FAP studies?

13 DR. LOMBARDO: So to comment on the cardiac
14 monitoring during the study, I'm going to call Dr.
15 Donna Grogan.

16 DR. GROGAN: Cardiac effects were monitored,
17 including ECGs and echocardiograms. But it's important
18 to note that in these patients with the V30M mutation
19 at this relatively early stage of disease, very few of
20 them had cardiac involvement. In fact, there was very
21 little -- no progression along the cardiac parameters
22 even in the untreated population.

1 DR. FOUNTAIN: Thank you. Dr. Cohen?

2 DR. COHEN: So as someone who doesn't have
3 the experience that's in Portugal, that has taken care
4 of these patients, the major disabilities are the
5 autonomic disabilities as well as the sensory
6 disabilities. When I was looking at those data, what
7 seems to be most important in your study is the muscle
8 weakness, as far as disability factors. It occurs
9 later in disease, so kind of help me with this.

10 DR. LOMBARDO: So Dr. Grogan can come up and
11 speak to the effects in the 005 study.

12 DR. GROGAN: Yes. I think the data that we
13 observed, even at the baseline data for these patients
14 enrolled in our trial, does demonstrate that they have
15 both a small fiber neuropathy, as noted by the summated
16 3 score, as well as a large fiber neuropathy, as
17 demonstrated by that summated 7 score.

18 Although you are correct, the muscle weakness
19 is the subscale which differentiated between the
20 treatment groups, again, this was related to the
21 placebo patients having greater progression. There
22 were numerical differences between the treatment groups

1 in the other subscales, that did not achieve
2 statistical significance.

3 DR. FOUNTAIN: Dr. Rosenberg?

4 DR. ROSENBERG: TTR stabilization certainly
5 has face validity as a plausible mechanism of drug
6 action. How are you proposing it as a surrogate
7 endpoint? How does it fit in logically?

8 DR. LOMBARDO: Sure. Actually, I'd like to
9 ask Dr. Kelly. Could you come up and please speak to
10 the TTR stabilization?

11 DR. KELLY: So our thinking along these lines
12 is that, in the genetic mutation that's protective,
13 where you see kinetic stabilization of transthyretin by
14 analogy, we also see kinetic stabilization of
15 transthyretin with tafamidis over the dosing range of
16 20 milligrams once a day, from Cmin to Cmax.

17 So the assay that we use to -- the challenge
18 with transthyretin in assessing its stabilization is
19 that it's an unusual protein in that it's kinetically
20 stable, meaning that the barrier is very high for
21 assessing denatured states. Most proteins go back and
22 forth very quickly. This protein does not.

1 So the destabilization assay that we use
2 involves adding urea and then looking over two days at
3 how much tetramer goes away as a consequence of
4 dissociation and denaturation. That test was validated
5 by amino turbidity and can be used in the clinic
6 readily. And I think by analogy with the genetic
7 mutations, and by analogy with the clinical data you
8 saw today, would be a very good way to assess patient
9 compliance, number one, and likelihood of clinical
10 benefit, number two, from my perspective as a chemist.
11 Okay?

12 DR. LOMBARDO: Dr. Grogan, would you like to
13 come up and speak to TTR as related to our clinical
14 program?

15 DR. GROGAN: Yes. Can I have the slide on
16 change in NIS-LL by TTR stabilization status? So when
17 we initiated this trial, we had this hypothesis, and we
18 did not know what proportion of patients would
19 demonstrate stabilization. So one of the analyses that
20 we pre- specified -- can you please show us slide 130 -
21 - is, at week 8, where we've already achieved steady-
22 state plasma concentration, what happens -- let's look

1 at those patients who have a stabilized tetramer at
2 week 8 versus those patients who are not stabilized at
3 week 8.

4 What happens to their NIS-LL over time? And
5 you can see on this graph here that in the upper red
6 line, it's those patients who do not have stabilization
7 of a tetramer. And in the lower green line is those
8 patients who do have stabilization of their tetramer at
9 week 8. And you see a statistically significant
10 difference between the treatment groups.

11 Now, as it turns out, obviously, the vast
12 majority of patients on tafamidis were stabilized and
13 almost no patients on placebo, so this does match what
14 we see in the treatment group response.

15 DR. FOUNTAIN: Did that sufficiently answer
16 your question? Is there a follow-up to that?

17 DR. KATZ: No.

18 DR. FOUNTAIN: Dr. Preston?

19 DR. PRESTON: I had a question about the NIS-
20 LL scale. In some of the analyses over time, it
21 appears that, that was analyzed as a continuous
22 variable, but that scoring is actually an ordinal rank.

1 So I want to know why the statistics were done that
2 way, because obviously the proper statistics for an
3 ordinal scale is different than a continuous scale.

4 DR. LOMBARDO: So Dr. Schwartz, could you
5 come up and please discuss the analysis method?

6 DR. SCHWARTZ: My name is Jeff Schwartz. I'm
7 a statistician at Pfizer. The analysis was performed
8 on the NIS-LL change from baseline as a continuous
9 variable. It's a combination of lots of subcomponents
10 forming a numerical score. So analysis as a continuous
11 variable is a reasonable method for analyzing that
12 variable; used in MMRM analysis, which also takes into
13 consideration the available data. So it adjusts, in a
14 sense, for the missingness of the data as well.

15 DR. FOUNTAIN: Is that adequate? Is that an
16 adequate answer for you?

17 DR. PRESTON: The problem I have here is
18 that, obviously, the difference between, say, a score
19 of 2 and 4 is different than a score of 10 to 12. You
20 could have it many different ways. So I was just
21 bothered when I saw that it was a continuous variable
22 because the proper statistics are usually different for

1 that. I'm still not 100 percent sure why that was
2 done.

3 I mean, obviously, when I see that, I'm
4 concerned about, well, if the statistics were done for
5 -- an ordinal scale may not have shown clinical
6 significance, but when they're done for a continuous
7 scale, they do. The continuous scale is not the proper
8 statistics here.

9 DR. FOUNTAIN: So maybe we can discuss the
10 properness of it when we discuss the other issues, but
11 is there a specific response to that?

12 DR. LOMBARDO: Dr. Schwartz, do you want to
13 come back to address that?

14 DR. SCHWARTZ: So I believe the range of
15 values for the NIS-LL scale is 0 to 88, if I'm correct,
16 so the variable has a possible range of 88 points.
17 These patients are repeatedly measured over time. It
18 seems like a reasonable way as to take into
19 consideration that continuous value from 0 to 88 as a
20 possible score.

21 DR. FOUNTAIN: Thank you.

22 Dr. Logigian?

1 DR. LOGIGIAN: I just had a couple of
2 questions. But I wonder if someone can address the
3 balance with respect to the severity of the NIS and the
4 QOL scores in the dropouts. That is, do we know that
5 the treatment group dropouts were, in terms of
6 severity, about the same as the placebo group dropouts
7 and that they weren't more severe?

8 DR. LOMBARDO: Dr. Grogan, could you come to
9 address that, please?

10 DR. GROGAN: Yes. We did look specifically
11 at the liver transplant patients who discontinued, as
12 you recall, 13 in each treatment group. And when you
13 look at the baseline demographics and disease
14 characteristics of those patients who dropped out for
15 discontinuation, two things are apparent.

16 One is, as a whole this group had longer
17 disease duration and worse NIS-LL scores than those who
18 did not drop out due to liver transplant. And we
19 interpret this as being that patients have been on the
20 liver transplant longer. They've been waiting longer
21 for their organ and their name finally got called.

22 But when you look at those patients who did

1 drop out due to liver transplant across the treatment
2 groups, their severities and disease durations were
3 similar. There were 13 in each treatment group and,
4 although they were more severe than the ones that did
5 not drop out, the placebo patients looked similar to
6 the tafamidis patients.

7 DR. LOGIGIAN: So are you saying there was no
8 statistical difference or significant difference
9 between the NIS scores in the treatment dropouts and
10 the placebo dropouts?

11 DR. GROGAN: Correct.

12 DR. FOUNTAIN: Dr. Katz?

13 DR. KATZ: There are two things. One follow-
14 up to that. You say they're similar. Do you have a
15 slide of the actual scores? The other thing is, were
16 all 26 transplanted patients on the transplant list
17 prior to the study?

18 I mean, generally, patients are on the
19 transplant list, but do we know for a fact that all 26
20 were actually awaiting it prior -- awaiting transplant
21 prior to the study?

22 DR. GROGAN: Right. We know the vast

1 majority of patients were on the transplant list. I
2 can't give you the exact numbers of the 26 patients who
3 went to transplant, but the vast majority of them were.
4 I can't tell you 100 percent that every single one of
5 them were.

6 DR. KATZ: You can't tell us now? I mean,
7 that information is not available. Is that correct?

8 DR. GROGAN: Right. Correct. Yes.

9 Could I have slide E273, please? So on this
10 slide is the disease characteristics for subjects who
11 underwent liver transplant. You see it's 13 subjects
12 per treatment group. The NIS-LL mean is 15 for the
13 tafamidis patients, 13.8 for the placebo patients, and
14 similar scores, summated 7, summated 3, again,
15 similarities in the scores between the groups.

16 DR. KATZ: Just to follow up, do you have on-
17 study data for any of these patients --

18 DR. GROGAN: Yes. We do.

19 DR. KATZ: -- before they left?

20 DR. GROGAN: Right. Could I have slide E274,
21 please? So the majority, 73 percent, of these patients
22 had no data post-six months. And many of these

1 patients had no data after baseline. So the number of
2 patients represented on the slide here is small, but
3 you can see this is the change from baseline at six
4 months in those subjects who discontinued due to liver
5 transplant and obviously for those patients who had six
6 months' data. And you can see it's the change from
7 baseline across the various endpoints.

8 So there does not seem to be an apparent
9 difference in the worsening of these patients at the
10 six- month time point.

11 DR. LOMBARDO: And just to follow up on that
12 in terms of the liver transplant, in Europe for
13 patients with TTR-FAP, as Dr. Grogan had mentioned,
14 they aren't assessed or moved up the list because of
15 disease severity. Since they don't have liver disease,
16 their assessment and placement on the list is due to
17 time on the list, and they move up according to that.
18 So she had mentioned that this was not salvage therapy,
19 but their name had come up and they were called for
20 transplant during the course of study.

21 DR. FOUNTAIN: Thank you. I'd like to remind
22 the panel members, if you have a question, please raise

1 your hand. Follow-up or no? Okay, Dr. Chaudhry?

2 DR. CHAUDHRY: So the question is -- I guess
3 you started by saying there are no prior directional
4 trials for this disease. So I'm wondering whether
5 there is any opportunity to look at the patients who
6 did go for liver transplant and tell us what numbers
7 they had;; if you did follow them out, those 26
8 patients, if there is a comparison.

9 I mean, is it, 100 percent of those patients
10 get less than 2 point change in their NIS-LL versus the
11 45 percent, if you have similar 18-month data on the
12 liver transplant patients, to give us an idea of what
13 we're looking at; if there is a comparison, I mean, in
14 the future perhaps, of a study between this drug and
15 the folks who undergo liver transplant?

16 DR. LOMBARDO: Dr. Grogan?

17 DR. GROGAN: If I understand the first part
18 of your question, you wonder if we have data on these
19 endpoints post-liver transplant in those patients who
20 underwent liver transplant. And then you questioned
21 perhaps that might be a further investigation.

22 So of the 26 patients who discontinued, 5

1 died relatively immediately post-transplant, so they
2 were not available to come back. We did request for
3 the sites to have these patients return at least for a
4 post- discontinuation follow-up visit. But many of
5 these transplants were performed at sites other than
6 the enrolling centers, so we have very limited data on
7 the use of these endpoints or what happened to these
8 patients with these specific endpoints.

9 But perhaps to address the question about
10 what happens to patients post-transplant, Dr. Teresa
11 Coelho, who again sees a majority of the patients in
12 the world, could come up and give her clinical
13 perspective about what happens to patients post-liver
14 transplant on some of these neurologic measures.

15 DR. COELHO: As Dr. Grogan said, we have no
16 regular assessment of patients that went to liver
17 transplant because even if you call patients to come
18 back, sometimes it's very difficult because they are
19 being followed at transplant centers. But I think, in
20 general, we can see that when we look at the results of
21 liver transplant, we know that there is a very
22 significant impact on the survival of these patients.

1 And we know that patients that receive liver transplant
2 early in the course of their disease -- the majority of
3 patients in the course of disease have a stabilization
4 of the progression of disease for several years.

5 But we don't have from the literature much
6 information about those patients that do progress and
7 how much do patients progress after liver transplant.
8 And from my clinical experience, I know there are
9 patients that continue to progress after liver
10 transplant without a significant effect of liver
11 transplant, and there are patients that slow
12 progression but continue to progress. And you have also
13 patients that have a quite stable situation after liver
14 transplant and those are the patients that receive
15 liver transplant early in the course of the disease.

16 DR. FOUNTAIN: Thank you. We do want to move
17 to have a break soon, so please limit your questions to
18 clarifying questions because we'll have opportunities
19 to discuss other specific questions later as well.

20 Next is Dr. Frank.

21 DR. FRANK: So how many patients in the U.S.
22 were exposed to tafamidis? And I ask this

1 for two reasons, one from the agency perspective. Is
2 there a precedence for approving a drug with very few
3 U.S.

4 residents being exposed to a drug?

5 Also, the U.S. is not an endemic region and
6 there may be genetic and clinical characteristics,
7 differences in characteristics, that may have
8 implications for the generalizability of the studies.

9 DR. LOMBARDO: So the patients from the U.S.
10 who were in the clinical program, were in the
11 1-A-201 program, I believe there were 10 U.S. patients
12 in that study. The generalizability question that you
13 get at, to speak to that, first it's important to
14 recognize that although the U.S. is a non-endemic
15 region with a number of different mutations, the V30M
16 mutation is still the most common single mutation in
17 the U.S.

18 patient population, representing
19 approximately 40 percent of patients.

20 Then, as we think about the generalizability
21 of tafamidis's effect for these patients, we do know
22 that the underlying mechanism of TTR destabilization

1 actually occurs with all tested mutations, so all
2 mutations that are known form these unstable tetramers,
3 as Dr. Kelly had provided.

4 So in the 1-A-201 study, eight different
5 mutations were enrolled. And then in addition to that,
6 there was ex vivo data where a total of 36 mutations
7 were tested with tafamidis and shown to be stabilized.
8 So given the mechanism of action and the universal
9 destabilization of tetramer, as represented in the V30M
10 mutation with the clinical effect, we believe these
11 results are generalizable to the U.S. patients.

12 DR. FOUNTAIN: All right. Dr. Farkas?

13 DR. KATZ: Just let me quickly answer part of
14 Dr. Frank's question, which had to do with the
15 precedent for approving a drug with very few patients
16 in the U.S. There's certainly precedent for approving
17 drugs where there may be no U.S. patients. But of
18 course, we have to be confident that the data that were
19 generated, wherever they were generated, are applicable
20 to the U.S.

21 population. And here, we've heard that
22 there's sort of a general sense, I think, being

1 described that, once you have stabilization, you're
2 going to respond the same regardless of your geographic
3 location or independent of your mutation. I think that
4 probably remains to be seen.

5 But to answer the simple question of, is
6 there precedent for approving drugs with few to no U.S.
7 patients, the answer is yes, assuming we can
8 conclude that the patient studied were like the
9 patients in the U.S. and that patients in the U.S. will
10 respond similarly. And there are a lot of things that
11 go into trying to answer that question.

12 I had a question. You can decide if this is
13 a clarifying question. We can deal with it this
14 afternoon. That's fine with me. But a lot of the data
15 presented were open-label, unblinded data. So in
16 those, particularly Study 006, settings we always are
17 concerned about outcomes and knowledge of treatment
18 assignment, particularly outcomes that are highly
19 subjective, whether a patient is assessing them, or a
20 clinician, or a caregiver. But some of the outcomes
21 are asserted to be objective. And of course, those are
22 the sorts of things we're interested in, in open-label

1 settings because presumably they're not susceptible to
2 blind breaking. Specifically, there were the sum 7 and
3 the sum 3.

4 So my question is, can we get a detailed
5 description of the components that go into those
6 measures, and are they truly objectively rated? Could
7 we get a machine printout or does someone have to look
8 at the output? And again, there are many components to
9 these things and we can deal with that this afternoon,
10 and whether or not those are susceptible to knowledge
11 of treatment assignment.

12 DR. FOUNTAIN: Perhaps that might take a few
13 minutes to get that slide together, so maybe this would
14 be an opportune time to take a break for a few minutes
15 and then come back after the break and answer the
16 question. That might give you an opportunity to get
17 those specific things together.

18 The specific question, if I can reiterate, is
19 what are the subcomponents of the sigma 3 and the sigma
20 7, and exactly how are they measured, so we can make an
21 assessment about how objective they are.

22 DR. KATZ: And how susceptible they are to

1 knowledge of treatment assignment by the assessor?

2 DR. FOUNTAIN: So we'll now take a 10-minute
3 break. Panel members, please remember that there
4 should be no discussion of the meeting during the break
5 amongst yourselves or with any member of the audience.
6 So we'll resume in 10 minutes at 11:13.

7 (Whereupon, a recess was taken.)

8 DR. FOUNTAIN: All right. Please take your
9 seats.

10 All right. If we can resume the panel
11 discussion. Before the break, the question at hand
12 that Dr. Katz asked was, what are the specific
13 subcomponents of the sigma 3 and sigma 7 that might be
14 objective, or are there other objective measures that
15 might be less influenced by knowledge of being on the
16 treatment?

17 DR. LOMBARDO: So to speak about the
18 objectivity specifically of the measures that were
19 used, certainly I think that the mBMI and the TTR
20 stabilization are very objective measures that were
21 used both in 005 and 006.

22 Then more globally, just to note, as patients

1 entered into 006, in all their measures, both patients
2 and physicians were blinded to the treatment that they
3 had been on 005. Certainly, as we're looking across
4 the group and the changes in slope between the placebo-
5 tafamidis patients and then the tafamidis-tafamidis
6 patients, that maintains the indication that the blind
7 was maintained.

8 But specifically to speak to your question
9 about the sum 3 and sum 7, I'm going to have Dr.
10 Freeman come to talk to the components of those
11 composites.

12 DR. FREEMAN: So if I could have the slide on
13 the sigma 7 and sigma 3 on the screen. While we're
14 waiting, the sigma 7 you will recall is the
15 predominantly large fiber measure and the sigma 3 is a
16 small fiber measure. The sigma 7 comprises standard
17 measures of nerve conduction. The peroneal nerve,
18 tibial nerve, and sural nerve, these are the major
19 motor nerves tested by any clinical neurophysiologist
20 in the lower extremity.

21 These are totally objective tests. So there
22 is an electrical stimulus. There is a response. If

1 done by somebody trained, this will be an objective
2 test, no patient response, no patient involvement at
3 all.

4 Continuing on the left side, we have
5 quantitative sensory testing. Over here, there is
6 patient involvement. This is a graded, quantified
7 sensory test in which there is a stimulus and the
8 patient interprets the stimulus. There is the
9 potential for there to be some patient bias in the
10 testing, but it would be hard for the patient to even
11 know which direction to respond.

12 But this is a psychophysical test, and there
13 is some potential for subjectivity. The heart rate
14 variability components, for statistical reasons, in the
15 development of the test of the large fiber battery and
16 in autonomic tests, therefore, a component of the small
17 fiber battery, is again an objective test. There is a
18 stimulus, deep respiration, and a response, the heart
19 rate response, an objective measure.

20 So in answer to the question, predominantly
21 and in large part, an objective measure of
22 neurophysiological function.

1 DR. FOUNTAIN: Is there a follow-up question
2 to that or a separate question?

3 DR. JILLAPALLI: While I agree that nerve
4 conduction studies are quite objective, it's also true
5 that knowledge of unblinding can lead to all sorts of
6 manipulation by the operator in terms of the amplitude,
7 in terms of the voltage, the current delivered, and the
8 placement of the electrode. And there are experts here
9 who can speak to that. So it's not entirely as
10 objective as it might appear.

11 DR. LOMBARDO: If I may actually ask Dr.
12 Grogan to come up, because she can speak to
13 specifically the measures that were put into place as
14 we were conducting both 005 and 006 with regard to
15 potential unblinding.

16 DR. GROGAN: All of the investigators at the
17 sites were trained at an investigator meeting and they
18 were qualified for the performance of these various
19 physiologic measures by an independent neurologist
20 prior to them enrolling any patients into the 005
21 study. So these same investigators and
22 neurophysiologists followed patients from 005 into the

1 006. The prior blind in 005 was maintained, but the
2 sites were aware that this was an open-label trial,
3 with all patients on tafamidis.

4 DR. FOUNTAIN: All right. I think Dr. Farkas
5 was next.

6 Did that answer the question? But before
7 your presentation, did you have a question?

8 We have one or two more questions before your
9 presentation, one from Dr. Clancy, if you still wish to
10 ask it, if it's a clarifying question. This was a
11 discussion question.

12 DR. CLANCY: This is a clarifying question.

13 So I appreciated the talk that Dr. Coelho
14 gave from Porto in Portugal. And I guess my question
15 is, among these endemic centers, where the population
16 itself must be aware of this disorder because they've
17 got an uncle or grandfather with it and the doctors who
18 have seen many, many cases of this, were the systematic
19 differences in the patient status among all the endemic
20 centers that enrolled patients versus just the one in
21 Porto, Portugal?

22 DR. LOMBARDO: So I'm not sure if I

1 understand the question. Were you asking if there were
2 differences in the patient populations across the
3 sites?

4 DR. CLANCY: Yes. At enrollment, in terms of
5 the severity of disability, were they detected earlier
6 in a milder state in these endemic places?

7 DR. LOMBARDO: I understand.

8 Actually, Dr. Grogan, did you want to come
9 and maybe speak to the baseline characteristics of the
10 patients in Porto compared to the others?

11 DR. GROGAN: The only other major endemic
12 center that was participating in this trial was Sweden.
13 The patients in Sweden, although it is a major endemic
14 center with the V30M mutation, it's known in the
15 literature that these patients tend to be older at the
16 age of onset. But there actually was a publication
17 that looked at, regardless of the age of onset between
18 these sort of late onset patients versus early onset
19 patients, that once neuropathy has been established,
20 the progression is similar.

21 I don't have the baseline demographics of
22 Porto versus Sweden, but I can tell you that the

1 Swedish patients were definitely an older population.

2 DR. FOUNTAIN: Thank you. The last question
3 before we move onto the FDA presentation will be from
4 Dr. Gooch.

5 DR. GOOCH: I have a couple of clarifying
6 questions. The first is, in the 005 study, the
7 secondary endpoint analyses that shows statistical
8 significance, were those based upon the efficacy
9 evaluable population or were they intent-to-treat? Were
10 they all at 18 months versus baseline? Could you
11 comment on that?

12 DR. LOMBARDO: Actually, Dr. Grogan, could
13 you come up and maybe take us through the different
14 analyses from the co-primaries?

15 DR. GROGAN: All the change from baseline
16 analyses that we showed up here were in the intent-to-
17 treat population. You're just utilizing a mixed model
18 repeated measures analysis.

19 DR. GOOCH: Thank you. The second question I
20 have has to do with the 201 study. Have you
21 accumulated enough patients there to do variants versus
22 baseline analyses and compare with historical controls

1 to come up with significance, or have you had any
2 analysis of that kind on that study?

3 DR. GROGAN: Right. I mean, it's a
4 relatively small study. Eighteen patients completed
5 the trial across eight different variants, so it's
6 really hard to look at a by-variant progression. So
7 I'm not sure I can adequately answer that question.

8 DR. GOOCH: The third question I have is, in
9 the 303 study, do you have any data beyond 36 months
10 regarding continued benefits, potential benefits of the
11 medication with the statistical analysis?

12 DR. LOMBARDO: So the 303 study, as we
13 mentioned, is a continuation study, and patients remain
14 in that study. And some patients have been in for up
15 to five years. The data from those studies were not
16 included in this NDA. However, we continually analyze
17 those data and can say that -- very top line, if I may,
18 with permission -- that the data are consistent in
19 terms of the continued rate of stabilization.

20 It might be helpful, actually, if -- Dr.
21 Watsky would you like to come up and comment on 303,
22 please?

1 DR. WATSKY: Hi. Eric Watsky. I'm a
2 physician at Pfizer. And yes. The 1-A-303 study has
3 data out at this point to 42 weeks. This data,
4 however, was not for efficacy -- or this data was not
5 included in the submission. So without permission, we
6 would not be presenting that. But as Dr. Lombardo
7 indicated, the results are consistent. What we're
8 seeing in terms of response rates is consistent. More
9 than half of patients remain responders in the
10 population that are studied out to 42 weeks.

11 DR. FOUNTAIN: The sponsor will be here all
12 today, so you'll have opportunities to ask more
13 questions of them later if it's particularly for
14 discussion questions that aren't so clarifying. And we
15 want to be sure to be fair to give the FDA an
16 opportunity at their presentation as well.

17 So it's 11:26 now. Dr. Farkas will present
18 the FDA presentation. And we'll delay lunch until
19 12:15, but we do have to resume at 1:00.

20 Dr. Farkas, will that give you sufficient
21 time, or would you like to divide your presentation
22 between before and after lunch?

1 DR. FARKAS: Sorry. I didn't actually hear
2 what the time --

3 DR. FOUNTAIN: Would you like to divide your
4 presentation?

5 DR. FARKAS: I didn't hear what the time was,
6 though.

7 DR. FOUNTAIN: So it's 11:27 now, 11:30, and
8 we should probably break for lunch at 12:15 in 45
9 minutes.

10 DR. FARKAS: I think that's okay, and then
11 maybe the clarifying questions can be after.

12 DR. FOUNTAIN: The clarifying questions
13 after. That would be perfect.

14 DR. FARKAS: I think actually that Dr. Katz
15 covered a fair number of the things that are in some of
16 the slides.

17 DR. FOUNTAIN: You just take your time to do
18 whatever you think is necessary just in terms of
19 timing.

20 DR. FARKAS: Sure. Thank you.

21 So I think the panel would have noticed that
22 there really isn't any discussion of safety in these

1 slides. It really focuses on efficacy, but of course,
2 we can discuss safety this afternoon.

3 As Dr. Katz had said this morning, to be
4 approved, orphan drugs, like any drug, needs
5 substantial evidence of efficacy. That's usually two
6 positive studies or one very persuasive study plus
7 confirmatory evidence. There is one controlled trial
8 for tafamidis. And the FDA is committed to applying
9 flexibility in trying to figure out how the data from
10 that trial fits into the evidence that would be
11 necessary to support approval.

12 Dr. Katz also mentioned some characteristics
13 of a particularly convincing study. And I won't go
14 over all of them. But I think what I'll concentrate on
15 is the part about serious weaknesses. I guess what
16 happens is that if there are, for example, baseline
17 imbalances, baseline imbalances can arise by chance.
18 And then the study arms can be different, truly
19 different, but by chance -- and some of my later slides
20 will talk about that. Then if different endpoints are
21 used to measure differences between the arms, the
22 different endpoints are very consistent. They're

1 measuring this difference that arose by chance.

2 So that's one important reason that, for
3 approval based on one study, there have to be no
4 serious weaknesses.

5 Again, this red box mentions post hoc changes
6 in analysis, a clear prior hypothesis. And so I'll
7 also stress it a little bit later, but to mention here,
8 when we take a look at the data, as is usual in
9 science, we take a look at the primary endpoint. And
10 that is the most reliable endpoint.

11 So the co-primary endpoint in Study 005 was
12 the NIS-LL and the Norfolk. And so, as a co-primary,
13 the study is positive only if the p value for both is
14 less than 0.5. The reason for having co-primary
15 endpoints is that small changes in NIS-LL -- it's a
16 physician exam -- might not represent benefit that the
17 patient perceives. The Norfolk is combined with that
18 because that's measuring what the patient perceives, to
19 see if the change has a clinical impact.

20 Now, the p value is shown separately for the
21 NIS-LL and the Norfolk. And on the primary analysis,
22 it has been said it's .07 for the NIS-LL and .12 for

1 the Norfolk. And I should say that's commonly thought
2 of as negative. I mean, actually, that's I think
3 problematic terminology, and it's a little difficult to
4 go into. I won't. My boss is winking at me or
5 something.

6 (Laughter.)

7 DR. FARKAS: But I think that we should keep
8 in mind that .05 doesn't mean efficacy proven and .06
9 means efficacy absent or certainly not efficacy
10 disproven. So one interesting thing about taking a
11 look at co-primary endpoints is that we kind of
12 automatically do look at .07 separate from .12, which
13 brings up this problem of multiplicity.

14 So if we were looking at these two separate
15 endpoints, we would have thought the p values for
16 efficacy should be .025, so just doing that kind of
17 typical correction if we're looking at two different
18 endpoints.

19 And I think we've already done that. I mean,
20 when we got this application, we certainly did, I mean,
21 in the review division. And so that starts bringing up
22 the issue of multiplicity, that we've in a sense

1 already looked at three endpoints, looking at this one
2 slide.

3 In this slide, it just says that again. It
4 says that when we consider multiple endpoints, there is
5 an increased risk that we conclude the drug is
6 effective when it isn't. And I said here that it's in
7 ways that cannot be quantified, but it's a large effect
8 -- and I guess maybe it should have been bolded -- if
9 we keep looking at enough endpoints, we're guaranteed
10 to find endpoints that are positive. That's what a p
11 value really means. And that makes the study no longer
12 adequate and well-controlled, and not capable of
13 providing reliable evidence.

14 There's a caveat to that. And that is, we
15 don't only look at the statistics. If there's a really
16 big difference, that might be true, and we've talked
17 about the TTR stabilization. I think it's not clear to
18 the division what that means. But when there's a
19 really big difference, then we're not so stuck by the
20 multiplicity problem that we would ignore that.

21 So this is a sensitivity analysis on the
22 efficacy evaluable population, and we've talked about

1 that. And this can be helpful, again, with caveats,
2 multiple testing, perhaps biases. It can be helpful
3 for understanding the data. It really doesn't replace
4 the primary endpoint. I think that really does need to
5 be stressed. But it can help in interpreting the
6 primary endpoint.

7 Then there's this question of baseline
8 imbalances. I'll spend a couple of slides talking
9 about that.

10 So it's reasonable in the previous slide to
11 explore the robustness of the data by taking a look at
12 the efficacy evaluable population, and that led to a
13 lower p value. And then this slide is a sensitivity
14 analysis considering baseline disease severity.

15 Certainly, when the study was being planned,
16 it was realized that, that might be an important
17 covariate. And while it wasn't included in the primary
18 analysis, it was pre-specified. Again, pre-specified
19 doesn't mean there was an order of analysis, so we've
20 tried to keep that distinct. But it's a pre-specified
21 analysis, and a reasonable analysis, and an important
22 analysis because one could worry that baseline disease

1 severity would affect how patients progressed.

2 So by that analysis -- and I should say,
3 there are different ways to do this analysis. But by
4 the analysis done by the FDA statistician, which is a
5 typical way to do it, the p value is .16. So we start
6 collecting a number of p values, some greater than the
7 primary pre- specified analysis and some less.

8 Then to explain a little bit more about what
9 might happen in a study by chance and how we might
10 separate that from what might happen from a drug
11 effect, the NIS-LL, in the tafamidis arm, was 2 points
12 less severe. You should keep that number in mind. And
13 that was despite 12-month longer symptom duration.

14 So we would think -- we don't know, but we
15 might think -- that knowing what we do about the
16 disease, that if patients had the disease for 12 months
17 longer, they should have a more severe NIS-LL score.

18 So putting those two imbalances together, it
19 makes one concerned that, despite randomization and
20 purely by chance, the prognosis of patients in the
21 tafamidis arm was better than the prognosis in the
22 placebo arm. And the p value of that difference

1 actually says something interesting. It can't be
2 stressed enough. It does not mean that the imbalance
3 was important. What reasonable interpretation is, is
4 that this kind of imbalance happens in a lot of
5 studies, which could be seen as one reason that a
6 single study is less reliable than two studies showing
7 similar findings. These kinds of imbalances can be
8 important and they occur not uncommonly.

9 So to try to understand the implication of an
10 imbalance, we have to look at the size in the
11 implications and how it fits with our understanding of
12 the disease.

13 So getting back to the size of the imbalance,
14 so the top shows a 2-point difference in severity.
15 That's the imbalance. And then the bottom shows a 2.5
16 difference between the arms at 18 months. There's no
17 disagreement that the top 2 points arose by chance.

18 I think one has to be concerned that when one
19 sees the two point differences arise by chance -- at
20 the end of the study, a 2.5-point difference might have
21 arisen by chance -- which is really what the p value is
22 telling us for the primary endpoint to begin with. We

1 don't know that it occurred by chance, but there's
2 certainly that concern.

3 The concern had been expressed before about
4 most of the patients coming from a single site in
5 Portugal. Perhaps this has already been covered, but
6 there certainly is reason to be concerned in FAP that
7 there are differences that we do not understand in the
8 course of the disease in Portugal versus in the United
9 States.

10 I think it's already been mentioned, but just
11 to stress, the penetrance is very different with the
12 same gene mutation, V30M. Penetrance is very
13 different. It's related to age of onset, but age of
14 onset is very different, different by something like 20
15 years. And that number is actually from France, but I
16 didn't come across numbers for the United States, but
17 in endemic regions versus non-endemic regions.

18 In this particular disease, that might give
19 increased reason to be concerned that there could be
20 differences in the way the disease acts, the way the
21 drug might act in one site versus another.

22 Probably a stronger worry that the division

1 has is the one about evidence of efficacy from more
2 than one site. And it really does go to the heart of
3 internal replication. What does internal replication
4 mean?

5 In our guidance document on efficacy, there's
6 a quote here, that, "If analysis shows that a single
7 site is largely responsible for the effect, the
8 credibility of a multi-center study is diminished." So
9 that's certainly something that we worry about.

10 Now, the secondary endpoints, I'll talk
11 about, but just to remind you, we have a problem with
12 multiplicity, and we have to consider that. And so
13 we've already looked at the co-primary endpoint, the
14 individual endpoints, the efficacy evaluable endpoints.

15 So even before we start looking at the
16 secondary endpoints, we know there is multiplicity that
17 needs to be accounted for. And then the secondary
18 endpoints did not have a pre-specified order of
19 analysis, which was mentioned before, and that
20 compounds the problem. And really, the secondary
21 endpoints don't represent an adequate and well-
22 controlled trial. And the statistical significance

1 doesn't apply to nominal p values. And the reason is
2 that small p values happen by chance, and perhaps not
3 extremely, extremely small p values. That was maybe
4 what comes up with the stabilization assay. But pretty
5 small p values occur by chance when one looks at a lot
6 of endpoints.

7 Now, the large nerve fiber secondary endpoint
8 had a p value of .06, which by usual accounting would
9 be considered negative. And the small nerve fiber
10 function had a p value of .005. I think it had been
11 brought up before -- well, actually it was a different
12 point that had been brought up. But those two
13 endpoints actually aren't really consistent with each
14 other. And then when one looks at the small fiber
15 endpoint, a .005 p value was seen in Study 005. And
16 then in the continuation, circled in red, it looked
17 like the endpoint worsened. It looked like the
18 patients got worse.

19 I wrote "worsened" there, too, actually, but
20 it just looks like that, maybe. I mean, you don't
21 know. I guess that's the point. You don't know. But
22 taking a look at the error bars, maybe the more likely

1 explanation is that that's what experimental noise
2 looks like, that the .005 p value occurred due to
3 experimental noise. And it was one of many endpoints
4 tested. One was caught when it was a small p value.
5 And then the next time one looked, it wasn't such a
6 small p value, and that's to be expected.

7 Now, the modified body mass index is an
8 interesting endpoint, because if you just take a look
9 at body mass index, it actually helps to illustrate
10 problems with biomarkers. So the body mass index in
11 this disease is not a good measure of nutritional
12 status without the modified part because, when albumin
13 goes down, edema can go up, and you can get the false
14 impression that the patient is gaining weight when
15 they're doing worse. They're just gaining water.

16 Now, BMI ought to, all other things being
17 equal, correlate with your weight, nutritional status,
18 or whatnot. But we can see already that it doesn't
19 really work unless you account for other factors. And
20 that here is edema.

21 But the concern would be that you know this
22 measure is susceptible to problems, to not predicting

1 the clinical outcome. But do you know in all the ways
2 that, that could happen?

3 So the pattern of change in, again, the p
4 values, it does look like, even despite multiplicity,
5 something maybe did happen with the modified BMI. The
6 meaning of that isn't clear to us. That's a question.

7 If you first take a look at the pattern,
8 there's an increase in mBMI in treated patients in
9 Study 005, but that doesn't really seem to keep
10 increasing. So if there was some continued benefit,
11 some continued increase in nutritional status, one
12 might think that that would keep increasing in Study
13 006.

14 There are other things, too, one might be
15 worried about. The increase happens very quickly, so
16 I'm not sure if there was any measures before month 6,
17 but at month 6, there was an increase, and then it
18 seemed, as far as we could tell, to be stable.

19 So it might be some kind of -- I don't know
20 the right word -- maybe biochemical effect. And we had
21 written down, "Well, many drugs can change weight
22 without changing nutritional status." You can think of

1 the simplest maybe being salt. So that's a concern.

2 Just going back to the pattern, too, when the
3 placebo patients were switched to drug in Study 006,
4 there was a rapid increase in the mBMI. And there was
5 an analysis in Study 006 about an early start effect,
6 where you could try to show that the drug worked
7 because, after you started all patients on drug, they
8 would stay separate from each other, that there would
9 have been an advantage to treating patients early.

10 So here, it doesn't look to the division
11 perhaps like this would support that.

12 Then there are other really more technical
13 questions about what this assay is showing, what
14 effects it's sensitive to. So the TTR binds to
15 albumin. Sorry. The tafamidis binds to albumin. And
16 there are concerns that the division has that this
17 could change the accuracy of the test, so a purely
18 analytical issue. But then maybe there is some change
19 in the amount of the albumin. Tafamidis binds to
20 albumin. Tafamidis binds to TTR. We think we see --
21 it wasn't really talked about -- an increase in the
22 amount of circulating TTR. But I don't think there's

1 any thought that that contributes to efficacy.

2 So tafamidis increases circulating TTR. It
3 doesn't seem to be connected to efficacy. Tafamidis
4 increases, perhaps, circulating albumin. And it isn't
5 clear that that would be associated with efficacy.

6 So looking at the open-label study 006, it's
7 been mentioned that this is not adequate and well-
8 controlled. But still, we pose the question, could
9 this provide confirmatory evidence?

10 Some of these points were raised about open
11 label, concerns about unblinding. But there's some
12 other points worth mentioning. Many endpoints were
13 tested, but that is a multiplicity problem.

14 But when one looks at effects in Study 006,
15 it's not independent confirmation there were effects
16 from Study 005. And I think we have to be cautious in
17 double- counting, as you might say, effects that
18 occurred in 005 as having occurred in 006, so when an
19 analysis is done over 30 months, where is that
20 difference coming from?

21 Now, the division took a look at the pattern
22 of change in endpoints in Study 006. And I picked a

1 couple because they're kind of opposite. So the one on
2 the bottom, the small nerve fiber I had shown before
3 with that red circle around it.

4 Now, there's kind of two possibilities about
5 what happened to the small nerve fiber endpoint in
6 patients who started on tafamidis and continued on
7 tafamidis. Maybe they got worse. As I said before,
8 maybe that is just an expected pattern of experimental
9 noise.

10 With the change in Norfolk, there was some
11 discussion before. I mean, the division has some
12 concern about unblinding and subjective endpoints, but
13 just kind of looking at the size of the differences,
14 one might worry that, that fits into size of change
15 that can happen by chance, too.

16 Now, I should say, this is a little bit more
17 complicated, but one has to think about what pattern of
18 disease progression and really what pattern of endpoint
19 progression one might expect.

20 So with the small nerve fiber endpoint, a
21 within-arm comparison was done, and actually for the
22 Norfolk, too. So the slow untreated was worsening more

1 rapidly than the slow after treatment began. And so
2 there's a thought that maybe the slope decreased
3 because of treatment. But this is a problematic
4 analysis with this kind of data, this kind of endpoint.

5 So the rate of change of the endpoint may
6 change with progression of the disease in untreated
7 patients. So this is from the observational study, FX1-
8 A-001.

9 So I should say, too, that this is cross-
10 sectional, not longitudinal data, so it is open to some
11 kinds of biases itself, but the pattern is really
12 concerning. And it shows that, seemingly, either the
13 endpoint is less sensitive to change as time goes by,
14 or maybe perhaps the progression of the disease
15 changes. You can't really tell.

16 But when you go back, and you look, and you
17 think about change over time in patients who went from
18 placebo to tafamidis, what would need to be calculated
19 in would be the change in the endpoint, how the
20 endpoint responds. But that's extremely difficult to
21 do. I mean, we really can't do that. We don't have
22 the data that we need. And then some endpoints -- this

1 is the large nerve studies -- seem -- and again, this
2 is cross-sectional data, so it could be open to some
3 problems with this interpretation. But it certainly
4 suggest that you could see something that looked like
5 stabilization in this part of the curve because the
6 endpoint isn't measuring change anymore.

7 These analyses of efficacy are based on
8 change, but once something isn't changing anymore, say
9 nerves in the leg, once those aren't functioning, they
10 don't get any worse. So that introduces a great deal
11 of complexity -- well, it makes it more than complex.
12 It makes it unreliable to try to interpret what's going
13 on with these open-label endpoints, which brings up the
14 question of a path to approval. And this is just
15 repeating from the first slide, that top bullet, and
16 the second slide, too, Dr. Katz had gone over that, for
17 subpart H approval, we need substantial evidence for an
18 endpoint that's not actually the clinical endpoint of
19 interest.

20 This just kind of shows graphically,
21 diagrammatically, the confusion that often arises. So
22 maybe it's worth looking at just one last time, that

1 what we need for subpart H is high confidence that the
2 surrogate changed and reasonably likely that it
3 predicts clinical benefit. But subpart H does not
4 apply if it's reasonably likely that an endpoint
5 changed, be it a biomarker or a clinical endpoint, even
6 if there is high confidence that that change would
7 predict clinical benefit.

8 So it's worth noting pathways that we don't
9 have available to us in the United States, and, of
10 course, tafamidis is approved in Europe.

11 In the exceptional circumstances -- I'm no
12 expert in explaining this, but I copied this from the
13 European site -- is that comprehensive data cannot be
14 provided based on several factors. There is yearly
15 review of new information, but normally, that will not
16 lead to completion of a full dossier, or normal
17 marketing authority, or authorization for the drug.

18 That's quite different from the pathway that
19 we have available through subpart H, for which again we
20 need substantial evidence. We did the post-approval
21 study and that must show efficacy for the drug to stay
22 on the market.

1 So the division considered -- with all the
2 caveats about, worries about, the integrity of the
3 study, the vision considered if there were endpoints
4 that could support subpart H approval.

5 So the large nerve fiber function might be or
6 if it was reasonably likely to predict clinical
7 benefit. The p value was .06, again, normally
8 considered negative. And then there are the other
9 weaknesses and multiple testing.

10 The small fiber function, more or less, I've
11 gone over before, that with multiple testing, it's not
12 clear what the .005 means. And then there's other
13 behavior of the endpoint that we're able to see in
14 Study 006 that makes one worry about random variation,
15 that would fit with the kind of effects that we see
16 with multiple testing.

17 The NIS-LL could be considered a surrogate
18 endpoint because, again, small changes might not be
19 perceived by the patient, but using NIS-LL, again, goes
20 back to, is there substantial evidence supporting that.

21 Now, the TTR stabilization assay has been
22 perhaps maybe a little bit of confusion about what the

1 -- used in the study was actually testing. And maybe
2 we'll have to discuss this later this afternoon.

3 But it does seem clear that non-physiological
4 conditions were used to measure tafamidis stability in
5 the clinical studies, and that that assay gives a
6 measure of stabilization that is something like,
7 instead of 100 percent or almost 100 percent, something
8 more like two times slower dissociation or three times
9 slower. There was some conversation about, maybe that
10 assay is really taking the place of some other assay
11 that would have been better. But perhaps that's part
12 of the confusion.

13 I think that with the division's current
14 understanding, it still seems to us that even under
15 more physiological conditions, looking at other papers
16 that were published, that dissociation still occurred
17 at a much slower rate, but we'd probably be best to
18 talk about it this afternoon.

19 So then there's just the stabilization and
20 the idea of reasonably likely. And I think Dr. Katz
21 had mentioned that we really need to understand the
22 biomarker well, and we really need to understand the

1 disease well. And there are some particular
2 characteristics of FAP that seemed very mysterious,
3 like the difference in penetrance, and age of onset,
4 and clinical course that one sees in different regions
5 even though there's the same mutation.

6 So the division looked at the inherited
7 protection by the T119M variant, too. But it isn't
8 clear to us how comparable this kind of genetic
9 therapy, if you will, from conception is to treating
10 active disease. I mean, certainly, not only is an
11 ounce of prevention worth a pound of cure, but some
12 treatments that are preventative clearly don't do
13 anything to treat an active disease.

14 Finally, of course, there's countless
15 examples, as was mentioned before, of assays not
16 predicting clinical benefit. And then maybe it's
17 helpful to take a look at where we are with
18 stabilization versus where we'd like to be with
19 clinical symptoms.

20 I think, normally, the way the FDA thinks
21 about endpoints reasonably likely to predict clinical
22 benefit is effects that have changed. Here, it's

1 actually changes that are at the organ level or even at
2 the level of clinical signs. It doesn't mean that we
3 can only think that way; we just usually do. But even
4 before that, there's questions about something
5 happening at the cell level or at the tissue level, and
6 even what's going on with intermediates in the blood of
7 patients.

8 So we're really at the very earliest part,
9 something going on in a test tube, but we don't know.
10 We know almost nothing about what's going on in the
11 patient. So then there's some ideas about a path to
12 approval if more data is necessary. And let me first
13 say that the everybody in the division knows that
14 saying another study might be necessary means a lot of
15 difficulty. Ad I think we really tried to think of
16 everything before we bring up another study. But once
17 we do bring up the idea of another study, we really try
18 to figure out how it can be done.

19 So V30M patients -- which there are not a
20 lot; we understand that. One thing, though, is that
21 perhaps the knowledge from Study 005 might make it
22 possible to do a better study if another clinical study

1 was done. There are also patients from other endemic
2 regions, or there are not a lot of patients, but it's a
3 consideration there are patients.

4 Non-V30M patients, there's a hundred
5 different mutations. If all those patients respond the
6 same way to the drug, those patients could all be
7 studied, essentially just like the V30M patients.
8 There's also pre-symptomatic patients, which is an
9 interesting idea because there's no data available for
10 those patients. And yet, seemingly, with a treatment
11 like this, the first thing that you might think of is,
12 should we intervene earlier.

13 So that's definitely data that we would like
14 to have and, in a way, a new population or additional
15 population that could be studied.

16 Then familial amyloid cardiomyopathy was
17 mentioned before, and that is a closely related TTR
18 amyloid disease. And efficacy for FAP can be supported
19 by efficacy data from FAC if we decide that the two
20 diseases are similar enough. But that seems to be the
21 argument that's being made. We could discuss that, but
22 it seems perhaps reasonable. There's also age-related

1 TTR amyloid cardiomyopathy, which is not a mutant TTR,
2 but a wild type that causes an amyloid disease.

3 Now, these diseases are certainly under-
4 diagnosed, and I don't think that there's tens of
5 thousands of patients today diagnosed in the United
6 States with these conditions, but they're almost surely
7 there. So for example, 3 percent of the African-
8 American population carries a mutation that causes
9 familial amyloid cardiomyopathy.

10 As far as options for study design, A just
11 shows normal accrual of unexposed patients, but the FDA
12 is flexible about study designs. And the randomized
13 withdrawal design has the benefit that patients have
14 already been identified, minimizes the accrual time,
15 and patients can be withdrawn from the drug. And I
16 know that that's a concern.

17 But if done carefully, a very, very small
18 amount of change can be identified in patients. I
19 think that's the key. Nobody has the intention of
20 putting patients on placebo for years at a time and
21 doing nothing as they get worse. But through careful
22 study design, that kind of concern can be addressed.

1 There's some other options here, like high or
2 low dose, or low-dose response. And I think it gets
3 back to the efficacy that was seen from the 20
4 milligrams, in that while there's perhaps a sound
5 theoretical reason to say that the drug doesn't get any
6 better than this, it certainly seems like there's
7 reasons to try to look, to see if the drug can do any
8 better than this.

9 The adaptive design comes in because we think
10 that there is ways that those response studies can be
11 done. And while there's the concern that it takes too
12 many patients, we can try to enhance efficiency of such
13 studies through adaptive design.

14 This is the last slide. The box really
15 points out two things that we need, that the patients
16 need. They need evidence that drugs are effective, and
17 they need a minimal wait time for an effective
18 treatment. It really needs to be effective.

19 It was brought up before that there are
20 actually options that there are actually options that
21 could be discussed about expanded access, that is
22 giving tafamidis to some patients while other patients

1 are being studied. And in TTR diseases, there are some
2 seemingly natural populations that one might treat and
3 that one might study. So there are FAP patients with
4 the polyneuropathy and there's FAC patients with the
5 cardiomyopathy. And we don't have any information
6 available about efficacy in the cardiomyopathy patients
7 right now.

8 So one might think about allowing patients
9 with FAP to be treated with the drug while patients
10 with the cardiomyopathy were being studied. And then
11 the cardiomyopathy data, if the study was positive,
12 would very much support efficacy in the polyneuropathy
13 patients.

14 There's other possibilities, too, so I had
15 mentioned before there is a study that's been done on
16 symptomatic patients with FAP, but not on pre-
17 symptomatic patients, so it would be possible to treat
18 symptomatic patients, but tend to have a study with
19 pre-symptomatic patients. Anyways, there are different
20 ways it might be structured. And, of course, one
21 advantage of this is that we kind of minimize the wait
22 for drug and seemingly maximize our ability to show

1 that the drug is effective. Thank you.

2 DR. FOUNTAIN: Thank you. I think we have
3 time for some clarifying questions now, if we could
4 delay lunch for a few minutes, so let's start with Dr.
5 Preston.

6 DR. PRESTON: I have a very important
7 question. I think that if both of the primary outcomes
8 had shown statistical significance, this proceeding
9 today would be very easy, at least for me.

10 So my question has to do with the intention
11 to treat versus the efficacy evaluable. Intention to
12 treat is obviously extremely important to keep the
13 power of randomization.

14 However, I'm concerned that this particular
15 study is quite unusual because the people who dropped
16 out, they dropped out because of liver transplantation.
17 When I think about people leaving a study, I think
18 about, maybe they decided to move, or they decide to
19 quit, or there's a side effect of treatment, or they
20 decide they want to stop a treatment and do another
21 treatment.

22 But in the case of liver transplant, the

1 patient is given this one opportunity, which they have
2 to jump at. So here we are. I have this disease that
3 has no cure. And here, a liver is available for me,
4 and no one's not going to jump at it.

5 So the question is, normally, I would really
6 stick to the intention-to-treat analysis no matter
7 what, but the question for you is that, is this a time
8 where the efficacy evaluable analysis may actually be
9 more apropos?

10 DR. FARKAS: I think that would be a great
11 question for discussion, and I'm not going to go there
12 right now. But I think we should talk about that this
13 afternoon. I mean, I would say, I guess, that I think
14 there were some concerns that I outlined with other
15 aspects of the study. I understand the question, but
16 maybe we can postpone that.

17 DR. FOUNTAIN: That would be great.

18 Dr. Shefner?

19 DR. SHEFNER: This would be more of a
20 clarifying question for me because, in your
21 presentation, it leaves me confused. It seems like
22 you're proposing potentially contradictory pathways.

1 At the beginning, you very clearly laid out
2 what the criteria are for approval, either under part H
3 or under normal regulatory approval. And then in your
4 last two slides, you proposed ways where the drug could
5 be made available and studied in other populations.

6 It seems to me that those potentially are
7 inconsistent. If we're being given a clear set of
8 guidelines, which are actually legally mandated, then
9 are we then being encouraged to ignore those and
10 encourage other ways to make the drug available?

11 DR. FARKAS: Yes. I think I didn't clarify,
12 and it's really important to clarify that during the
13 development stage, prior to approval, there are
14 regulations that allow treatment of patients,
15 therapeutic treatment under an IND. So it's prior to
16 FDA approval. It would be prior to any kind of
17 approval, subpart H approval, full approval. So it
18 comes up in situations where you are conducting the
19 studies, you can still successfully conduct the studies
20 if you have patients available to do that, to find the
21 evidence you need.

22 Then there are patients who aren't in the

1 study for one reason or another. And if you can decide
2 that treating those patients won't interfere with the
3 gathering of necessary efficacy data, that can be done
4 under the regulations.

5 DR. SHEFNER: The second part of my question
6 about clarity is that, in some ways in your
7 presentation, you seem to be using nominal p value
8 strength to gauge how seriously to take a given result.

9 You pointed out one set of inconsistencies,
10 which are that the small fiber subscore seemed to reach
11 a higher level of significance than the large fiber
12 subscore. I just wanted to point out that there is one
13 higher level of inconsistency, which is that the NIS-LL
14 is primarily driven by strength, which is a purely
15 large fiber phenomenon.

16 So it seems to me that the primary outcome,
17 which is a large fiber score, shows potentially
18 significance. The subsequent secondary outcomes are
19 inconsistent in that the large fiber sum score is less
20 dramatically significant than small fiber.

21 DR. FARKAS: Right. Thanks for pointing that
22 out. Yes. We're concerned about that.

1 DR. FOUNTAIN: Just to clarify your first
2 question, was your first question actually, is it
3 possible to approve the drug given the statements made?

4 DR. SHEFNER: No. I think my question was,
5 how should we guide our discussion? I mean, if in fact
6 we conclude, based on the instructions of how drugs are
7 approved, that this is not a study that allows
8 approval, how is it intellectually logical to go
9 forward basically by approving a plan that allows not
10 just an IND-level access, but expanded access to
11 everyone with this disease while studying an entirely
12 separate disease.

13 DR. FOUNTAIN: I just want to clarify that,
14 if that is your question, it got answered adequately.

15 DR. FARKAS: I think it didn't probably, but
16 I think Dr. Katz can take another shot at it.

17 DR. KATZ: Yes. The rules are the rules.
18 They're flexible, as you've heard. But they have to
19 follow -- one or another of the standards, for example,
20 showing effectiveness, has to be demonstrated whether
21 it's a clinical, or a lab, or a surrogate.

22 But I think what Ron was presenting was sort

1 of various options. We're saying, if we're thinking
2 about subpart H, the surrogate approval, accelerated
3 approval, let's look at what are the potential
4 surrogates and what are the problems with those data.

5 If we think that you can't get to subpart H
6 and it can't be approved, here's a way to make the drug
7 available to some patients while it's still being
8 evaluated. So I think those were just different
9 options that we could possibly go with.

10 DR. FOUNTAIN: Dr. Cohen? Dr. Kramer?

11 DR. KRAMER: Yes. Maybe the agency could
12 clarify. There's a guidance on compassionate use or
13 that equivalence. What kinds of efficacy criteria are
14 usually implied by allowing compassionate use?

15 DR. FARKAS: Let me think. I don't have a
16 slide with that, but the expanded access regulations
17 were recently updated, whenever, a year or two ago. And
18 I believe it was with the intention of allowing more
19 use of drugs by patients who were not being studied,
20 while studies that were capable of showing efficacy
21 were ongoing.

22 So there's a paragraph that describes the

1 kind of evidence that you would need to start an
2 expanded access protocol. And it's, I think, fairly
3 liberal and we could, of course, look it up at lunch.
4 But it says something like, there's one positive study,
5 or one study that leans, or something else that makes
6 you think the drug might be effective. And so it
7 really goes down to the level of using judgment.

8 DR. KATZ: But they aren't approval
9 regulations. They're ways to make a drug that is still
10 investigational, that is not approved, that is being
11 evaluated to ultimately perhaps be approved, to make it
12 available to a wider group of people. It's not a way
13 to make it more available attached to an approval.

14 DR. KRAMER: Just to clarify, my reason for
15 asking that is, there still has to be some level of
16 evidence that the drug might work and so by
17 recommending that, you have to have some thought along
18 that line.

19 DR. FOUNTAIN: Dr. Clancy?

20 DR. CLANCY: I have a clarifying question for
21 Dr. Farkas. On your slide 7, you look at the outcome
22 adjusted for the baseline characteristics of the

1 patients.

2 DR. FARKAS: Right.

3 DR. CLANCY: My question is, was this
4 calculation performed on the intention to treat or the
5 efficacy evaluable population?

6 DR. FARKAS: I think this was on the ITT
7 population. Yes. And Dr. Luan is nodding yes.

8 DR. CLANCY: Was there a calculation on the
9 efficacy evaluable one?

10 DR. FARKAS: I'm just looking at Dr. Luan.

11 DR. LUAN: No. The p value is based on ITT
12 population and the p value under the efficacy evaluable
13 population, I did not perform.

14 DR. CLANCY: That might be worth knowing if
15 that's one of your concerns. And we're going to have a
16 later discussion about what is the appropriate
17 population to include in our analysis. It might be
18 worth knowing that.

19 DR. FARKAS: Sure.

20 DR. FOUNTAIN: Thank you. Dr. Chaudhry?

21 DR. CHAUDHRY: The same question Dr. Clancy
22 had.

1 DR. FOUNTAIN: Dr. Frank?

2 DR. FRANK: I just wanted to clarify
3 something that you had said regarding the co-primary
4 endpoints. When we're looking at co-primary endpoints,
5 does the total p value need to be less than .05 for it
6 to be considered positive or each of the individual co-
7 primary endpoints?

8 DR. FARKAS: It's each of the individual
9 endpoints, so both less than .05, both at the same time
10 less than .05.

11 DR. FOUNTAIN: Thank you. Maybe we could
12 take the remainder of the questions after lunch just so
13 we don't get so far behind.

14 DR. FARKAS: I shouldn't interrupt. I
15 shouldn't interrupt you, I suppose, but Dr. Unger had
16 something to say. And when he has something to say, I
17 think I need to listen.

18 DR. UNGER: I just want to clarify one thing
19 about that because it may not have been clear to
20 everyone in the room. But Dr. Farkas was talking about
21 multiplicity and the issues that that raises. But for
22 a co-primary endpoint, where you have to win on both

1 endpoints, that actually does not present a
2 multiplicity problem. It's quite the opposite. It's
3 more conservative. If you win on multiplicity is when
4 you take alternate analyses for any endpoint or the
5 secondary endpoints. Here, we have four of them.
6 That's a multiplicity problem. The co-primary is
7 actually the opposite. It's more conservative.

8 DR. FOUNTAIN: All right. So maybe we could
9 take the rest of the questions after lunch, so there is
10 time. It's 12:15 now. We'll now break for lunch.
11 We'll reconvene again in this room in 45 minutes from
12 now at
13 1:00.

14 Please take any personal belongings you may
15 want with you at this time. The room will be secured
16 by FDA staff during the lunch break. You will not be
17 allowed back into the room until we reconvene.

18 Panel members, please remember that there
19 should be no discussion of the meeting during lunch,
20 amongst yourselves, or with any other member of the
21 audience. Thank you.

22 (Whereupon, a lunch recess was taken.)

1 DR. FOUNTAIN: Welcome back to the meeting.
2 We'll begin the open public hearing momentarily. I'll
3 read a statement first.

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

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

16 For example, this financial information may
17 include the sponsor's payment of your travel, lodging,
18 or other expenses in connection with your attendance of
19 the meeting. Likewise, FDA encourages you, at the
20 beginning of your statement, to advise the committee if
21 you do not have any such financial relationships. But
22 if you choose not to address this issue of financial

1 relationships at the beginning of your statement, it
2 will not preclude you from speaking.

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

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

16 Each public speaker will be allowed three
17 minutes. The microphone will turn off after three
18 minutes in the effort of fairness. We really want to
19 hear from everyone.

20 The open public hearing, where people have
21 important things to say, is valued by the committee,
22 but we have quite a few speakers, so, unfortunately,

1 we're limited to three minutes. So after three
2 minutes, the microphone will turn off and we'll
3 progress to the next speaker.

4 Speaker 1, when you approach the microphone,
5 please be sure to tell us your name so we can
6 acknowledge you.

7 MS. DORMAN: Good afternoon. My name is
8 Diane Dorman. I am vice president for public policy
9 for the National Organization for Rare Disorders. I
10 have no personal financial relationship with Pfizer.
11 However, NORD has received an unrestricted educational
12 grant from the company.

13 I am here today not on behalf of Pfizer or
14 the product under consideration by this advisory
15 committee. Rather, I am here on behalf of the millions
16 of men, women, and children in the United States
17 affected by one of the 7,000 known rare diseases that,
18 in the aggregate, affect 1 in 10 people in the United
19 States.

20 Rare disease research in the development of
21 orphan therapies to treat them are unique in many
22 respects. Patient populations are generally very small

1 and geographically dispersed across the United States,
2 Europe, and Asia. And few researchers and
3 biopharmaceutical companies are willing to take on the
4 financial risk associated with this vital and often
5 life- saving work.

6 For those reasons and many more, NORD has
7 been dedicated to helping people with rare orphan
8 diseases and assist in the organizations that serve
9 them. We are the primary non-governmental
10 clearinghouse for information on rare disorders, and we
11 are committed to the identification, treatment, and
12 cure of rare disorders through programs of education,
13 efficacy, research, and service.

14 Today, there are nearly 400 orphan products
15 that treat an estimated 250 rare conditions. Given
16 that there are thousands more rare diseases without any
17 specific treatments, it is easy to understand that
18 there are millions of people who can only hope that,
19 one day, someone somewhere will take on the significant
20 risk to develop a therapy for their condition.

21 As you deliberate today, I ask only that you
22 keep in mind a few things. Number one, patients

1 affected by rare diseases are willing to take on a far
2 greater degree of risk than someone affected by a
3 disease that affects very wide populations.

4 Understanding the pathogenesis of rare
5 disease and the development of orphan
6 biopharmaceuticals to treat them will only increase the
7 medical community's understanding of diseases that
8 affect larger patient populations.

9 Number three, there are few treatment options
10 available, as I mentioned before, in the rare disease
11 world because orphan products are highly specialized
12 for very small patient populations.

13 Last, because product development is such a
14 challenge, there is little incentive for companies to
15 develop these products, nor is there much incentive for
16 researchers to conduct basic and translational
17 research.

18 In closing, I would like to share something a
19 patient advocate wrote to me a few days ago.

20 "Amyloidosis affects virtually every organ.
21 Any improvement anywhere is a miracle. Our patients
22 are literally dying, waiting for a drug. Perhaps,

1 please keep in mind that patients affected by TTR are
2 not statistics. A liver transplant should not be a
3 person's only option. And when it comes to risk
4 tolerance in the patient community, the final decision
5 should be made by patients, their families, and their
6 doctors." Thank you.

7 DR. FOUNTAIN: Thank you. Speaker 2?

8 MS. GIBSON: My name is Patricia Gibson. I
9 serve as the public policy liaison for the Amyloidosis
10 Support Groups. The Amyloidosis Support Groups have no
11 financial relationship with Pfizer. In the interests
12 of full disclosure, I did attend a patient advocate
13 advisory meeting at Pfizer last year.

14 In one sense, amyloidosis, being so rare, is
15 an orphan disease, but its full name is familial
16 amyloidosis. It is no orphan when it is carried in the
17 genes of your family, reaching back many unknown
18 generations and is being carried forward into your
19 children and your grandchildren.

20 Eleven years ago, I watched my husband die of
21 this disease, five years after a liver transplant.
22 Since then, I have been working to find a therapy that

1 will save my seven children, and my 15 grandchildren,
2 and families everywhere from the ravages of
3 amyloidosis.

4 Last October, Amyloidosis Support Group
5 gathered over 160 patients with dedicated expert
6 doctors for a two-day emergent session on familial
7 amyloidosis, what it is, what it does, what we can do
8 about it now, and what the future holds. We left with
9 hopeful spirits. A new drug was coming. Maybe there
10 was a chance after all.

11 We have before us this day the first
12 opportunity ever for a drug therapy to slow or perhaps
13 even stop the progression of this terrible disease.
14 Yes. Liver transplants stop most of the production of
15 the mutant protein. But while you wait for months or
16 years, the amyloid keeps invading your nerves in your
17 GI tract and your kidneys. Soon, you may need a heart
18 transplant. And you know that neither transplant will
19 reverse the ongoing damage that is building as you
20 wait.

21 Today, we have listened to the analysis of
22 the tafamidis study. There is a question whether the

1 testing met its mark. In the deep interests of the
2 patients, I ask you to consider that this strategy of
3 the developers of the drug was to stabilize the TTR by
4 preventing the misfolding of the protein.

5 The test of the efficacy of the drug was to
6 prove improvement in peripheral neuropathy. A number
7 of the subjects achieved a slowing progression in the
8 symptoms of the neuropathy. The efficacy was proved.
9 TTR stabilization was not the endpoint in this study,
10 but is the overriding implicit goal of any drug for
11 amyloidosis.

12 We have no time. The patients sitting before
13 you have no time to wait. Even now, their amyloid is
14 building. Our children have no time. It makes little
15 sense to deprive them of a safe drug that may slow down
16 the infiltration and allow them to live normally.

17 I urge you to utilize your flexibility and
18 approve tafamidis.

19 DR. FOUNTAIN: Thank you. Public speaker
20 number
21 3?

22 MR. CLARK: My name is Mike Clark. I live in

1 Fairfax County in Northern Virginia and have no
2 affiliation with parties involved in this decision.

3 In February of 2009, my mother passed away
4 from malabsorption, a direct complication of FAP, as
5 amyloid deposits had so invaded her GI tract as to
6 render it inoperative, causing her to literally starve
7 to death.

8 Her symptoms started some 70 years prior,
9 with alternating constipation and diarrhea, tingling,
10 and numbness that started in her toes, worked up her
11 legs, and carpal-tunnel operations in each hand. After
12 a long story of time wasted with misdiagnosis and
13 incorrect treatments, she was finally diagnosed in
14 September of 2008 with FAP, caused by the T60A mutation
15 of the TTR protein.

16 She passed away within five months of the
17 diagnosis. Within two months after my mother's demise,
18 I too started having GI symptoms. A DNA screening in
19 July of 2009 showed I had inherited the same mutancy.
20 In fact, three out of four of my siblings have been
21 screened, and all three are positive carriers of the
22 same mutation, meaning there is high probability each

1 will contract FAP or may have it already. Gratefully,
2 I have not passed this onto my two daughters. However,
3 my oldest sister did indeed pass it onto her oldest
4 child.

5 This is a disease that wreaks havoc with
6 entire families. Even though I knew the cause of my
7 symptoms, it took until November of 2010 to receive a
8 biopsy that confirmed I was indeed depositing amyloids
9 in my GI tract, but a year had gone by.

10 The Boston amyloid treatment and research
11 program confirmed the condition, and on April 12th,
12 2011, I was placed in the Georgetown University
13 Hospital liver transplant waiting list. I have
14 received that surgery as of February 24th of this year.
15 And this is the message I would like the committee to
16 remember from this presentation.

17 The only tool in the toolbox to fight FAP is
18 the blunt hammer of liver transplant. And it is a
19 mediocre solution at best. Its efficacy is highly
20 dependent on a number of factors, the largest one being
21 how early in the disease progression you can have it
22 done.

1 It comes with its own significant risks. It
2 does not cure or reverse the disease, as its only
3 positive influence is to possibly stop or slow amyloid
4 deposition. It is life-changing, as you will be on
5 immunosuppressive drugs for the rest of your life, and
6 it is expensive.

7 We need other options. Tafamidis is the
8 first drug to reach the market specifically aimed at
9 ATTR. And although there is disagreement over the
10 statistical significance of the study's co-primary
11 endpoints, it has been shown to be positive and
12 resulting in stabilizing the TTR protein, as well as
13 other factors.

14 It needs to be put in the hands of the
15 specialists on the front lines of the disease to treat,
16 study, and find out how best to utilize as a tool to
17 fight this protein-folding disease. I urge the
18 committee to recommend approval of the NDA so that it
19 may be an option when my siblings and niece contract
20 this disease. Thank you for your time and attention.

21 DR. FOUNTAIN: Thank you. Public speaker
22 number 4?

1 MS. KLINE: My name is Jorja Kline and I have
2 no affiliation with anyone here or the companies of any
3 kind. I am here as an advocate and a caregiver.

4 My husband, Gary, was diagnosed with familial
5 amyloid in January of 2007. He participated in
6 clinical trials for Diflunos Boston Medical Center.
7 After six months of being in the trial, he was examined
8 at Lahey Clinical Medical Center in Burlington,
9 Massachusetts, placed on the transplant list for a
10 liver in September of 2007. As he waited for his
11 transplant, his amyloid symptoms continued to worsen.
12 The pain in his hands became so unbearable that he was
13 placed on Cymbalta, Lyrica, and morphine sulfate all at
14 the same time for the intense pain. His ability to
15 walk began to decline. He began to lose feelings in
16 his hands and feet.

17 Finally, after 20 months from being diagnosed
18 -- actually, 20 months from waiting, and 29 months
19 after being diagnosed, May 22nd, 2009, he finally
20 received a liver transplant. He had to stop all pain
21 medications once he received his liver and had to go on
22 an anti-rejection meds. He went through terrible

1 withdrawal symptoms, such as inability to sleep for
2 several days, inability to eat, extreme restlessness,
3 continued pain in his hands and feet.

4 His recovery did go well after that. He was
5 away from work for 13 months. He was cleared to
6 return. However, his position as a mechanic proved to
7 be too much for him and he had to go out on disability.
8 He was unable to stand on his feet for more than 10
9 minutes at one time. And the neuropathy in his fingers
10 prevented him from doing any of the detailed work he
11 needed to do as a mechanic.

12 By the end of the day, he was so worn out he
13 could barely even walk to his car. His condition and
14 the quality of his life were fast declining and over
15 such a short period of time since the transplant.

16 At the end of September, he went out of work
17 on total disability. And by the end of December, he
18 had declined in such a depression that he was sleeping
19 20 to 21 hours a day. He lost 30 pounds in three short
20 months and had gone down to 130 pounds. He finally
21 started getting some treatment in March of 2011 for
22 both his physical and his mental well-being. However,

1 during this time, the amyloid did continue to worsen.

2 Today marks the three-year, two-day
3 anniversary of his transplant. He can no longer stand
4 for any more than three to five minutes. And he can
5 walk no further than perhaps 100 yards. The neuropathy
6 in his hands and feet continues to progress. Some
7 evenings, he has to use Lidoderm pain patches on his
8 hands and his feet to even get sleep. At our house, a
9 good day is when he doesn't fall down more than twice.
10 He has difficulty buttoning his pants and his shirts.
11 His handwriting has become illegible.

12 A drug as tafamidis shows great promise in
13 improving his neuropathy. And tafamidis can offer
14 relief of pain that comes with this, allow for a more
15 active life, and give the patient the overall hope of a
16 higher quality and longer life. But in the bigger
17 picture, you also have to consider those who may still
18 be coming behind us. Within our family, there are 49
19 potential people who could develop this disease. A
20 drug that could treat this and keep the terrible
21 effects from developing would be a godsend for
22 everyone.

1 I ask that you please approve tafamidis.

2 Thank you.

3 DR. FOUNTAIN: Thank you. Public speaker

4 number

5 5?

6 MS. CAMERON: My name is Ellen Cameron, and I
7 have familial amyloidosis, variant ASP18GLU. My
8 familial amyloidosis caused me to have a heart, liver,
9 and kidney transplant back on December 15th, 2005. I
10 have watched my mother, all her brothers and sisters,
11 and my own sister die of this disease. I've seen
12 cousins die while others are waiting for transplant.

13 I've been one of the lucky ones. Diagnosed,
14 treated, and transplanted by the Mayo Clinic, I was
15 able to move to Rochester, Minnesota with my husband
16 and wait for someone to die to donate their organs.

17 I would guess many transplant recipients have
18 had their faiths tested. I know mine was. I didn't
19 know whether or not I would see my children marry or
20 have children of their own. I worry about passing this
21 disease onto them.

22 My variant of amyloid strikes every organ it

1 can. Since my transplants, I have had five eye
2 operations. I have severe gastric problems. I have
3 tumors in my lungs that makes breathing hard. The
4 neuropathy has caused me piercing pains, any part of my
5 body, without warning. God allowed me to have a new
6 heart, liver, and kidney and they work great. And this
7 is a gift. With this gift, I still have life.

8 I tell you these things and other things not
9 from ingratitude, not to complain, but to state the
10 facts. On days when the vertigo is bad and getting out
11 of the bed is difficult, my walking is done with the
12 help of a walker or a scooter. I could walk, but I
13 cannot walk straight. And sometimes, people fear that
14 I fall. Sometimes, I do. But I do the best I can,
15 pushing myself so that I do not lose what I already
16 have.

17 The gastro problems have caused me to wear
18 diapers all the time. It is a very humbling
19 experience, but if you want to get out of the house, I
20 must do what is necessary. This is a disease of
21 coping, cope with fear that this will happen to my
22 children, coping with what I must do to adjust my life.

1 Another option to organ transplant would help. Not all
2 people are as strong as me or as lucky to have the
3 family support that I have.

4 I look forward to the development of treating
5 this disease. I look at each of my four children and
6 my five grandchildren and cannot help to wonder whether
7 they will end up with this terrible disease. My prayer
8 focuses on protection for my family and a dream that we
9 will never have the experience similar to mine. Thank
10 you and have a good day.

11 DR. FOUNTAIN: Thank you. Next is public
12 speaker number 6.

13 MS. O'BRIEN: Hi. My name is Geri O'Brien,
14 and about a year and a half ago, my family started to
15 be diagnosed with amyloidosis. My husband and two of
16 his siblings have amyloidosis. We have gone from
17 doctor to doctor. We've had great care. And about a
18 year and a half ago, they started telling us that
19 tafamidis would be available to us, and just wait, and
20 hold on. So we were very hopeful.

21 About three or four months ago, they said to
22 us that that was really all they had to offer us, which

1 was nothing. And the doctors continued to tell us that
2 the lifespan is 10 years with treatment. Well, we're
3 sitting here with no treatment. We have nothing, but
4 yet we know that it's out there and we know that
5 there's something that can help us.

6 So I asked one of the senator's offices to
7 help me and he gave me the IND to give to my doctor,
8 which I gave to my doctor. And my doctor said it was
9 too cumbersome to fill out. It needed a review board.
10 It needed to go through the hospital. And it was just
11 too difficult and he couldn't do it. So then I called
12 other people, and they said that the compassionate use
13 was not going to be available to us.

14 So at this point, I'm asking for
15 compassionate use for my brother-in-law, who is unable
16 to be here, for my sister-in-law, who is unable to be
17 here, and my husband, who is here and will talk.

18 So thank you very much.

19 MR. O'BRIEN: Thank you. I just want to add,
20 I'm Bob O'Brien from Long Island, New York. We don't
21 have any affiliation with Pfizer, or any of the
22 committee, or any of that.

1 I have seven siblings. Three of us have
2 tested positive and have the disease. Two have come up
3 negative, and two have not been tested. My brother,
4 Joe, can't ride a subway or a bus anymore. He's pretty
5 much confined to his apartment, needs help dressing. My
6 sister, Marianne, falls down a lot and is in continual
7 pain.

8 I'm pretty good. I can still work and was
9 able to get here today. And I was unable to sit here
10 this morning, but if the big objection is the
11 population in the test, I can fill up a study of Irish
12 Catholics from my hometown pretty readily.

13 I want to thank my Drs. Gorvic, Callman,
14 Mauer, Archer, Papp. They've given us hope. And we
15 see a lot of hope in this drug. If I'm on the
16 committee, as a layperson, I'm asking myself, "What
17 happens if we do approve it? What happens if we don't
18 approve it?"

19 If we do approve it, a lot of people will be
20 helped and nobody will be hurt. If we don't approve
21 it, nobody will be helped. Research will be stymied
22 and our last weapon of hope really disappears for

1 another 10 years.

2 So thanks for the opportunity. Godspeed.

3 DR. FOUNTAIN: Thank you. Next is Robert
4 O'Brien. I'm sorry, public speaker number 7.

5 MR. O'BRIEN: Hi, how are you? I'm Bobby
6 O'Brien. Those are my parents. First, I'm going to
7 speak. My aunt from Scranton wrote a little letter and
8 I am going to speak on her behalf. She wrote the
9 following.

10 "Some of us were cruelly disappointed by the
11 announcement just two days before this hearing, that
12 the FDA's own staff was recommending tafamidis be
13 rejected.

14 "As laymen and women, we do not know whether
15 such announcements are normally made just prior to
16 public consideration of new medicines, and we sincerely
17 hope politics played no part in upstaging this hearing.

18 "All we can do is rely on your goodwill and
19 your best judgment, and true interests in what we, not
20 researchers, but the patients and their families have
21 to tell you.

22 "We understand that tafamidis is not a silver

1 bullet. We know it will not help all of us or perhaps
2 even most of us. But research on this drug has been
3 one of the very few points of hope for us over the past
4 years.

5 "It is already being prescribed in Europe,
6 which also has strict standards for this distribution
7 of drugs. When a new cancer drug is developed that can
8 hold off death by even just two to four months, it is
9 approved and heralded as another weapon in medicine's
10 arsenal against that terrible disease.

11 "Are those few months of a quality of life
12 worth less for the victims of this disease? They do
13 not number in the hundreds of thousands or even tens of
14 thousands, of course. But the suffering of our
15 husbands, and wives, and sisters, and brothers, and
16 parents is just as real. And their disease is also
17 painful, and emotionally crushing.

18 "And finally, fatal. If this drug helps only
19 the smallest fraction of our loved ones, it will be
20 more than worth it to all of us. It will encourage
21 continued research and keep us hoping for something
22 better, not perfect, not even almost perfect, but

1 something better the next time around.

2 "Remember, there are limited effects to this
3 drug, limited side effects to this drug. It won't harm
4 anyone. Please approve tafamidis, even just for the
5 next few years, so we can try it. Please give us this
6 chance.

7 "Please don't remove one of the first rays of
8 hope we've had in decades. If it doesn't work, God
9 knows we will know that soon enough."

10 On another note, I spoke with my aunt,
11 Marianne, two nights ago, who is inflicted with
12 amyloidosis. And the two points she conveyed to me was
13 discouragement. She's been battling this disease for
14 years now and she's extremely discouraged and has lost
15 hope. But this drug has reinstated that hope, and her
16 primary worry is her children.

17 Now, on that note, I love them very much, but
18 I am not here on behalf of my aunts, uncles, and
19 parents. I'm here on behalf of my 19 cousins and we
20 feel that this drug will hopefully increase that
21 research, and increase that push, and hopefully help us
22 as well as our children and our great-grandchildren.

1 Thank you very much.

2 DR. FOUNTAIN: Thank you. Next is public
3 speaker number 8.

4 MR. GOLDSTEIN: My name is Arnold Goldstein.
5 I am 80 years of age, and I have no affiliation or
6 financial interest in Pfizer.

7 In 1994, I was diagnosed with atrial
8 fibrillation. And then in 2000, I had a congestive
9 heart failure. And between 2000 and 2003, I had stents
10 and a Pacemaker.

11 In 2007, I was biopsied and diagnosed with
12 wild- type transthyretin amyloid cardiomyopathy, the
13 familial type, senile type. In 2008, I was fortunate
14 enough to enter the New York Presbyterian FoldRX test
15 program for tafamidis meglumine, FX1006A, overseen by
16 Dr. Matt Maurer. Between 1994 and 2007, I had two
17 carpal tunnels, several trigger fingers, which I'm told
18 is not unusual with people who have amyloidosis.

19 However, since taking tafamidis, I've had no
20 further trigger finger symptoms, nor atrial
21 fibrillation, or heart failure. In addition to
22 tafamidis, I'm taking a number of other drugs, the

1 usual roster, eplerenone, amiodarone, aspirin,
2 simvastatin, ramipril.

3 For the past four years, I've been
4 experiencing significant sensations of pins and needles
5 in both feet. I have been informed that this is not
6 unusual for people with amyloidosis. It is my
7 understanding that the disease gets progressively worse
8 as time goes on and, if left untreated, could prove to
9 be fatal. I am not aware of the statistics, but I'm
10 told that without tafamidis, I probably would not have
11 survived the last five years.

12 While it is stressful climbing stairs or
13 hills or sleeping with only one pillow, I'm able to
14 live a normal life. I go to work four days a week, do
15 mild exercise. I'm able to socialize with friends and
16 family. I therefore believe that tafamidis, while not
17 curing the disease, has most probably restricted the
18 disease's progress.

19 In closing, I would like to thank Dr. Kelly
20 for the work he has done in developing tafamidis and
21 its continuing work in combating this terrible disease.
22 Thank you.

1 DR. FOUNTAIN: Thank you. Next is public
2 speaker number 9.

3 MR. MUI: Hi. My name is Kevin Mui. I'd
4 like to thank the committee for the opportunity today
5 to share my family's history and my experience with
6 familial amyloidosis.

7 It began with my mom, Sue Mui, when she was
8 40 years old. At that time, we didn't know much about
9 amyloidosis and there were no treatments available for
10 her. She suffered for six years and we lost her at the
11 age of 47.

12 Later, her brother, Ed Young, was diagnosed.
13 It was then we learned that liver transplant could be a
14 cure. He underwent the liver transplant, but the
15 disease progressed. He survived 10 years and we lost
16 him at age
17 45.

18 Then again, my brother, John, was diagnosed
19 at age 35. We thought, if we were proactive in getting
20 him a liver transplant earlier, while he was younger
21 and stronger and before the symptoms really set in,
22 that would stop the disease. But again, although the

1 transplant was a success, unfortunately, his symptoms
2 overall did not improve. Neurosymptoms developed and
3 continue to challenge him today.

4 I was diagnosed at the age of 31 three years
5 ago with ALA 71. Knowing my family's history, I did
6 everything I could do to build up my body stronger to
7 help defend myself against this disease, but I was
8 surprised how quickly symptoms develop and how
9 debilitating it can be.

10 The first year after diagnosis, I lost 80
11 pounds due to severe diarrhea and loss of appetite. I
12 suffer from bouts of dizziness, numbness in my feet,
13 legs, and hands. With my energy zapped and severe
14 muscle loss, I can no longer perform the physical
15 activities I once loved and eventually had to leave my
16 job, as I could no longer manage the demands of my
17 career and be a full-time patient juggling these
18 symptoms.

19 Today, I am 34 years old. Performing daily
20 activities and simple tasks like climbing stairs,
21 getting showered, or even dressed is becoming a
22 challenge. I am getting weaker and more limited,

1 despite my ongoing efforts with physical therapy and
2 even seeking alternative medicine like acupuncture.

3 This disease doesn't just cause physical
4 pain. It also destroys many of my hopes and dreams. I
5 am losing control over the basic things in life. How
6 can I plan for any future? I wonder if I can still
7 pursue my dreams, return to work, or maybe have a
8 family of my own one day.

9 I am here today to ask you to support the
10 approval of tafamidis. Time is not on my side, but I
11 am hopeful that this new drug, even if it's not perfect
12 today, can help keep me and many others coping with
13 familial amyloidosis alive while scientists, doctors,
14 and patients work together to gain a better
15 understanding of this drug's effectiveness, not only
16 through treating peripheral neuropathy, but also
17 understand its effects on other crippling symptoms that
18 affect our heart, our eyes, the autonomic nervous
19 system, and more.

20 Again, please approve tafamidis today. We
21 are in desperate need of a miracle. Thank you.

22 DR. FOUNTAIN: Thank you. Public speaker

1 number

2 10?

3 MR. SUHR: Good afternoon. My name is Dean
4 Suhr. I am humbled by all of the prior speakers who
5 are directly affected by this disease. I have no
6 financial interests to disclose. However, I am a rare
7 disease dad. I have metachromatic leukodystrophy in my
8 family, not even related to this, a much more rare
9 disease. I'm president and co-founder of the MLD
10 Foundation and I'm chairman of the patient advocacy
11 advisory board for the Rare Project, representing the 1
12 in 10 Americans with rare diseases.

13 We've heard about this disease today, and we
14 know that it's devastating. It affects about 2500
15 people in the United States. Only 350 of those people
16 apparently had been identified. There are a lot of
17 patients in this country that need the services here.

18 But there seem to be two criterion in play.
19 One is primum non nocere, do no harm. That's the
20 foundation of the work that the FDA does. That's the
21 reason that you all sit, and deliberate, and work
22 through all of this. And the second is the facts.

1 The facts that we do know in this disease is
2 that death, which is 100 percent mortality, is 10 to 15
3 years without therapy. And we have heard about the
4 liver transplants. The mortality on that is 10 percent
5 right out the gate for a liver transplant, and goes up
6 to 30 percent for a 10-year lifespan, and even higher
7 when you have the cardiac involvement. Of course,
8 there are inconveniences with immunosuppressants and
9 those sorts of things.

10 So the alternative with this disease is
11 devastating. Today, we're using statistics to decide
12 the safety and efficacy of this drug, and that's how
13 all of your regulations and all of your rules are put
14 together. But that's interesting is what's driving the
15 statistics. As we've heard in the conversations, and
16 the questions this morning, and I imagine we'll hear
17 this afternoon, it's not the statistics that are the
18 issue. It's the assumptions on the facts. Did those
19 people leave the program because of something unusual
20 related to liver transplants? It's group A, group B,
21 what country, and so on, and so forth.

22 So the facts themselves -- as Mark Twain

1 says, "The facts are stubborn, but the statistics are
2 much more pliable." We can work these statistics to be
3 within the regulations by not adjusting the facts, but
4 by how we choose to interpret the facts.

5 We've heard a lot about the studies here. The
6 real question is, is the 005 study indicative and does
7 the 006 study add onto it or not? And you all need to
8 work through that. You're much more intimate with
9 that.

10 But what the sponsor has asked for today is
11 to be able to participate in the accelerated approval
12 of subpart H, which does require your ongoing
13 supervision. So while families could get therapies and
14 treatments, you would be able to supervise that through
15 ongoing trials, which the sponsor has acknowledged that
16 they would certainly accommodate.

17 Rare diseases do not ask for nor do we
18 deserve a pass on all the rules and regulations. But
19 the reality is that the risk-benefit tolerance for the
20 families with these diseases, kids, relatives, spouses
21 all dying, our risk tolerance is much higher.

22 There was a full-day session on this at the

1 FDA last Friday, talking about this particular issue.
2 The diversity in those studies is very difficult to do
3 as rare diseases because the patient populations are
4 small and you need to take that into consideration.

5 So I ask that you do no harm and that you
6 consider approval of this and the ongoing monitoring
7 with subpart H. Thank you.

8 DR. FOUNTAIN: Thank you. Next is public
9 speaker number 11.

10 MR. MCGARRY: Good afternoon. My name is
11 Martin McGarry. I stand here before you, representing
12 five siblings, four children, five grandchildren, 26
13 nieces and nephews, 42 nieces and nephews, grandnieces
14 and nephews, many cousins in the United States,
15 Ireland, England, and the memory of my mother, two
16 brothers, an uncle, and a cousin who have passed away
17 from amyloidosis as a result, as all of those who are
18 or who have been affected by this disease as well.

19 I was born in County Mayo, Ireland, the
20 youngest of eight children. I came to Chicago in
21 September of 1969, when I was 18 years old. I worked
22 in the construction field. I am a former professional

1 amateur boxer, boxing in England, Ireland, and the
2 United States.

3 In 1976, I married my wife, Kathleen. We had
4 four children within the next 10 years. I was a very
5 active parent, helping coach my kids in various sports.
6 My two oldest brothers, John in Chicago and Pat in
7 England, and my mother in Ireland all became ill at
8 about the same time, the early 1990s. They had chronic
9 diarrhea, were losing weight, and had neuropathy in
10 their legs, affecting their mobility.

11 After a few years of surfing, John was
12 diagnosed with amyloidosis in 1998. He had a heart and
13 liver transplant at Mayo Clinic in 1999, but the
14 disease had done a great deal of damage to his body,
15 and he died after three years, in 2002.

16 My brother, Pat, was diagnosed at about the
17 same time and had a liver transplant in London. He
18 also lived for three more years and died in 2003.

19 My mother died in 2002 of the suffering with
20 neuropathy and for many years as a result of
21 amyloidosis. Her older brother died of the disease
22 about 10 years before her.

1 I have first cousins with amyloidosis in
2 County Mayo, Ireland. One died a year ago. His two
3 brothers have been diagnosed recently. This past
4 summer, I started to lose weight. My legs started to
5 get tired after jogging a short distance. I have
6 always been physically active. I work out regularly.
7 I'm a certified amateur boxing coach and trainer. I
8 coach boxers. I spend a great deal of time working
9 with young men and women, helping to develop their
10 boxing skills.

11 Knowing the health history of my family, I
12 suspected that this might be the beginning of this
13 terrible disease in my body. I found out about an
14 amyloidosis conference last October. We went to find
15 out more about the disease. We learned a lot about
16 amyloidosis and the latest research for a cure. My
17 blood was tested and I found I was positive for ALA 60.
18 I also had a fat tissue biopsy that tested positive for
19 amyloidosis.

20 I went to Mayo Clinic for more extensive
21 tests. I was given three options, do nothing and hope
22 for the best, have a liver transplant, or wait for a

1 medication that may come on the market.

2 My first option would be for the medication.

3 None of my brothers had good luck with their

4 transplants and I can't sit around without doing

5 anything, knowing that there is research being done

6 now, working to find a cure.

7 As of now, I have neuropathy in my legs. My

8 energy level is diminished. I feel that, if there is a

9 drug to control amyloidosis, I will travel anywhere to

10 obtain it.

11 Time is of the essence for me, my family, and

12 everyone who is affected by this disease. Thank you.

13 DR. FOUNTAIN: Thank you. Public speaker

14 number 12? Public speaker number 12?

15 (No response.)

16 DR. FOUNTAIN: How about public speaker

17 number

18 13?

19 (No response.)

20 DR. FOUNTAIN: Public speaker number 14?

21 MS. PIRES: Good afternoon. I am Natacha

22 Pires with the Neuropathy Association. I have no

1 financial relationship with Pfizer. Pfizer has and
2 does provide grant support for the association's
3 programs.

4 I want to thank everyone here for recognizing
5 the challenges of the 20 million Americans whose lives
6 have been devastated by a neuropathy diagnosis and
7 particularly by transthyretin familial amyloid
8 polyneuropathy, or FAP. FAP is a progressive and fatal
9 form of neuropathy, affecting approximately 2500
10 patients in the U.S. For them, no pharmacological
11 therapies exist. FAP is caused by mutations of the TTR
12 gene, causing buildup of abnormal protein in the
13 peripheral nerves, as well as other organs.

14 For most patients, the first symptoms occur
15 during the third or fourth decade. Typically, patients
16 present with sensory motor neuropathy. They also
17 develop autonomic neuropathy, impacting vital body
18 functions, including blood pressure, heart rate, bowel
19 and bladder emptying. Over time, the gastrointestinal
20 involvement results in weight loss, loss of muscle
21 mass, physical wasting, and ultimately leading to
22 death.

1 Currently, FAP patients in the U.S. have only
2 one interventional therapy, liver transplant. A liver
3 transplant removes the abnormal protein from the
4 circulation and stops amyloid deposition.

5 Patients who are fortunate enough to receive
6 a transplant also face significant transplant-related
7 morbidity and mortality. Without a transplant, FAP is
8 fatal. It's a death sentence, usually within a decade,
9 unless these patients move to Europe where tafamidis is
10 an approved therapy.

11 All the more reason to consider the potential
12 benefits of indicating tafamidis for FAP, this gives
13 physicians one more tool to help patients, and it gives
14 patients access to a life-saving therapy that addresses
15 the underlying neuropathy.

16 With 20 million Americans living with over
17 100 types of neuropathy, 6 million with chronic
18 neuropathic pain, our community is underserved. We
19 have only seven FDA-indicated therapies, one for CIDP,
20 and the remainder for diabetic neuropathy, and post-
21 herpetic neuralgia. This helps about a third of our
22 patients, which begs the question, what are the other

1 two-thirds supposed to do? What are the 25 patients
2 with FAP supposed to do?

3 Thanks to the tireless efforts of researchers
4 and advocates alike, we continue to discover new
5 therapies with potential to give our patients a
6 fighting chance. This meeting recognizes the
7 significant unmet needs of people with FAP and our
8 broader neuropathy community. Please consider the
9 possibilities as you review the data presented today.
10 Thank you.

11 DR. FOUNTAIN: Thank you. Next is public
12 speaker number 15.

13 MR. (b) (6): Thank you, Mr. Chairman and
14 members of the committee. I appreciate very much your
15 willingness to listen to me and the other sufferers
16 from this disease.

17 DR. FOUNTAIN: Excuse me. Can I ask you to
18 state your name? I'm sorry to interrupt you, but if
19 you could, state your name before you begin.

20 MR. (b) (6) I'm so sorry. I'm (b) (6).
21 I'm number 15. I appreciate very much your willingness
22 to listen to the patients in addition to the medical

1 and pharmaceutical experts. And thank you for that.

2 I did figure out this morning that QOL must
3 mean quality of life, and mine is going downhill. I
4 used to be a runner and now just walking is sometimes
5 difficult. But when I really jumped was when Dr. Coelho
6 this morning referred to this problem as calling
7 "severe progression invariably leading to fatal
8 outcomes." And that's not statistics. That's me
9 dying. I just can't stress enough how I know you all
10 know it, but how important this is to those of us who
11 have this problem.

12 Without a pharmaceutical solution, I have
13 either a transplant or I have death. And I'm being
14 treated at two of the top amyloid centers in America,
15 and they both agree on that.

16 We have a drug here that's been extensively
17 tested in Europe and it's been approved by presumably
18 knowledgeable people in Europe. And my hope is that,
19 that accounts for a lot. I'm sure Dr. Farkas is right,
20 that there are statistical issues that ought to be
21 sorted out, but my hope is that we can begin to use the
22 solution that the Europeans have identified, including

1 the last six months apparently of very small side
2 effects in Europe.

3 If this drug had just popped out of Pfizer's
4 lab, I wouldn't be here today. It would be a waste of
5 time. But here, the testing and the background, it
6 seems to me, puts it in quite a different perspective
7 from the point of view of approval or at least some
8 kind of a partial approval.

9 So my purpose in being here today is to ask
10 you to help the thousands of people who suffer from
11 this and related amyloid problems by some kind of an
12 approval so that we can begin to move ahead on some
13 sort of a high- speed track.

14 I don't know all the rules of section H and
15 this sort of thing, but to begin using it in America,
16 and then benefitting from the testing that's already
17 been done, and benefitting from the testing that would
18 be done as we move ahead.

19 A liver transplant or dying is a terrible
20 option for me. I was very impressed as I came in to
21 see the poster that you have up of the FDA's efforts on
22 orphan diseases. And I just think it's wonderful that

1 you're focusing on that. And I commend you and I hope
2 that you will help with this one, too.

3 Thank you very much for your consideration of
4 all of us and I appreciate it.

5 DR. FOUNTAIN: Thank you. Next is public
6 speaker number 16.

7 MS. PRETE: My name is Kristin Prete. I have
8 no affiliation with Pfizer. I am here today in honor
9 of my father, Anthony, whose life was claimed by FAP
10 exactly one year ago tomorrow after enduring a decade
11 of anguish and agony.

12 After years of misdiagnoses, unnecessary
13 surgeries, and treatments, he was finally diagnosed in
14 2006. Dr. Skinner at Boston claimed he was one of the
15 most severe cases she had seen. Despite already six to
16 eight years into the disease, a liver transplant in
17 2007 was his only option. He only waited five days on
18 the transplant list, luckily, but he sustained
19 significant complications and the disease continued to
20 progress.

21 My dad suffered almost all of the known
22 symptoms of Met 30 FAP before dying, many of which have

1 been mentioned today. Paralyzed and bed-bound, he
2 suffered syncope episodes, required a Pacemaker, a
3 fully catheter, a feeding tube. He had vitreous
4 opacities and double vision. He lost well over 100
5 pounds in just a few years, and had multiple
6 hospitalizations, and unbearable pain.

7 He mourned at the loss of his hands the most.
8 He often quipped that he would cut off his legs if it
9 meant getting his hands back. He was a writer, a
10 Biblical scholar, and a teacher, and spent most of his
11 days at the computer. His voice-activated speech
12 recognition program rarely worked well and as his voice
13 began to weaken, it caused frustrating problems.

14 He was locked out of the outside world,
15 unable to e-mail or read the news. He was unable to
16 hold a book, or a newspaper, or a magazine. He was
17 unable to operate a remote control. He needed someone
18 with him all the time.

19 The most unbearable part of this was the
20 emotional pain. Psychologically, he was just as broken
21 as his body. He had lost everything, his body, mind,
22 spirit, independence, all he enjoyed, and even his

1 faith in God after dedicating a lifetime to God. It
2 had also exhausted my mother and all of our family's
3 finances.

4 Make no mistake, this disease is wretched and
5 far-reaching. Exacerbating his mental anguish was
6 finding out that his brother and sister, his only
7 siblings, were also diagnosed, his brother already
8 developing symptoms. His cousin was diagnosed. And
9 then finally his only biological child, me, was also
10 diagnosed.

11 This is a disease that wipes out families, as
12 you have heard from many who have testified today. I
13 am a grieving daughter and a fearful victim. I am a
14 mutant, but I have no special powers like in the
15 movies. My only power being exerted here today is my
16 attempt to persuade you to pave the way to save my
17 life, to save my family, and to fight for all who
18 suffer, who have few or no options to avoid the
19 horrific fate my father faced, so that his death not be
20 in vain.

21 Any treatment is better than a transplant in
22 my opinion. I know this is not a panacea, but it is

1 safe, and it brings hope and help to those who cannot
2 wait, and will pave the way for future therapeutics and
3 hopefully a cure.

4 We are on the precipice of minimizing, if not
5 ending, intolerable suffering for thousands. While you
6 all are not mutants, you too have special powers and
7 can be heroes. All you have to do is open the door.
8 Thank you.

9 DR. FOUNTAIN: Thank you. Next is public
10 speaker number 17.

11 MR. ROBINSON: Hi. My name is Darren
12 Robinson. I am not affiliated with Pfizer or anything.
13 I am here on behalf of my uncle. He's just recently
14 been diagnosed with amyloid TTR, and he's suffering at
15 this moment. He's not a candidate for a transplant, but
16 I only recently found out about this a few days ago and
17 he's only been diagnosed a month ago.

18 So I'm here on behalf of my uncle to state to
19 everyone here that the opportunity that you have in
20 front of you, as we've heard and I've sat here and
21 heard, I know there's thousands of people out here that
22 need this. And I'm asking the panel to please consider,

1 because there are people that are suffering right now
2 in the hospital, as well as my uncle. And it's
3 overwhelming. And my family doesn't know. It's new to
4 us, so we don't know what stages, and all the things,
5 and tests that we have to go through.

6 I have a five-year-old grandson. I have my
7 mother, my uncle. My uncle is here, my brothers. I
8 have family members, so I'm here on how it affects the
9 family.

10 So I'm here on behalf of him to just ask you
11 to, please, if there's any other way -- excuse me. It's
12 out here. It's helping people. There are people dying
13 today right as we speak. And my uncle has no chance
14 with a transplant, but if this medication can sustain
15 him a few more years to be with us, then I'm asking you
16 people to please do what's necessary, pass this drug,
17 so that it can help thousands, millions of people in
18 the future. Thank you very much.

19 DR. FOUNTAIN: Thank you. And thank you to
20 everyone who made public comments. I know it can be
21 difficult to speak in public about such personal issues
22 and the committee appreciates it.

1 The open public hearing of this meeting has
2 now concluded, and we will no longer take comments from
3 the audience. The committee will now turn its
4 attention to address the task at hand, the careful
5 consideration of the data before the committee as well
6 as the public comments.

7 We'll now proceed to the questions to the
8 committee and panel discussions. I'd like to remind
9 the public observers at this meeting that while this
10 meeting is open for public observation, public
11 attendees may not participate except at the specific
12 request of the panel.

13 We will be using an electronic voting system
14 for this meeting. Once we begin the vote, the buttons
15 will start flashing and will continue to flash even
16 after you have entered your vote.

17 Please press the button firmly that
18 corresponds to your vote. If you are unsure of your
19 vote or you wish to change your vote, you may press the
20 corresponding button until the vote is closed.

21 After everyone has completed their vote, the
22 vote will be locked in. The vote will then be

1 displayed on the screen. And the DFO will read the
2 vote from the screen into the record. Next, we'll go
3 around the room. And each individual who voted will
4 state their name and their vote into the record.

5 You can also state the reason why you voted
6 if you want to. We will continue in the same manner
7 until all questions have been answered or discussed.

8 So we'll turn our attention to the questions.

9 Does anyone need to follow up on any of the
10 questions to Dr. Farkas before we begin the discussion,
11 since we cut off that early? Dr. Gooch?

12 DR. GOOCH: This is a clarification, which
13 will relate to part 1A. This has to do with the FDA
14 rules regarding subpart H, and perhaps Dr. Katz or one
15 of the other FDA staffers could help to clarify this
16 for me and perhaps for some others.

17 How much flexibility is there in terms of a
18 situation in which the primary endpoints of a study are
19 not met under subpart H? And then that's my first
20 question.

21 Then the second is if we could just have a
22 brief review of the regulations regarding the

1 consideration of surrogate endpoints. It was gone over
2 this morning, but just a capsule summary before we
3 begin the deliberations.

4 DR. KATZ: I'll take a stab at part of that.
5 As far as the flexibility, I think the first part of
6 your question was the flexibility in p values with
7 regard to subpart H.

8 DR. GOOCH: Yes.

9 DR. KATZ: As we were talking about this
10 morning, the rules -- or the standards for approving a
11 drug for subpart H are the same for any other type of
12 approval with regard to the effect on the surrogate
13 that you're talking about. So subpart H means, in
14 effect, on a surrogate that is reasonably likely. We
15 don't know it's going to predict, but we think it's
16 reasonably likely.

17 There has to be substantial evidence of
18 effectiveness for the effect on the surrogate, whatever
19 the surrogate is, whether it's a lab test, whether it's
20 a clinical outcome.

21 So the same standard for substantial evidence
22 of effectiveness for any other type of approval, just a

1 regular approval based on a clinical outcome, no
2 surrogate involved, the same degree of substantial
3 evidence of effectiveness has to be found for the
4 surrogate under the subpart H rules.

5 So as we discussed, there are really two ways
6 to get to substantial evidence of effectiveness. One
7 is at least two adequate and well-controlled trials
8 where a statistical significance is achieved on the
9 primary outcomes. Statistical significance is usually,
10 almost always, considered to be a p of less than .05,
11 two-sided p. We can talk about that, but the
12 traditional standard for two studies is the p less than
13 .05 on the outcomes for both studies.

14 The other way to get to substantial evidence
15 of effectiveness is one adequate and well-controlled
16 study plus something called confirmatory evidence. In
17 that case, when there's only one study, you really want
18 the results of that single study to be very robust. And
19 you saw, I think, Dr. Farkas showed a slide and I
20 talked about some of the elements of a single study
21 that would make it very robust, like a very low p
22 value, so maybe a p of .01, or .001, or something along

1 those lines, multiple subsets going in the same
2 direction at multiple centers, multiple study sites
3 going, all being positive.

4 Confirmatory evidence could come from that
5 study itself if it's extremely robust, everything
6 moving in the right direction, including low p values,
7 or confirmatory evidence could come from some other
8 outside source. But you have to have substantial
9 evidence of effectiveness for the surrogate. And that
10 substantial evidence standard is the same as it is for
11 any other kind of approval.

12 So then you have to take the extra step from
13 the point of view, if we're talking about subpart H,
14 that you have to conclude that the effect on the
15 surrogate for which you have to have substantial
16 evidence is reasonably likely to predict the outcome of
17 interest.

18 We can talk about what reasonably likely
19 means in any given case, but it often involves a
20 detailed understanding of all the effects of the drug
21 and a detailed understanding of all the events and the
22 disease that produce symptoms, so you can be reasonably

1 likely that the effect you see on the surrogate will
2 have the clinical effect that you care about down the
3 road.

4 So that I hope answers your question with
5 regard to the first part. I no longer remember the
6 second part.

7 DR. GOOCH: So thank you. That does clarify
8 the rules regarding the surrogate evidence in the case
9 of a single study approval. In any case, though, the
10 primary endpoint measures must be met. Is that
11 correct?

12 DR. KATZ: We're talking about subpart H? It
13 doesn't really matter. Again, in subpart H, the
14 primary outcome could be a lab test or something. But
15 yes. We would routinely expect that to be the case
16 unless there is some compelling reason to look at
17 another analysis, in other words, with a primary
18 analysis, which in this scenario fails to meet the
19 usual rules of statistical significance, where we find
20 that that analysis was wrong, it was chosen poorly, the
21 data don't allow that analysis to be done, some
22 compelling reason to move to a different analysis than

1 the one that was prospectively designated. And there
2 can be circumstances in which that is the case.

3 DR. FOUNTAIN: Dr. Mielke? I'm sorry. Yes.

4 DR. MIELKE: I have a question following up
5 with that. Again, kind of regarding the flexibility,
6 there was a mention in terms of orphan drug status,
7 that there is a little bit more flexibility with a .05
8 p value.

9 So how much flexibility is there? What would
10 be the confidence interval, I guess, around that?
11 That's one of my questions.

12 Then the second question is, getting back to
13 the analysis of secondary endpoints and multiple
14 testing, there are a couple ways to look at it. If the
15 directions are all very similar for the secondary
16 analyses, even if they're not all significant, is that
17 still sufficient evidence, I guess? Would that be
18 considered?

19 DR. UNGER: In terms of orphan diseases, we
20 do have a license to be more flexible and we certainly
21 try to be more flexible. But in terms of how the
22 flexibility is spelled out in the regulations, it's

1 really not.

2 So we still need substantial evidence of
3 efficacy, as Dr. Katz told you first thing this
4 morning. So it's not clear exactly how we carry out
5 this increased flexibility, but whatever it is, we try
6 to do it.

7 In terms of the secondary endpoints, I mean,
8 at the end of the day, when one integrates all the
9 evidence of effectiveness and all the safety data, it's
10 a judgment call for us. And I guess that's where the
11 extra flexibility comes in. And that's why it's not
12 written down anywhere what that actually means.

13 So when we gauge all the data, the fact that
14 it's a co-primary endpoint, it didn't win on either
15 component, but if you do alternative analyses, they can
16 win the multiplicity in the secondary endpoints. We
17 have to put all that together, hopefully with the help
18 of your discussion here in the next couple hours and
19 try to figure out what it all means.

20 I don't know if that answers your question
21 and Dr. Katz might want to add something.

22 DR. KATZ: Yes. It's sort of impossible in a

1 vacuum to answer the question as to what the required p
2 value is for an orphan. As we've said, for an orphan
3 disease, there needs to be substantial evidence of
4 effectiveness. And that's usually defined in the ways
5 that we've defined them already a number of times. We
6 have to convince ourselves -- the point here, I think,
7 is that, again, there's a traditional standard we all
8 know at .05, in two studies something less than that,
9 in one study with everything else, if it's one study,
10 going in the same direction, hopefully some nominal
11 significance in some of those outcomes.

12 That's sort of what we take. Let's take the
13 traditional non-orphan, non-surrogate, just regular
14 approval, two studies, .05. That provides us with a
15 certain amount of confidence that the effect is real.
16 That's the goal, whether it's a subpart H approval,
17 whether it's one study plus confirmatory evidence
18 approval, whether it's an orphan product. We need to
19 be able to conclude that the effect that we saw was
20 caused by the drug, and not chance, and not biased, and
21 not fraud, of course.

22

1

2 So we have to convince ourselves that the
3 drug has produced the effect that we have seen. The
4 usual standard that we apply is the one we've talked
5 about. Anything less than that, we're less confident
6 about.

7 As Dr. Unger says, if it's not exactly
8 according to the usual rules, we look at everything
9 else and we just try to convince ourselves that the
10 effect that we're seeing is not due to bias or chance,
11 that it's related to the drug. And it's hard to give
12 you a number.

13 DR. FOUNTAIN: Thank you. Dr. Clancy?

14 DR. CLANCY: This is also a question for Dr.
15 Katz regarding flexibility. So the .05 number is sort
16 of a standard number for any kind of a statistical
17 analysis, and you want to be sure that differences
18 between the two groups aren't just statistically
19 fluked. There's less than 5 chances in 100 that it's
20 just a fluky thing.

21 I wonder if the FDA would be flexible enough
22 to consider a real focus of treatment effect, though,

1 on the efficacy evaluable patients. We started off
2 with a lot of patients. Very few dropped out for small
3 reasons, a couple pregnancies, having adverse effects.
4 Almost all of the dropouts were for the liver
5 transplant. And there's an old Quaker -- you take the
6 cookies while they're passed. If someone offers you a
7 liver, you take a liver right now. You don't wait
8 around for the end of a drug.

9 If you want to know it's real, those
10 patients, though, treated in the intention to treat are
11 treated as failures, and yet we don't really know
12 they're failures. We're assigning them that value, but
13 some may have improved and some may not have.

14 So the question I want to know is, if a
15 patient has the disease, and takes the drug, and stays
16 on the drug, are they or are they not better at the end
17 of that time? And to me, the answer is yes. It looks
18 like it is.

19 So would there be flexibility enough to weigh
20 the intention to treat classic population analysis for,
21 in this specific scenario, efficacy evaluable patients?

22 DR. KATZ: Yes. All this can weigh in, but I

1 think that the short answer is, is there flexibility to
2 rely on an analysis that wasn't a prospectively
3 designated analysis -- the prospectively designated
4 study population in the protocol? Yes. There is
5 flexibility to do that. The question is, is it
6 appropriate to do so? And that's one of the questions
7 we have for the committee.

8 By the way, I have a question for the company
9 specifically about this point, which I think is very
10 important. I can ask it now.

11 DR. FOUNTAIN: Why don't you ask it?

12 DR. KATZ: The analysis that we have seen,
13 that presumably -- it might have been slide 80; there
14 might have been other slides as well -- that presumably
15 takes into account the fact that a lot of the dropouts
16 were due to a liver transplant, was presented as the
17 efficacy evaluable analysis. It was a nominal p value
18 of .041 or something.

19 The term "efficacy evaluable" or "evaluable
20 patients" usually includes -- and I think it did here,
21 too, and if I'm wrong, tell me. But it usually
22 includes a whole bunch of folks who left the study

1 early. They didn't complete, they only took 80 percent
2 of the prescribed drug. There's a whole series of
3 things. So we don't, as a general matter, like those
4 sorts of analyses because those folks could have left
5 related to the treatment somehow.

6 So I'd like to know if that analysis was that
7 type of an evaluable patient analysis or was it an
8 analysis just with the transplant patients excluded. If
9 it's not that analysis, do you have an analysis where
10 you just excluded the transplant patients and included
11 everybody else? Let's call it a modified intent-to-
12 treat in that sense, because I think slide 80 is the
13 more traditional evaluable patients, where a bunch of
14 people are not included.

15 I could be wrong, but I think it'd be a very
16 important point because everybody is saying the
17 evaluable patients analysis is the real analysis, but
18 I'm just not sure who was included in that analysis.
19 Maybe we can get that clarified.

20 DR. GROGAN: Sure. We specified the efficacy
21 evaluable population as those patients who completed
22 the full 18 months' treatment per protocol. So the

1 majority of patients who dropped out of the study were
2 due to liver transplant.

3 But however, we looked at all the patients
4 who completed the full 18 months of treatment. 91
5 patients completed the full 18 months' treatment and
6 two additional patients from each treatment group, who
7 we believed and were assessed prior to unblinding, had
8 important protocol deviations. They were dropped from
9 the efficacy evaluable. So almost all the completers
10 were included in the efficacy evaluable.

11 The rationale for that in this pre-
12 specification is, for disease-modifying therapy like
13 tafamidis, you really want to follow patients across
14 the full 18 months of treatment. If there is a true
15 treatment effect, the placebo patients would worsen
16 over that 18 months' period of time and the tafamidis
17 patients would worsen less or not worsen at all.

18 So the reason why we pre-specified this
19 analysis is we wanted those patients who were able to
20 complete the full 18 months on therapy. So again, we
21 do believe that this does represent the treatment
22 effect of tafamidis as we've presented in the totality

1 of the data.

2 DR. KATZ: But it's not -- again, what I'm
3 calling, defining here, the modified intent-to-treat
4 now, it's not everybody except the transplant patients.
5 Correct?

6 DR. GROGAN: That's correct.

7 DR. KATZ: Do you have that analysis?

8 DR. GROGAN: Not in that way. What we had
9 and what's included in our file is the sensitivity
10 analysis that, instead of calling the liver transplant
11 patients non-responders, we imputed their response,
12 should they have stayed into the trial for the full 18
13 months. That's the sensitivity analysis of the NIS-LL
14 responder analysis.

15 Perhaps I could ask Dr. Schwartz to come up
16 and give you just perhaps a little bit more detail on
17 that.

18 DR. FOUNTAIN: Can I clarify something,
19 though, as part of that? So that means there were 125
20 people. 91 of them were in the efficacy evaluable
21 group. And 26 had liver transplant. So that leaves
22 six that were included that didn't have liver

1 transplant.

2 Does that sound numerically accurate?

3 DR. GROGAN: There were 87 patients in the
4 efficacy evaluable population.

5 DR. COHEN: Eighty-seven.

6 DR. SCHWARTZ: Maybe I could provide an
7 alternative analysis that gets at what you're asking
8 for. The NIS-LL change from baseline to month 18, a key
9 secondary analysis, on the intent-to-treat group, uses
10 all the patients, including the liver transplant
11 patients up to the time at which they dropped out for
12 liver transplant.

13 So there were no exclusions for the other
14 criteria that are usually the case in efficacy
15 evaluable. So we have those analysis results as well
16 and those are significant.

17 DR. KATZ: We can talk about whether that's
18 the perfect substitute, but again, just to get back to
19 your question so it doesn't get lost, is there
20 flexibility? Sure. But the question is -- and this is
21 the case -- is it appropriate to focus more on the
22 efficacy evaluable population than it is to focus on

1 the protocol-specified analysis? And we'd like to hear
2 your views on that.

3 DR. FOUNTAIN: I have a question for Dr.
4 Farkas. I was a little confused by the presentation of
5 some of the analysis which you suggest maybe the
6 differences were due to chance rather than actually
7 statistical differences.

8 But did your overall analysis identify any
9 things that didn't change in the right direction? It
10 looks like, from the data that I've seen, things all
11 seemed to change in the right direction or be neutral,
12 rather than changing in the wrong direction, even
13 though it wasn't statistically significant.

14 DR. FARKAS: Yes. I think that's a fair
15 statement. I mean, I guess that -- if there weren't
16 small changes -- this is going to sound a little bit
17 negative, a negative world view. But if there weren't
18 small changes in a positive direction -- sometimes it
19 doesn't help to know if it -- we wouldn't be here
20 today, even if by chance there were changes in the
21 wrong direction.

22 So I guess that I'm not quite sure personally

1 how reassured I am by that, because there's other
2 studies that fail. Studies sometimes show, again by
3 chance, that the drug is inferior to placebo. I think
4 in our guidance about efficacy, it explains that, that
5 if we just went by the .05 p value standard and none of
6 the drugs that were tested had any efficacy, then we
7 would approve 5 percent of them. So I think that's
8 just, again, a consideration.

9 DR. FOUNTAIN: Yes. So my question wasn't
10 about the statistical significance, just about the
11 trends, the numerical differences between groups.

12 DR. FARKAS: Right. Anyway, I think that
13 pretty much things were numerically in the right
14 direction.

15 DR. FOUNTAIN: Next, Dr. Shefner?

16 DR. SHEFNER: I'll just respond to this point
17 before I raise my point, which is that on slide 84 from
18 the sponsor, where responders are broken apart by
19 initial baseline level, those subjects that were least
20 affected at baseline, actually had changes in the
21 opposite direction, at least as I read that study, that
22 the responder rate was higher in the placebo groups for

1 those patients than it was in the treated patients. So
2 there is that, anyway.

3 What I wanted to just discuss a little bit
4 more is this idea of flexibility in orphan diseases.
5 I've spent my career looking at and trying to treat
6 patients with an orphan disease that is fatal in about
7 half the time that this disease is. And I have come to
8 the view that, that doesn't change your need for
9 certainty or at least confidence that what you're
10 observing actually is real. But I have looked at
11 study, after study, after study with near statistically
12 significant p values in phase 2 and been very excited
13 by them. I've also seen many studies where virtually
14 all of the outcomes were near significant in that
15 direction, only to be disappointed by the phase 3
16 studies.

17 As a sideline, this in terms of absolute
18 numbers is a very small study that would qualify as a
19 phase 2 study in most more common diseases. And so I
20 just think that we have to be focused on the confidence
21 level that we have.

22 I personally feel that there's a big question

1 in that regard. And so the flexibility that we're
2 talking about, I think also reduces our ability to be
3 confident.

4 There was a question buried in there
5 somewhere. And the question was that, in addition to
6 this flexibility, the lack of hitting the primary
7 endpoint, one other big potential problem is that more
8 than half of the patients were enrolled at one site.
9 And we've been told that if you take those patients
10 away, there's no signal. But I haven't seen any data,
11 so it would be very useful to me to actually see the
12 numbers of this analysis on the patients that were not
13 from that site. I don't think we saw that.

14 DR. FOUNTAIN: Could I ask the sponsor to
15 pull up those numbers while we're answering the other
16 questions? I'll give you an opportunity to do that.

17 So to rephrase your question, you want to
18 know the primary endpoint efficacy analysis, separated
19 out by this single site that's high-enrolling compared
20 to all the others.

21 DR. SHEFNER: Right. I mean, the side that
22 was presented was efficacy by site, but I didn't see a

1 combined analysis of all other sites besides the single
2 one.

3 DR. GROGAN: Yes. To do this analysis, we
4 looked at the continuous change from baseline across
5 all of the endpoints. And we grouped Porto, the
6 highest- enrolling site, and all other sites together.
7 We showed you the analysis that we had, the by-site
8 analysis, and we have all those for all the endpoints.

9 But if I could see slide AH1, please? So I
10 showed you the point estimates slide, which had the
11 full population. This is a very similar slide that I
12 showed in our main presentation, for which we conclude
13 that the results across all these various endpoints,
14 all numerically, and many statistically, support the
15 effect of tafamidis across these various measures.

16 So the top panel is the point estimates and
17 the 95 confidence intervals for Porto. And the bottom
18 is the same assessments for the other sites. And you
19 can see, except for sensation and reflexes on the line,
20 we have similar directionality, obviously very wide
21 error bars. These are small populations.

22 As you mentioned, this is a small study,

1 although it's a large study for this very rare disease.
2 And then when you start dicing this population into
3 even smaller and smaller groups, obviously, you're
4 going to lose significance, but at least the
5 directionality is the same.

6 DR. SHEFNER: Thank you.

7 DR. FOUNTAIN: Is there a response to that
8 relative to this slide and this question? Dr. Cohen?

9 DR. COHEN: I deal with ALS, too, and we
10 really do want to have therapies, but like Jeremy, I'm
11 slightly hesitant. Looking at this -- and probably I
12 didn't ask this question correctly. But just
13 clinically taking care of patients with FAP, on the
14 NIS-LL, the major component that's causing that to go
15 in the best direction is probably the muscle weakness?
16 That's improving?

17 DR. GROGAN: Correct.

18 DR. COHEN: So medication has most profound
19 effect on weight or BMI measure, as well as quality of
20 life, as well as muscle weakness?

21 DR. GROGAN: Yes. And I would say, actually,
22 from a point estimate, similarly for summated seven

1 score, I think the point estimate is very similar to
2 the
3 NIS-LL.

4 DR. COHEN: So things that are very
5 troublesome to the patients and limit activities of
6 daily living like sensory deficits, autonomic syncope,
7 that really is not coming out in this analysis?

8 DR. GROGAN: Well, again, when you dice this
9 population into a smaller population, you do see, at
10 least at the Porto site, that you have significant
11 difference between the treatment groups in sensory and
12 also very close to reflexes.

13 DR. COHEN: Just, I'm not saying you should,
14 but if one takes Porto out, then it's not. Okay.

15 DR. GROGAN: Yes.

16 DR. FOUNTAIN: Yes, Rusty?

17 DR. KATZ: Yes. Just, if I heard you
18 correctly, at least for the NIS-LL, I don't think that
19 was the primary outcome. If you look at the primary
20 outcome, the responder rate, I have it on page 12 of my
21 memo -- I assume I got the numbers right. You tell me
22 if I didn't. But if you look at the non-Portugal sites

1 in responder rate, the responder rate on placebo is 32
2 percent and on tafamidis is 25 percent. So it's in the
3 wrong direction, not whoppingly in the wrong direction,
4 but it doesn't seem to have --

5 DR. GROGAN: Right. I would like to sort of
6 address that and have Dr. Schwartz come up as well, but
7 one of the things we've learned from this program --
8 and I think this is often the case in rare diseases --
9 is, you start the trials and you're dealing in programs
10 with the best information that you have.

11 Sometimes, that's flawed. And I think it is
12 clear now that the dichotomous reduction of this NIS-LL
13 continuous variable is probably not the best method of
14 analyzing this endpoint. And I think the continuous
15 change variable that we analyzed is probably a better
16 reflection of a true treatment effect.

17 But I'd like to have Dr. Schwartz just talk
18 about the responder, non-responder analysis.

19 DR. SCHWARTZ: So one of the issues that we
20 wrestled with, with the responder analysis, is how it
21 behaves at the different sites. There is a significant
22 site-by-treatment interaction when we look at the

1 responder analysis and we put a site-by-treatment
2 interaction in the model. But if we look at the change
3 from baseline analysis, the site-by-treatment
4 interaction is not significant. The p value for that
5 test is .2406.

6 So this is the analysis of the change from
7 baseline, looking at the site-by-treatment interaction.
8 The site-by-treatment interaction term is not
9 significant, although the pattern appears what we would
10 call a quantitative interaction had it been
11 significant, meaning that the directionality of the
12 differences are still preserved. The tafamidis group
13 is still showing a better response than the placebo
14 group at the Porto site, as well as at the other sites,
15 although the differences are much narrower at the other
16 sites.

17 DR. FOUNTAIN: Anymore discussion of this
18 question and this specific topic?

19 DR. FARKAS: So we actually had p values for
20 the site 1 versus other sites. And the actual p values
21 -- or the analysis that we saw -- I don't know if that
22 gave the committee all the information that they needed

1 because it was in kind of a different format, I think,
2 than some people are accustomed to looking at.

3 So I guess the question would be if any
4 committee members thought that they wanted the p values
5 from site 1 versus the other sites.

6 (No response.)

7 DR. FOUNTAIN: I take that to be a no, unless
8 that's a comment.

9 DR. PRESTON: Yes. Just a comment about the
10 p value and the latitude in the p value -- everyone
11 knows this. But a p value of .05 is an arbitrary set
12 value. I understand this is in the scientific
13 literature, but this means that the chances that these
14 results occurred by chance was 1 out of 20. That's all
15 it means.

16 If a p value is at 0.68, which is either the
17 NIS-LL score, that's a random chance of 1 out of 15. So
18 I think that's what we're talking about. So I think,
19 when it comes to a rare disease, it's a fatal disease.
20 Are you willing to say that the efficacy has shown 1
21 out of 15?

22 Yes. It would be nice to have a second study

1 to confirm that and make it much more likely to be
2 true. But when you have such an orphan disease, from a
3 practical point of view, it's very difficult to pull
4 that off.

5 DR. FOUNTAIN: So now I think we've now
6 progressed onto really discussion of the points. So
7 unless you have a very specific, factual question to
8 ask specifically to Dr. Farkas about his presentation,
9 just so we don't lose sight of any of this, before we
10 move onto the specific issues in the discussion -- so
11 Dr. Chaudhry, was your specific question to Dr. Farkas
12 about his presentation, or is it a more general
13 comment?

14 DR. CHAUDHRY: It's kind of specific, I hope.
15 So this is coming back to what Dr. Clancy raised, and I
16 still want to have somewhere this information before,
17 at least, I'm satisfied one way or the other.

18 So there are two things that continue to be
19 of some concern. One is, of course, this p value. And
20 second is the difference in baseline between the two
21 groups.

22 I know that Dr. Farkas made this sensitivity

1 analysis considering baseline disease severity. And
2 that moved the .04 efficacy evaluable to 0.16. I'd
3 like to see that same data to see whether, if you just
4 take the efficacy evaluable patients and then did the
5 baseline disease severity, that .04 becomes .06 or .08,
6 I'm less convinced. But if it stays at .04 or even
7 becomes better, I am more leaning towards this positive
8 outcome because we all agree that liver transplant was
9 a genuine reason to drop out. But that still doesn't
10 take away the baseline disease severity difference.

11 So is it too much to ask to evaluate that? So
12 I don't know whether you can do it in your head with
13 statistics.

14 (Laughter.)

15 DR. CHAUDHRY: But it would be nice to have
16 that information. And I don't want to lose my chance
17 because I have a second follow-up question which is
18 unrelated, if I may.

19 DR. FOUNTAIN: Sure. Why don't we ask Dr.
20 Farkas to answer that first question?

21 DR. FARKAS: I'm actually a comment back
22 already, so I was thinking about something else. But

1 if I could just address the meaning of a p value of,
2 say, .05. And I guess -- I can just kind of mention
3 briefly for a second about the ability of a p value to
4 predict that the drug actually works. And I think the
5 best way that I can explain this -- and certainly I'm
6 not a statistician -- is that if there were a group of
7 drugs that were tested, and you knew ahead of time that
8 none of them were effective, some would have a p value
9 of .05, if you knew that none were effective, you're
10 guaranteed, if you test enough drugs that are not
11 effective, to get a p value of .05.

12 The p value of .05 does not tell you anything
13 about if the drug truly works outside of -- well, I'll
14 say the Bayesian thing -- outside of the probability
15 that the drug actually worked. We don't normally use
16 Bayesian statistics, but if you knew that the drugs
17 didn't work, you would get false positives. All your
18 positives would be false positives.

19 So we just should try to think, really, of
20 exactly what the p value is telling us and not telling
21 us.

22 DR. FOUNTAIN: So your second question,

1 clarifying question?

2 DR. SHEFNER: He didn't answer the first
3 question.

4 DR. CHAUDHRY: Yes. I don't think you
5 answered the first question.

6 DR. FARKAS: Could you repeat it?

7 DR. CHAUDHRY: So I mean, on your page 4, or
8 whatever, this slide 7, you nicely demonstrated
9 sensitivity analyses considering baseline disease
10 severity. And you did that analysis for NIS-LL. The p
11 .07, the intention to treat, now becomes .16.

12 So that kind of takes away my first thing.
13 Well, the p value is going in the wrong direction once
14 you include the baseline disease severity. But now,
15 I'm coming back to the efficacy evaluable patients,
16 which is the point Dr. Clancy had raised and I had been
17 concerned about. There, the p value is .04.

18 If you now do this analysis with the same
19 sensitivity analysis, considering those baseline
20 differences in severity of 2 points or more, would the
21 NIS-LL move from .04 to a different direction? If it
22 does, that really influences my decision.

1 DR. FARKAS: But I think it came up before,
2 and we didn't do that analysis. I guess what I tried
3 to do in my talk is kind of caution about the way that
4 we do calculations. And there was kind of one little
5 phrase.

6 Actually, the more calculations that you do,
7 the more that -- even if they're just kind of slightly
8 different, each one comes out a little bit different.
9 And I think Dr. Preston did mention -- I mean, we're
10 talking about actually fairly small differences in p
11 values. Maybe that's the thing to concentrate on. And
12 again, I tried to kind of briefly say this during my
13 talk. And that is that it isn't like a p value of .04
14 means the drug works and a p value of .06 means it
15 doesn't work.

16 So I could guess, perhaps, that if that
17 calculation was done, I would have no idea. It would
18 either be a little bit bigger than .16 or it would be a
19 little bit smaller than .16. But again, with this
20 multiple testing problem, you don't know how much faith
21 to put in that.

22 The second thing is that, really, in the

1 sense of the amount of evidence that we have, a change
2 in the p value of some small amount doesn't make a
3 large difference.

4 DR. CHAUDHRY: But at the same time, you're
5 using that argument to move the .07 to .16.

6 DR. FARKAS: Yes.

7 DR. CHAUDHRY: I mean, you can't have it both
8 ways. If you're going to tell us -- if you do use the
9 disease severity, I'm convinced that the intention to
10 treat is a genuine excuse, that there are people -- I
11 shouldn't say excuse, but a genuine reason for efficacy
12 evaluable to be used. And if that's the case, I would
13 very much like to know, even though the numbers are
14 small, because you do show slide number 7 for a reason.
15 I want to see a slide 7A or something that says, is it
16 still .04 or has it moved to .2? Even though it's not
17 even a sub-analysis, it just makes me think a little
18 bit differently.

19 DR. FOUNTAIN: Could I summarize the
20 discussion maybe, so we could move onto some of the
21 other points? So your question is, you'd like to see
22 analysis of the efficacy evaluable population either as

1 Dr. Farkas did it in the sensitivity analysis or as in
2 the other analysis, as the sponsor did it. And Dr.
3 Farkas doesn't have that analysis. He hasn't done it.
4 And the response is that you don't think it would make
5 that much difference. The sponsor did a sensitivity
6 analysis, imputing the answer, and you don't have the
7 other result from the evaluation.

8 Is that correct? Since that seems to be the
9 focus of our discussion.

10 DR. LOMBARDO: Dr. Schwartz, do you want to
11 come up to discuss that? We'll have Dr. Schwartz come
12 up to address that.

13 DR. SCHWARTZ: So if there was a sensitivity
14 analysis done in the original study report, a logistic
15 regression that also adjusted, within the efficacy
16 evaluable population, for baseline and other
17 explanatory factors.

18 In that analysis, the significance also was
19 greater than .05. There are some reasons why this is
20 the case.

21 If I could have slide 84, please? So in
22 slide 84, you'll notice that there is a differential

1 relationship with baseline between placebo and
2 tafamidis.

3 So as you move from left to right in
4 increasing severity, there's a decreasing response rate
5 with placebo. However, the tafamidis rate seems to be
6 relatively constant with respect to the baseline
7 severity levels. There is some decrease at the very
8 end.

9 We've done an additional analysis, looking at
10 the slopes for those baseline adjustments, and it turns
11 out there are two different slopes. So doing a single
12 baseline adjustment in the logistic regression is not
13 the best baseline adjustment for that test. However,
14 if we look at the continuous change from baseline, NIS-
15 LL, to month 18, and we put a baseline-by-treatment
16 interaction in the model, it's not significant.

17 So the simple baseline adjustment that we
18 included in that analysis retained significance,
19 whether we look at either the intent-to-treat or the
20 efficacy evaluable population.

21 DR. FOUNTAIN: So you do that also with the
22 efficacy evaluable population?

1 DR. SCHWARTZ: Right.

2 DR. FOUNTAIN: These results are from the
3 intent-to-treat population?

4 DR. SCHWARTZ: The upper left is the efficacy
5 evaluable population. The three other displays were
6 taken from the FDA's analysis and they're the intent to
7 treat.

8 DR. FOUNTAIN: Dr. Farkas?

9 DR. FARKAS: Yes. I think that Dr. Chaudhry
10 expressed confusion about what I was trying to say
11 about the p values, and I didn't address that, I don't
12 think.

13 We can have the most confidence in the pre-
14 specified endpoint, as that was calculated. And there
15 are two of them, so if you kind of average them today
16 and say a .09, or something, or .08. Then I guess I
17 tried to show that there's different sensitivity
18 analyses that you could do to try to understand how
19 that primary endpoint came about. And some of those
20 will give you a bigger number and some a smaller
21 number. And it's very difficult to know which one is a
22 better number. Okay? And they're pretty symmetrical

1 around the original number that you got.

2 So I guess to be kind of perfectly clear -- I
3 mean, I think that there is room for judgment, but
4 still, the best kind of numerical answer is still the
5 primary endpoint, is still the p value from the primary
6 endpoint.

7 DR. FOUNTAIN: Thank you. Perhaps we should
8 move onto some other discussion. Does anyone have any
9 other clarifying questions before we have other
10 discussion?

11 Dr. Bagiella, is it in regard to clarifying
12 or just a more general discussion?

13 DR. BAGIELLA: No. I was wondering whether
14 we can know from the company how was the study powered,
15 what were the assumptions in the power analysis.

16 DR. FOUNTAIN: So let's actually make it a
17 point to -- there are many, many things we could
18 discuss, so let's make it a point maybe to follow to
19 the questions to make sure we actually get to the ones
20 we need to address. And that'll come up very quickly,
21 so I think we can address that.

22 If we need to come back to some other

1 discussion, we can, so that all the panel members have
2 an opportunity to ask their questions and participate.

3 Is there a direct comment in regard to that?

4 DR. UNGER: This is not exactly a clarifying
5 question, but it's an important issue, though, a
6 burning issue.

7 DR. FOUNTAIN: It won't be covered in the
8 questions? That wouldn't be covered in the questions?

9 DR. UNGER: I think we should discuss it for
10 a minute before the questions, if that's okay. We take
11 confidence from multi-center studies, where most of the
12 centers go the same direction. And we worry about
13 studies where we have the predominance of support of
14 efficacy from a single center. And this is essentially
15 what we have here. The rest of the study tends to lean
16 in the other direction, so it makes us nervous. De
17 facto, this is more or less a single-center study, with
18 58 percent of the patients from Dr. Coelho's site.

19 We talked this morning a bit about the
20 objectivity of the endpoints. And certainly, the
21 Norfolk QOL is all subjective and the NIS-LL is
22 objective, but it requires an operator to measure

1 things. So there are subjective elements there and, as
2 such, they are susceptible to bias. And the way we get
3 around that, we hope, is to have a double-blind study.

4 So my question really is for Dr. Coelho. I
5 hadn't recognized that she was going to be here, but
6 this is a golden opportunity. The question is about
7 the blinding, because it's so critical for these
8 endpoints.

9 My question is, with 58 percent of the
10 patients at your site, I'm wondering if there are maybe
11 subtle effects that the drug has, that are not recorded
12 as adverse events, but subtle effects that would lead
13 patients to be unblinded, or -- I mean, as far as I
14 remember, these are capsules. If you held both the
15 capsule for the placebo and the drug in your hand, can
16 you tell the difference between them? What would you
17 say about those questions?

18 DR. LOMBARDO: So I guess, as Dr. Coelho is
19 coming up, just to introduce that more generally, there
20 was no evidence of unblinding, certainly, that we could
21 determine in terms of GCP and all of the evidence that
22 we found.

1 Specifically, as I had mentioned before, as
2 we move from Study 005 to Study 006, the fact that the
3 change across the tafamidis-tafamidis group and the
4 placebo-tafamidis group was different, I think, also
5 gives some overall confidence in the fact that there
6 wasn't unblinding.

7 But to your specific question, Dr. Coelho?

8 DR. COELHO: So I have no reason to think
9 that there was any sort of unblinding. The capsules
10 looked exactly the same way. And I think the patients
11 had lots of doubts during the course of the study if
12 they were on drug or not. Even the dropout rate for
13 liver transplant probably reflects the doubts the
14 patients had during the first year of the trial.

15 DR. UNGER: I very much appreciate hearing
16 that from you. Thank you.

17 DR. FOUNTAIN: So now, just to organize the
18 rest of our discussion, we've really already been
19 discussing it, so this might be more procedural. But
20 just to make sure we get to all of the points and
21 discuss the questions at hand, the first issue isn't
22 really a voting issue. It's a discussion issue, which

1 is why I'm anxious to move to it, to make sure we reach
2 all the points.

3 Please discuss the strengths and weaknesses
4 of Study 005, including the effects of the following
5 factors, on its ability to provide substantial evidence
6 of effectiveness. Please discuss how regulatory
7 flexibility might be applied with regard to these
8 factors; of course, that's exactly what we've been
9 discussing. But it might be useful to organize our
10 discussion around some of these things. And I'll go
11 through them first so you know what's coming.

12 First is the p value for the pre-specified
13 co-primary endpoint, then the nominal p values for the
14 individual components of the co-primary endpoint, the p
15 value for the efficacy evaluable population, the lack
16 of control for multiple testing analyses of secondary
17 endpoints, results of secondary endpoints, baseline
18 imbalances, and then disproportionate support of
19 efficacy from site 1 in Portugal, as we were just
20 discussing, with little to no efficacy support from the
21 combination of remaining sites.

22 Now, if we can, in that context -- this might

1 be with regard to the ultimate p values. If you could,
2 ask your question again.

3 DR. BAGIELLA: Can we know how the sample
4 size was calculated and what are the assumptions in the
5 sample size?

6 DR. LOMBARDO: Dr. Schwartz can take you
7 through those estimates.

8 DR. SCHWARTZ: Can I see the other slide that
9 shows the comparison?

10 So your initial assumptions for the sample
11 size estimate was a 50 percent response in the treated
12 group with a 20 percent response in the placebo group.
13 This would provide a 90 percent power, .05 alpha.

14 There was an assumption of a 5 to 10 percent
15 dropout rate. The actual dropout rate was about 20
16 percent, equally split in both treatment groups for
17 liver transplant. With the other few patients that
18 dropped out for other reasons, there was a total of 30
19 percent dropout.

20 So to do an initial assessment to see how
21 badly underpowered this placed us, I did a simple
22 analysis to see, with the actual observed effect size

1 and the actual sample size that occurred, what we would
2 have needed. So in the ITT population, we had a 45
3 percent response rate and a 30 percent response rate in
4 the placebo group. In the tafamidis group, that was a
5 delta of 15 percent as opposed to the 30 percent
6 assumed.

7 We would have needed 230 patients per group
8 without any adjustments for dropout, compared to the 58
9 per group that we assumed earlier. If you gross up for
10 a 5 to 10 percent in the original plan versus the
11 actual 30 percent that we obtained, the discrepancy
12 between the actual study size and the required study
13 size in this situation is quite a bit different.

14 DR. FOUNTAIN: So to summarize -- or I guess
15 we can comment as well. So it seems to me, ultimately,
16 you were underpowered because of the increased number
17 of dropouts from liver transplantation and a smaller
18 treatment effect than you anticipated.

19 So I guess the argument would be that
20 although the p value is small, if you had had a larger
21 group with the same effect, it might have shown a
22 difference.

1 Anymore discussion, particularly about the p
2 value for the pre-specified co-primary endpoints?

3 Dr. Shefner?

4 DR. SHEFNER: I guess it's directly relevant
5 to this, but it also is relevant to the standards that
6 we're being asked to apply and I just want to state my
7 understanding for validation ,which is that if we're
8 being asked to approve a drug on the basis of a single
9 trial, the p value of .05 is actually something we're
10 hoping to see much smaller than.

11 We're hoping to see very robust p values on
12 the primary endpoint. And so we're worrying about the
13 other direction. But in fact, to follow the
14 guidelines, which I actually think are reasonable, we
15 should be looking for significantly more robust p
16 values than .05.

17 Would that be a fair summary for our
18 guidance?

19 DR. KATZ: Yes. I think, if you're talking
20 about the one study plus confirmatory evidence, then,
21 which I think we're talking about, whether it's subpart
22 H or just a traditional clinical outcome, yes, I think

1 that's the point we've been trying to make, which is
2 that, again, when you're only dealing with one study,
3 you'd like to have the same amount of evidence or the
4 same amount of confidence that the effect is drug-
5 related, as you have with your two studies at .05,
6 again traditionally.

7 So yes. And Dr. Farkas talked about the
8 document that we have which lists the elements -- I
9 think I mentioned the elements of when one study would
10 be considered acceptable for that sort of approval.
11 And, yes, one of the first things you read about is a
12 lower p value than you typically would see with the two
13 studies.

14 DR. FOUNTAIN: So the specific discussion is
15 about the p value for the pre-specified co-primary
16 endpoints, and the general consensus has been so far --
17 obviously, it doesn't meet 0.05. Is that right?

18 So the question is anything that mitigates
19 that, or would change it, or other analyses, or other
20 issues just for the co-primary-specified endpoints.

21 Dr. Luan, would you still like to make a
22 comment from earlier or a question? I'm sorry. I

1 skipped over you earlier.

2 No? Dr. Oaklander?

3 DR. OAKLANDER: I've been wondering what the
4 right time is to discuss the impact of neuropathology
5 on the analysis. I'm not sure that this is the right
6 time, but I'm not sure when the right time is.

7 DR. FOUNTAIN: You can discuss it now if you
8 think it's relevant.

9 DR. OAKLANDER: I think we've spoken a lot
10 about the flexibility that may be needed for an orphan
11 drug, but I don't think we've adequately addressed the
12 problems that come with the pathology of this kind of a
13 disease. And I think that has a real bearing on the
14 analysis as well. And the problem is that this whole
15 methodology that we all use and rely on is designed
16 mostly to look at acquired diseases.

17 But this is a genetic disease, where the
18 pathology has been ongoing since birth. And yet, the
19 symptoms of it develop only at the very end, falling
20 off the cliff. And so while 18 months is a very long
21 time for a clinical trial, it's actually a very short
22 time in terms of the proportion of the disease course.

1 So I think we're struggling because the data
2 are equivocal, and that's why we're spending so much
3 time on how to slice and dice them.

4 But looked at from a pathological
5 perspective, this whole design is not going to be
6 optimal to capture what we really want to know about
7 this drug. And the way to think about that is how
8 would this drug be used if it were available? It would
9 not be used the way it was used for this clinical
10 trial.

11 If there were a potentially effective
12 treatment, all of the family members who might be at
13 risk for this would go out and get tested. And then
14 people who are asymptomatic or pre-symptomatic go on
15 this medication. And then the kind of analyses that,
16 really, we would care about would be Kaplan-Meier type
17 analyses, where does being on this medication for 10
18 years, for 20 years, delay or slow your onset to
19 symptom or to death?

20 So I think that that is germane in the sense
21 that we're trying to pull out some information -- it's
22 not designed the way the drug would really be used

1 because of the length of the illness.

2 DR. FOUNTAIN: Dr. Marder, did you have a
3 question or comment?

4 DR. MARDER: I do. My problem is that we're
5 being asked to look at a flawed study for many
6 different reasons. And the way the analyses have been
7 performed, it's not clear what we're exactly going to
8 be voting on, the ITT group or the other group.

9 In addition to that, we're being forced to
10 make assumptions about what things might mean or what
11 does it mean when you have populations that are
12 different, different disease duration, where are they
13 on the disease, line of the disease, and so on.

14 I just find it very confusing. You want to
15 do something good, but on the other hand, you have to
16 face the facts that the data just isn't there at this
17 point. But it's because the study perhaps is flawed,
18 poorly designed, underpowered. So I'm a little
19 confused about that.

20 DR. FOUNTAIN: I would let you respond, if
21 you like, or I could say, I guess while we're here,
22 solve it?

1 DR. KATZ: Yes. I mean, you seem to have
2 gone right to the end. But these are the questions we
3 want you to grapple with and we want to hear what you
4 have to say. I mean, that's your view. That's fine.
5 We understand what you're saying. Yes. We need to
6 hear it.

7 Just as long as this is live, the comment
8 about the pathology, and that it would be used early if
9 it were available, and that this design may not really
10 have been appropriate for the setting, that of course
11 may be true, but this is what we have. So I'm not sure
12 what the conclusion is from your comments, even though
13 they may be completely correct.

14 DR. OAKLANDER: I didn't mean -- I agree the
15 study was done as best as it possibly could be done, so
16 I wasn't intending to criticize it in that regard. But
17 I'm saying I think that that should be as much a reason
18 for flexibility as the fact that this is an orphan
19 condition.

20 DR. KATZ: Again, I guess I'm just not sure
21 how that -- and we're perfectly willing to follow this
22 out. But I guess I don't understand how that would sort

1 of factor into our being flexible.

2 Are you saying that we should presume it
3 works in those people who are asymptomatic, or we
4 should make it available because it might work in those
5 people and they're going to take it anyway? I'm just
6 not sure how that translates into our being flexible.
7 About what? I'm just not clear on that.

8 DR. OAKLANDER: My major point was that it's
9 difficult to know about whether something is going to
10 be helpful overall in a disease with a lifelong course,
11 that has been damaging neurons for decades before the
12 symptoms even appear.

13 So we're trying to make judgments from a
14 trial that's done at a time when the horse is already
15 out of the barn, to speak colloquially. And we really
16 have no data and cannot have any data about what the
17 efficacy might be if this were used for long periods of
18 time in people who are pre-symptomatic.

19 So I think you're right. I'm not coming down
20 on one side or the other in particular. I'm just
21 saying that we're being asked to discuss about
22 regulatory flexibility and other considerations. And I

1 think it's not just that it's an orphan disease that's
2 grounds for other considerations, but the fact of a
3 lifelong disease that we're trying to catch only at the
4 very end.

5 DR. FOUNTAIN: So you're suggesting, for
6 future reference, that for neurodegenerative diseases,
7 that long-term studies longer than normally considered
8 might be necessary or important to understand if the
9 drug is effective? Does that summarize what you were
10 implying? Dr. Bagiella? Dr. Rosenberg?

11 DR. ROSENBERG: I think the regulatory
12 flexibility applies as much to the underlying science
13 as to p values. And personally, it's hard to divide it
14 up strictly question by question. I'm going to take
15 the liberty of addressing two questions at once.

16 I think that the Study 005, whatever you call
17 it, isn't robust. It's confirmatory because just the
18 results are sensitive to how you cut the data. But
19 they're pretty impressive. They apply to a wide
20 variety. It's not just that it's a bunch of endpoints,
21 but they're very different endpoints, subjective
22 neurology, subjective neuro exam, objective nerve

1 conduction, quality of life, and even your weight.

2 I'm very impressed by how broad that effect
3 is. And I'm impressed by many of the effect sizes. We
4 talk a lot about p values, but just forget about the p
5 values. These are big differences. I mostly work on
6 Alzheimer's disease. I doubt that I will live long
7 enough to see these effect sizes in Alzheimer's
8 disease. These are impressive.

9 I do think the regulatory flexibility may
10 have to do to some extent with the biomarker and the
11 measures. We all know, in Alzheimer's, it's taken a ton
12 of money and a ton of work just to establish how
13 biomarkers are relating to the underlying disease. In
14 an orphan disease, we will not have that. There are
15 not enough patients. The resources are not likely to
16 be applied. We have to work with less evidence.

17 I think the TTR biomarker is quite persuasive
18 to me because it closely mimics the genetic models. I
19 know nature didn't make a model, but still, we've got
20 an unusual situation where we have a series of mutants.
21 They all have the same chemical effect, roughly, and
22 they all cause the same disease. We've even got a

1 mutant that protects and we've got a drug that seems to
2 mimic the protective effect. I'm very impressed by
3 that.

4 Now, you could drive a truck through that and
5 say, "Well, you can't establish how well it reflects
6 the underlying disease." It's true. What we want with
7 a biomarker is to say there's a latent variable, which
8 is the actual disease, the progression of the disease.
9 And it's a little bit of a leap of faith to go from
10 what I said to saying this reflects the underlying
11 disease. I think the regulatory flexibility is, I
12 don't think we're ever going to get the 10-year ADNI
13 study in this disease to answer that question.

14 So once again, I'd say I think we've got a
15 confirmatory level of evidence. Hold it like this, and
16 look at the graphs, and you see pretty sizeable
17 effects, but you see p values all over the place,
18 suggest to me that there's a fair amount of variance in
19 the measures, and we're not sure which measures are
20 most sensitive to change, and we're not going to find
21 out. Once again, in Alzheimer's, we've spent millions
22 of dollars answering those questions. It takes many

1 years.

2 But I think the biomarker is pretty
3 persuasive and the idea, to me, I think meets whatever
4 you call it, subpart H because I think there's
5 substantial evidence for the biomarker. I mean, it's
6 very clear they affected the biomarker. And I think
7 the biomarker is reasonably likely -- do you follow me
8 -- based on the genetic models.

9 It says it does not allow for approval based
10 on weak evidence of effect on clinical endpoint. I
11 don't find the evidence weak. That's my personal
12 opinion. It's not as robust as it could be, but it's
13 not weak evidence. And once again, let me repeat it's
14 because of the variety of measures. And the last is,
15 there's got to be a post-approval study.

16 I'm sorry to go all over the place, but I
17 think it's hard to just answer one question at a time.

18 DR. FOUNTAIN: Dr. Clancy?

19 DR. CLANCY: Yes. I'd like to throw my two
20 cents in about the p values. I was just imagining that
21 the sponsors did a huge study. They did 500 patients
22 in each side, the placebo side and the active drug

1 side. And when all was said in done, they could show,
2 with a p value of .0001, that there was 1 percent
3 better response rate in the drug compared to the
4 placebo group. And we'd be very satisfied. This is
5 significant because the p value is so small. But would
6 we really care about such a small chunk of change in a
7 disease that's so progressively relentless?

8 It seems to me that, for something that's
9 measured over 10 or 15 years, to be able to find, I
10 think, a clear signal in 12 months to 18 months, is
11 meaningful. And again, if you get back to the fact
12 that this is a disease [sic] that you want the patient
13 to take every day, every day, every day for a month or
14 a year, that is the patient population I'm interested
15 in, not the ones that fall by the wayside. We're
16 looking at a chronic disease.

17 So anyhow, I'm less focused on the equivocal
18 p value than what seems to be a consistent signal in
19 the primary, and secondary, and some of these objective
20 things. That tells me there's some help to offer these
21 patients from this drug.

22 DR. FOUNTAIN: Does someone have a direct

1 response to that or onto another question?

2 DR. SHEFNER: Basically, a response to both
3 together, dealing with the size of the point estimate
4 rather than the p value, I just think it's important to
5 say that the point estimate in a study this size is
6 almost meaningless. Basically, all it tells you is
7 that you have a 95 percent chance of being between two
8 very large numbers, which go from close to nothing or
9 negative in some values to very large.

10 So if those point estimates actually were
11 reliable and indicated something, then they would be
12 incredibly valid. But there is example, after example,
13 after example of small studies in neurodegenerative
14 disease with humongous point estimates that, on repeat
15 study, go away entirely. And they include ones where
16 many measures change together.

17 DR. FOUNTAIN: That would seem to be the crux
18 of the problem, two views. Dr. Kramer?

19 DR. KRAMER: I don't have a question anymore.
20 It was already kind of asked and answered.

21 DR. FOUNTAIN: Dr. Gooch?

22 DR. GOOCH: Yes. I'd like to make a couple

1 of points, I think. So the first point, I think I just
2 want to echo what's been said about the evaluable
3 efficacy population in this study and the fact that the
4 liver transplantation situation creates a fairly unique
5 circumstance here. And I think it's important to look
6 very carefully, and it's on our list. And I'm going to
7 jump around a bit, too. But I do believe the efficacy
8 evaluable population in this circumstance has
9 particular relevance to the significance of the study.

10 I want to talk about surrogate endpoints
11 because that's come up. And I'm, in large part, a
12 neuropathy specialist, as are a number of the
13 neurologists on the panel. And I want to talk about
14 two specific things that, in looking at some of the
15 surrogate markers, came out as being quite significant
16 in this study.

17 One is the effect on small fiber function, so
18 this was looked at, at the sigma 3 subscore and had a
19 high level of significance. This is important for two
20 reasons.

21 One is that this is really the first
22 population of neurofibers to be affected in this

1 particular condition, so in a sense, this is in essence
2 a canary in the coal mine in regards to this particular
3 kind of neuropathy.

4 It is, as has been alluded to, a brief
5 duration to test for a long-term disease. So to see
6 significance in the earliest part or in the part of the
7 nervous system where you would see the earliest effects
8 of the disease over this brief window of time does
9 carry some special importance.

10 I think we have to think about that. It's
11 also important to remember that most of these patients
12 were ambulatory patients when they came in, so these
13 are not the most severely affected patients.

14 So we're looking at that point of the curve
15 where small fiber dysfunction, I think, has special
16 relevance. And small fiber dysfunction, as measured by
17 quantitative sensory testing, has been correlated quite
18 clearly in diabetic neuropathy with significant
19 pathology and morbidity. The development of pressure
20 ulcers is one of them. Neuropathic pain is another. So
21 it has direct clinical relevance, which is applicable
22 to subpart H.

1 The second thing I want to emphasize, which
2 has already been mentioned early on but is of great
3 importance to the patients is the effect on strength,
4 so particularly distal leg strength.

5 So this is another classic feature of distal
6 symmetric neuropathy. And when patients begin to lose
7 significant distal leg strength, it dramatically
8 affects their ambulatory ability. It affects their
9 mobility. It puts them at increased risk for all kinds
10 of injuries.

11 In this study, when we look at the distal
12 muscles, especially in the subanalysis that was done,
13 we see that there is quite robust p values, looking at
14 those distal muscles in the legs in this particular
15 study. And that, for the patients, is very important.
16 So I think, as we begin to dissect it out -- and again,
17 these are surrogate markers; they're not the payment
18 endpoints -- taking together the fact that if we look
19 at the efficacy evaluable population, and then we look
20 at these very important, very relevant endpoints for
21 patients with neuropathy and with particular
22 application to this individual neuropathy, that it

1 makes a relatively compelling case, even given the
2 weaknesses of the study, that this is an effective
3 drug.

4 DR. FOUNTAIN: Is it directly related to
5 that, or in response to that, or another question?

6 Ms. House? I'm sorry. You want to respond
7 to that first, Dr. Katz and then Ms. House?

8 DR. KATZ: Again, just to remind folks of
9 some of the points that Dr. Farkas had made earlier
10 about this small fiber test -- slide 13, small nerve
11 fiber test -- a couple things. First of all, it does
12 have a small nominal p value, but again, in the
13 background of many, many things being tested in no
14 prospective order of testing, it's difficult to know
15 what that p value means, again, in the setting of the
16 lack of significance on the primary endpoints.

17 I know we've been talking about evaluable
18 patients -- but maybe if you have the slides at your
19 desk -- that point, the 18-month point, where you see
20 this nominal significance, patients continued to get
21 worse on that, even patients who were on placebo before
22 who now in Study 006 are getting the drug, and now

1 they're getting worse.

2 That point, as Ron pointed out, could have
3 been a chance finding. It seems to be, if you tried to
4 draw the curve, connecting the dots. That seems to be
5 perhaps out of line. And again, given the multiple,
6 multiple comparisons, the meaning of that particular
7 comparison and the meaning of a nominal p value of .05
8 at that particular point, I just raise again for people
9 to consider.

10 Obviously, people can conclude what they want
11 about that.

12 DR. FOUNTAIN: If it was random, though,
13 wouldn't you expect it to have some variance around
14 that, rather than just not follow the same trajectory?

15 DR. KATZ: Yes. But it's just potentially
16 anomalous, again, given the multiple comparisons.

17 DR. GOOCH: May I respond? Yes. So I wanted
18 to actually address this slide. I'm glad you brought
19 it up. So in this particular circumstance, in some of
20 the work that we have done and others have done, in
21 terms of neuroprotective drugs and the way that they
22 often work, we will often see an early effect that is

1 more dramatic and that creates a separation of the
2 curves between the untreated population and the treated
3 population, and then the patients begin to progress
4 further. And our theory, my theory about that, is that
5 there are some nerves, in this case small fibers, that
6 are, if you will, barely alive, barely functioning, and
7 that the treatment basically salvages them and enables
8 an ordinary repair processes that the peripheral nerves
9 have to kick in and bring them back into function,
10 which gives the patients an early bump. Then after
11 that, the disease process continues at some level and
12 further progression occurs, although there may be
13 further benefits.

14 However, this does not mean the drug is of no
15 benefit. It actually is kind of like the horse getting
16 out of the gate, and getting two lengths on the rest of
17 the horses, and maintaining it going forward. There
18 still is benefit.

19 So to me, this is actually a pattern that
20 suggests, actually, in my mind, reinforces this
21 particular paradigm of pathophysiologic benefit. But
22 it is true that the separation is not getting wider and

1 wider.

2 DR. FOUNTAIN: Unless we have a direct
3 response to that, maybe we should take the opportunity
4 to take a break and then follow up with the other
5 questions. Quick response to that?

6 DR. SHEFNER: Really quick, just two points.
7 One is that if you look at the sensory component of the
8 NIS, both in the Porto cohort and in everybody else,
9 it's changing less than everything else. So these are
10 two inconsistent observations. And I guess I'll stop
11 at that.

12 DR. FOUNTAIN: Ms. House, would it be all
13 right with you if we broke first and then have your
14 comment afterwards? Thank you. And I realize there
15 are also others waiting as well.

16 So right now, let's take a break for 15
17 minutes. It's 3:10, so let's be back at 3:25. And
18 please remember not to discuss the topic of the meeting
19 outside the meeting.

20 (Whereupon, a recess was taken.)

21 DR. FOUNTAIN: Welcome back to the meeting,
22 to the voting portion of the meeting. And we'll resume

1 where we left off. I think we were up to Ms. House's
2 question or comment.

3 MS. HOUSE: Hi. Thank you. There has been a
4 lot of discussion about p values, and I'm not going to
5 talk about that because that's not my place as a
6 patient representative. I wanted just to make some
7 comments about some of the things the patients said,
8 some of the things that I've heard around the table.

9 First thing I wanted to note was, one of the
10 patients, when he spoke, said that if we decide to go
11 ahead and approve today, that we will help a lot of
12 people, that no one is going to be hurt. And I think
13 that's something that I'd like us to think about real
14 carefully because nobody's talking about the safety or
15 any risks here, because I don't think there are any.
16 From the AEs that I've read, the serious AEs, all of
17 that, they aren't related to the drug. Or if they are,
18 they're pretty minor and can be managed.

19 So if there isn't a risk, then we need to be
20 really focusing on benefit, which we are. And I think,
21 again, as has been talked about, all of the trends seem
22 to be in the direction of there is a good chance that

1 there's a benefit.

2 So that leaves us at, how do we approve it if
3 that's where we want to go? And we're not talking
4 about traditional approval because I think the sponsor
5 has agreed that's not the direction we're going. We're
6 looking at an accelerated approval with a study
7 attached. So we're not giving broad-label approval to
8 use it with anybody. We're trying to make it available
9 to patients who need it now.

10 Like the FDA suggested, there's always a
11 chance of expanded access for these patients. But you
12 heard one of the patients say doctors aren't interested
13 in it. Speaking as a patient with a rare disease, I
14 know that's true. A lot of doctors are going to step
15 back and say, "I see what you're saying, but it's too
16 much work for me."

17 So if we say it's safe enough and there's
18 enough suggestion that there's a benefit to go with
19 expanded access, why don't we just say, "Let's go
20 ahead, and give it accelerated approval, and come up
21 with a good study design," because we're having the
22 same effect that we'd want to have, giving it to the

1 patients, but we're not facing these insurmountable
2 hurdles. And expanded access can be an insurmountable
3 hurdle. So that's all I wanted to say.

4 DR. FOUNTAIN: Just as a minor point of
5 clarification, we're not really voting for approval.
6 We're just voting on the questions to give our opinions
7 about the issues at hand.

8 DR. KATZ: Can I just make a comment? I
9 appreciate your comments very much. I know there's
10 been a lot of talk here at the table about p values,
11 and it's a very arcane discussion and analyses. And it
12 seems as if the patients are secondary in these
13 discussions.

14 I think our obligation is to make sure that
15 only drugs that work are approved. And I think
16 everybody would agree it doesn't do anybody any good to
17 put drugs out there that don't work. So how to
18 determine whether drugs work could be complicated and
19 it's obviously complicated in this case, but that's at
20 least our minimal obligation, I think.

21 I just don't want people to think that the
22 patients aren't critical. Everything we're talking

1 about ultimately is about the patients. We're just
2 trying to figure out whether the drug works. It
3 doesn't have to work a lot. We just have to convince
4 ourselves that it works. And the only way to get there
5 is to talk about p values and analyses. And so I know
6 there's a perception that the patients aren't critical.
7 Everything we do here is about the patients. It's just
8 a question of how do we get there.

9 DR. FOUNTAIN: Yes?

10 DR. ENSRUD: Hi. Erik Ensrud. I had a
11 question for Dr. Grogan or someone from marketing in
12 Pfizer. We've talked about how few patients have this
13 disease, which of course doesn't matter for the
14 patients and families who have it.

15 It's difficult to identify these patients.
16 There's been a lot of delay, it sounds like, in some of
17 the families who spoke today about diagnosis. And
18 there's been a pretty vigorous marketing effort from
19 Pfizer about identifying people with idiopathic
20 peripheral neuropathy and for education as to whether
21 they might be candidates to being tested for TTR.

22 I wanted to ask, it seems like there's

1 somewhat of a precedent that's been set for rare
2 diseases in terms of Genzyme, that they will now pay
3 for the testing for acid maltase disease and Pompe
4 disease. Because the cost of a test -- and it's my
5 understanding that the testing for TTR, the genetic
6 testing, is about \$500. Actually, the modern-day
7 American healthcare system can actually be a
8 significant hurdle. And I wanted to ask if there's any
9 plan on the part of Pfizer, similar to Genzyme, to pick
10 up the cost of that testing.

11 DR. LOMBARDO: Thank you. So I'm Dr.
12 Lombardo. I'll take that question. And certainly, as
13 you've mentioned, with TTR-FAP as with other rare
14 diseases, it's very underrecognized, and as has been
15 mentioned, underdiagnosed. Obviously, when a drug is
16 approved, it affords us an ability to help with patient
17 education and with some types of disease awareness as
18 well.

19 The actual activities that we would be doing
20 in the post-approval setting obviously haven't been
21 committed to yet, but we certainly are committed to
22 this disease, to continue working in this area, and

1 certainly working with patients and physicians with
2 TTR-FAP.

3 DR. FOUNTAIN: Dr. Logigian, did you actually
4 have a question from earlier? I'm not sure if you
5 still have the question.

6 DR. LOGIGIAN: Yes. Maybe I'll just sort of
7 ask the question at this point. There have been a
8 couple of remarks, I think, headed in this unvalidated
9 surrogate direction, one using the assay and then one
10 for more small fiber function.

11 So at this point, if we think the weight of
12 the evidence is not strong enough in terms of p values,
13 and in terms of validation, more than one site, and
14 that sort of thing, to approve based on one study with
15 confirmatory evidence, then one then turns to the
16 possibility of the surrogate, an unvalidated surrogate
17 pathway?

18 First of all, correct?

19 DR. FOUNTAIN: Dr. Katz?

20 DR. KATZ: Again, you certainly can consider
21 the surrogate subpart H pathway, but you still have to
22 have substantial evidence of effectiveness for the

1 effect on the surrogate. And that still, I think, puts
2 you in the realm of one study plus confirmatory
3 evidence standard for demonstrating that there is that
4 effect on the surrogate. Then you could talk about, is
5 it reasonably likely to predict the clinical benefit
6 you care about. But we have to find that there's
7 substantial evidence of effectiveness for the
8 surrogate.

9 So even if you're talking about subpart E, we
10 still have to deal with the question of how robust --
11 is the evidence for the effect on the surrogate robust
12 enough that the one study plus confirmatory evidence
13 standard applies?

14 You could find that it does, but we have to
15 make that finding to move forward.

16 DR. LOGIGIAN: So of the five -- using the
17 changes from baseline to 18 months, of the five various
18 tests, we have the NIS, the QOL, small fiber function,
19 large nerve fiber function, and the modified BMI. And
20 of those, the strongest ones -- and I guess you could
21 add maybe the assay. I'm on page 39, slide 77 from the
22 sponsor.

1 Actually, these are baseline. I think
2 there's a summary.

3 (Pause.)

4 DR. LOGIGIAN: I guess one could use those,
5 but there are p values, I know, and I've lost the
6 original page here. But the p values are the strongest
7 for BMI muscle, the NIS, particularly muscle weakness
8 and the small fiber function. So I guess my question
9 is, what does one have to show to prove that one of
10 those would be eligible for this pathway?

11 One would have to have two things, as I
12 understand it. The surrogate data has to be
13 substantial and also that the effect on the surrogate
14 is reasonably likely to predict a clinical benefit.

15 So one could make that argument certainly for
16 muscle strength and potentially for small fiber
17 function. And then the question that I have in my mind
18 is, is that data substantial? The p value for the
19 muscle weakness, I think, is .01 and .005, I think, for
20 small fiber. Yes.

21 Does that constitute substantial evidence, or
22 is that surrogate data substantial? Does one need two

1 pieces of information, for example, for muscle strength
2 or the same for small fiber?

3 DR. FOUNTAIN: Would you like to respond to
4 that or is that the nature of what you're asking us?

5 DR. LOGIGIAN: Yes. I'm asking.

6 DR. FOUNTAIN: Yes. Please respond.

7 DR. KATZ: Again, the determination that, for
8 a particular outcome, there is substantial evidence of
9 effectiveness is a judgment. There are the usual sorts
10 of standards that we apply. We talked about two
11 studies with a .05 or one study with usually a lower
12 .05, plus something called confirmatory evidence, which
13 is also something that is a judgment.

14 Again, I would only point out, for the ones
15 that have been discussed, which we just mentioned,
16 there is the multiplicity question, the question of the
17 muscle weakness at .01, but it wasn't a primary -- it's
18 a component of one of the primary outcomes. It's one
19 of many things, similarly with the .005 for the small
20 fiber function.

21 So you can recommend that, of course, in your
22 judgment, in your view, there is substantial evidence

1 of effectiveness for an effect on muscle weakness or
2 the small fiber. But again, I would just raise the
3 point that when you're talking about a single-study
4 standard for a particular outcome, whatever your
5 outcome that you choose is, we would normally expect
6 that to be quite robust, more robust than either of two
7 study approvals.

8 So you would have to decide whether you
9 thought that met that standard. But the standard for
10 one study, substantial evidence, is a study that's very
11 robust, whether it's on the clinical outcome or the
12 proposed surrogate, typically.

13 DR. FOUNTAIN: Dr. Mielke, did you have a
14 comment or question?

15 DR. MIELKE: Yes. I guess more of a comment.
16 I mean, as we've been talking a lot about the p values,
17 and what's significant, or not, and flexibility. I
18 think one thing that's been in the back of my mind,
19 that I'm struggling with a little bit, is, we're
20 focusing on the endpoints. But as was mentioned a
21 little bit earlier, when you think about the risk-
22 benefit ratio and adverse effects, I guess I'd be a

1 little bit more concerned about the very highly
2 significant p values if there were a lot more adverse
3 events.

4 Since there aren't really a whole lot -- I
5 mean, certainly there are some risks. There are risks
6 with any kind of drug and this hasn't been conducted
7 long term in a lot of people, so there's potential for
8 risks. But that gives me or pushes me a little bit
9 more in the direction where I'm not quite as concerned
10 about the lack of very highly significant p values. I
11 don't know if that's something that we should consider
12 or not, but that's kind of been in the back of my mind
13 a little bit.

14 DR. FOUNTAIN: Dr. Shefner?

15 DR. SHEFNER: I just wanted to caution once
16 again about the equivalent version of that slide that
17 took away that one site, where the pattern was not at
18 all seen in every other site. And I think that
19 concerns me significantly.

20 DR. FOUNTAIN: Can I ask a point of
21 clarification from the sponsor? I think I heard you
22 say that the total exposure of the drug was 127. But

1 yet, there were 125 in Study 505?

2 DR. GROGAN: Throughout the whole development
3 program for FAP, the total number of patients exposed
4 is 127, so that includes the 65 patients in the
5 tafamidis group from 005, the patients that were
6 previously on placebo that went on tafamidis in 006,
7 and then the patients that were exposed in the 1-A-201
8 study.

9 So all the total number of patients ever
10 exposed to tafamidis is 127.

11 DR. FOUNTAIN: So not all of the placebo
12 patients went on tafamidis in 006?

13 DR. GROGAN: Of the 91 patients who completed
14 the trial, 85 went in, so very few did not roll over
15 into that trial.

16 DR. FOUNTAIN: So I guess my comment is,
17 that's still a pretty small N in terms of safety.

18 Yes, Dr. Farkas? Did you want to make a
19 comment, Doctor?

20 DR. JILLAPALLI: During the last hour, Dr.
21 Shefner asked for site 1 versus an all-of-the-sites-
22 combined analysis. We have some p values if some of

1 you may prefer that.

2 These are all ITT analyses. At month 18,
3 NIS-LL response rate at site 1 was 0.0044. At all of
4 the sites, it was 0.5723. And for the NIS-LL change
5 from baseline, at site 1 it was 0.0090. And at all of
6 the sites combined, it was 0.7347.

7 For the TQOL change from baseline, at month
8 18 at site 1, it was 0.133 and, at all of the sites,
9 0.865. Large fiber change from baseline, month 18, at
10 site 1 was 0.0419 and, at all of the sites, was 0.8364.

11 DR. FOUNTAIN: Dr. Chaudhry, did you have a
12 comment or question?

13 DR. CHAUDHRY: Yes. So this is my first time
14 in such a hearing, and I was very touched by the
15 emotionally powerful testimony by family, and friends,
16 and individual patients, and thank them for coming.

17 I don't know how we're supposed to
18 incorporate that into this, but one thing I did learn
19 in my own experience as well is the fact that small
20 fiber neuropathy, painful symptoms, and autonomic
21 symptoms are pretty much part of this disease.

22 As this analysis was done, I mean, there are

1 two things I'm looking for, subjective improvement and
2 an objective improvement. In this case, the
3 subjectivity is by quality of life, which didn't show,
4 and objectivity is by the testing, the NIS-LL, which
5 also didn't show in intention to treat any change.

6 I just wonder why -- I mean, is there any way
7 we can have -- from the quality of life, find out
8 whether there was a pain scale measured or if patients
9 complained? I mean, we heard today that patients are
10 on narcotics and such. All the autonomic testing,
11 which in this case is listed for some reason under
12 large fiber and small fiber.

13 Was that in any which way changing? Because
14 those are two main components of this disease as
15 functionally subjective. And I know, through the
16 progressive process, the weakness comes in as well.

17 So I guess a direct question to the sponsor
18 is, why wasn't a visual analog scale or any pain
19 measurement given? In general, my experience is,
20 subjectively, patients report much more improvement
21 than objectivity. In this case, we don't see that.
22 Perhaps it's in that TQOL, and I didn't see that in

1 detail. Was that done? And did the heart rate
2 variability with deep respiration change through this
3 whole study?

4 DR. FOUNTAIN: So if we could ask you to
5 respond if you have any data about that, what about the
6 quality of life contains a pain scale and again, show
7 whether or not heart rate variability changed?

8 DR. GROGAN: Sure. Yes. I can show you the
9 components of the quality of life. Approximately 30
10 percent of the patients enrolled in the trial across
11 the treatment groups had pain as a component of their
12 neuropathy. So although it's definitely a component,
13 it may not be quite as common as in, say, diabetic
14 neuropathy.

15 If I could show slide E188, please. So these
16 are the individual domains for the total quality of
17 life score. Again, remember that this study was not
18 powered to show differences between these individual
19 domains. Symptoms scored there, you can see numerical
20 differences favoring tafamidis, small fiber function,
21 and in particular the large fiber function, which does
22 match with what we saw with the NIS-LL, muscle weakness

1 scale.

2 If I could have the adverse advent profile
3 from the core deck, please?

4 So I went through safety fairly quickly in
5 the interest of time. Slide 123, please? And we
6 highlighted at least those adverse events that were
7 reported more frequently in those patients on
8 tafamidis. We did not do a visual analog scale in this
9 trial, but the adverse event profile is listed there.
10 And you do see that at least paresthesias and
11 neuralgias were reported more frequently in patients on
12 placebo.

13 Then can I have the heart rate response to
14 deep breathing, please? The one measure of specific
15 measure of autonomic function, the heart rate response
16 to deep breathing, as Dr. Freeman noted, was assessed.
17 And this is the normal deviate values for that. And
18 you can see that there is virtually no change in the
19 heart rate response to deep breathing in patients on
20 tafamidis and a worsening in patients on placebo.

21 Higher normal deviate scores show a
22 worsening. If we looked at the raw values, the beats

1 per minute, you'd see a decrease in the patients on
2 placebo.

3 DR. CHAUDHRY: Can I have a follow-up on
4 that?

5 DR. FOUNTAIN: Okay.

6 DR. CHAUDHRY: Is there a plausible
7 explanation why the large fiber function appears to
8 improve more? Is this drug not able to or is the
9 deposits of amyloid -- you're not able to penetrate
10 smaller fibers or something? Because I'm looking at,
11 is strength improving, large fiber function improving,
12 but not particularly at least the p values. I know the
13 trends look in the direction of the drug.

14 DR. FOUNTAIN: So maybe in the interests of
15 time, we could have a yes or no answer about whether or
16 not you have an explanation.

17 DR. GROGAN: I don't think that's an accurate
18 assessment, actually. I think we have similar effects
19 on both small and large fiber function.

20 DR. FOUNTAIN: Thank you.

21 We do need to move onto the questions, so I'd
22 like to summarize the discussion points that we

1 considered before, which we talked about in various
2 considerations. The first one was the p value for the
3 pre-specified co-primary endpoints. I think we talked
4 about that in quite some detail.

5 I'm not suggesting we reached a consensus
6 opinion, but I think the issue is whether or not those
7 are significant. And the general answer was no, that
8 some may think differently. The nominal p values for
9 the individual components of the co-primary endpoints,
10 which I think follows directly on A, having similar
11 issues; the p values for efficacy evaluable population.
12 So we had a separate discussion about the efficacy
13 evaluable population and the p values, and looked at
14 some other data that wasn't presented before.

15 DR. PRESTON: Could we discuss that? That
16 was one of my questions from this morning that was
17 tabled until this afternoon.

18 DR. FOUNTAIN: Yes. So if you have a
19 specific issue or question --

20 DR. PRESTON: My specific issue is, I really
21 would like to hear from the statisticians from the FDA
22 and the statisticians from the sponsor. And that is,

1 the intention to treat clearly did not show that this
2 treatment, with confidence, actually works. But it's a
3 very unusual thing because people were taken out
4 because of this liver transplant. And this is a very
5 unique situation where, when someone's offered a liver,
6 they're likely not going to say no.

7 When you look at the efficacy evaluable p
8 values and the robustness, it's actually pretty good or
9 at least much more impressive. But I'm not used to
10 seeing this, but I think this is a distinctly unusual
11 situation because, normally, I would stick to the
12 intention to treat, period. But this is so unusual.
13 It's not a patient who's deciding by themselves to go
14 out. It's almost like they have a gun to their head
15 about, do you want this liver transplant or not? Here's
16 your one opportunity. They're going to jump at it and
17 take it. And the question is, because of that, should
18 we put more emphasis on the efficacy evaluable than we
19 normally would?

20 DR. FOUNTAIN: So I think that's a question
21 that's kind of asked to us in the nature of these
22 discussions. So if you have a specific question about

1 some clarifying data or analysis, unless someone would
2 specifically like to respond, I think the question
3 before us is, is that acceptable? I think that's the
4 nature of your question.

5 DR. KATZ: I would just say, I don't think
6 it's a statistical question, actually. I think it's a
7 question of whether or not you think it's appropriate
8 to essentially ignore the primary analysis because it's
9 not appropriate in this setting and that the efficacy
10 evaluable population is the more appropriate population
11 to analyze.

12 I don't know. Call it a clinical judgment or
13 whatever. I don't think it's a statistical question
14 strictly. It's a judgment thing, I think.

15 DR. FOUNTAIN: Dr. Luan?

16 DR. LUAN: Just to continue Dr. Katz's
17 discussion, I think we have brought this up, the
18 efficacy evaluable population, several times during the
19 discussion. I just want to add a few of my quick
20 comments.

21 I think in principle, we all know that the
22 primary efficacy analysis should be based on ITT. And

1 the purpose of the analysis based on the efficacy
2 evaluable population is just to assess if the primary
3 efficacy analysis on ITT -- whether or not it's robust.

4 The p values from the efficacy evaluable
5 population should not be interpreted as evidence for
6 efficacy. But we all know in this particular case,
7 it's often judged rare disease, super rare disease. How
8 much flexibility do we want to exercise here? But
9 before we reach a conclusion, I want to bring up two
10 points that maybe the committee can consider.

11 The first is, this is a very small trial.
12 It's 125 patients for the ITT. And out of the 125
13 patients, 26 patients went to a liver transplant.
14 That's about 20 percent of the ITT population. Whether
15 or not we threw away all the 20 percent population, 20
16 percent of the patients, whether or not it's
17 appropriate, is worth consideration.

18 The second point is, I think, this morning,
19 the sponsors showed us slides which compared the
20 baseline characteristics of the patient that had a
21 liver transplant and a patient who did not have the
22 liver transplant. I think, in that slide, we see that

1 the patient, actually, who went through the liver
2 transplant seemed to have the most severe disease. And
3 for the patient who has the most rare disease, based on
4 the data, they are more likely to become a non-
5 responder.

6 So I think, if we throw away all the patients
7 that had a liver transplant and do the analysis, I
8 think the results will be biased and will favor the
9 drug. Thank you.

10 DR. FOUNTAIN: Anymore discussion?
11 Personally, I think like you, Dr. Preston, that it's a
12 very special circumstance.

13 Anymore other discussions about that? Yes?

14 DR. JILLAPALLI: I just want to add one more
15 thing regarding the efficacy evaluable population. On
16 the one hand, the dropouts due to adverse events were
17 low and even, and the dropouts due to liver transplant
18 were more fairly even. So that just provides us some
19 limited reassurance about the bias being introduced.

20 But there is one important thing, as Dr. Luan
21 pointed out, is that the number of people that dropped
22 out were not trivial. They were 20 percent. And that

1 introduces all sorts of biases in a sum that we can
2 find difficult to quantify. And there will be other
3 biases that might be introduced that we may not even be
4 aware of, that might be influencing one treatment group
5 over the other.

6 DR. FOUNTAIN: Thank you. So we talked about
7 lack of control for multiple testing and, now,
8 secondary endpoints, results of secondary endpoints,
9 which I think we talked about, proposed even some
10 surrogate markers, baseline imbalances, which I think
11 were covered very well, and disproportionate support of
12 efficacy from site 1 in Portugal, with little or no
13 efficacy support from or in combination of the
14 remaining sites, which I think we also heard a detailed
15 analysis of and clarified the issues on, regardless of
16 which side of the coin you agree with.

17 So now, let's turn to the voting questions.
18 For approval based on a single study plus confirmatory
19 evidence, this study is expected to be particularly
20 robust. Note, however, that not all characteristics
21 that might make a study particularly robust need to be
22 present.

1 So we'll vote on this question. In the
2 context of the above discussion, are the findings of
3 Study 005 sufficiently robust to provide substantial
4 evidence of efficacy, similar to that usually provided
5 by two supportive studies for a clinical endpoint?

6 So we'll begin voting, and during voting,
7 your microphone will flash. And you can press the
8 button as many times as you want, but the last time you
9 press it, it will register your vote. So begin voting
10 now.

11 (Voting.)

12 DR. JOHNSON: I will now read the vote into
13 the record. We have 4 yeses, 13 nos, and zero
14 abstentions.

15 DR. FOUNTAIN: Now, we'll go around the room
16 and ask you to state your vote. And if you wish, you
17 can provide an explanation. Before you begin, please
18 state your name. And why don't we start with, I guess,
19 Dr. Cohen?

20 DR. COHEN: So this is a weird situation for
21 me because I'm always consumer patient advocate. What
22 I had trouble with was the one study, the study in

1 Portugal versus the findings with the other studies.
2 And kind of in the sense of being a clinician, taking
3 care of these patients, those data didn't jive really
4 with my clinical experience. So, yes, I would like to
5 have this drug available in a select group of patients.
6 I think it's important. But this study, as Dr. Marder
7 said, was really flawed.

8 DR. SHEFNER: So this is Jeremy Shefner. I
9 voted no, primarily for two reasons, first the finding
10 that the primary efficacy signal was in one site and
11 not replicated in an almost equal sample of the other
12 sites combined, and second, just in comparing this
13 dataset in its entirety to my experience of other
14 similarly-sized studies that didn't have confirmatory
15 evidence when larger studies were performed.

16 DR. CHAUDHRY: This is Vinay Chaudhry. I
17 voted no for pretty much the same reasons as the other
18 two have just said.

19 DR. PRESTON: This is David Preston. I voted
20 no as well, with a heavy heart because I realize that
21 this drug probably has little toxicity, but I think,
22 looking at the question, there really is no evidence

1 for efficacy and certainly not robust by any stretch of
2 the imagination. Unfortunately, as noted earlier, the
3 study was really underpowered. And really, we can't
4 draw any conclusions.

5 DR. VERMA: This is Dr. Verma. I voted no.
6 But I'm convinced the directional effect is there, but
7 the magnitude of effect is not there to vote yes. So
8 given the criteria, I think it's no.

9 DR. OAKLANDER: This is Anne Louise
10 Oaklander. I voted no with difficulty, but this study
11 is not just flawed in one regard, but it's flawed in
12 virtually every single way. It has virtually every
13 single kind of flaw that it could have.

14 So I think we really have to draw the line
15 between wishful thinking and looking at the data.
16 Furthermore, I think I listened with caution to the
17 statements that this drug is safe, because I don't
18 think we really know if this drug is safe or not. The
19 number of patients studied and the time that the drug
20 was taken for, as compared to the time that it would be
21 used for in clinical practice is so small that I don't
22 feel confident that we have enough data to judge

1 safety, either.

2 DR. BAGIELLA: Emilia Bagiella. I voted no.

3 And as the others said, I don't think that a single
4 study provides sufficient evidence of efficacy of the
5 drug.

6 DR. MARDER: Ellen Marder. I voted no for
7 all the same reasons.

8 MS. HOUSE: Tiffany House, and I voted yes. I
9 understood all the concerns that were raised, but I
10 think, with a degenerative disease like this, where you
11 are not going to get better, and it's fast, it's 10 to
12 15 years, that any slowing is evidence that it's
13 working. And I think that all of the trends were enough
14 for me to say that it was effective.

15 DR. FRANK: Samuel Frank. I voted yes, but
16 it would be a very weak yes. I think if you look at
17 the primary outcome, the co-primary endpoints in the
18 efficacy evaluable, they did reach a statistical
19 significance, and I think we have to start with that.
20 And all of the trends in the secondary outcome measures
21 were in the right direction.

22 I say yes with hesitation because of the

1 issues that we've already discussed, but I think that
2 it's important enough that -- the other thing I wanted
3 to say is Dr. Oaklander's comment about this being a
4 snapshot of a disease, which is very true. We're
5 looking at 12 months, 18 months, up to 30 months of a
6 disease that lasts 15 years. So to even get a
7 suggestion of a clinical response, I think, is actually
8 impressive for such a short time.

9 DR. OAKLANDER: It lasts your whole life.

10 DR. FRANK: It lasts your whole life. Yes.
11 You're born with it.

12 DR. OAKLANDER: It may not become symptomatic
13 until the end.

14 DR. FRANK: Right.

15 DR. OAKLANDER: The nerve degeneration has
16 been going on for 40 years.

17 DR. FRANK: To see a signal, I think, was
18 enough clinical evidence for me to say yes.

19 DR. FOUNTAIN: Nathan Fountain. I voted no
20 because the emphasis on this question is for clinical
21 endpoints and I believe that's true for the primary
22 endpoints, although I believe, for the biomarkers and

1 other issues, there may be other evidence. But in this
2 specific question and context, I voted no.

3 DR. CLANCY: Robert Clancy. I voted yes. We
4 talked about flexibility a lot. And it seems to me
5 that the place where we can apply this again is in
6 defining who the populations are we're interested in.

7 The reality of this disease is that people
8 are going to get liver transplants. And if you do two
9 more studies or a longer study, there's still going to
10 be a lot of dropout from liver transplants. That's not
11 cherry-picking the population. It's not like picking
12 the good cases that seemed to work. It's just the way
13 the cards fall for these people.

14 Again, for a chronic disease that's going to
15 be progressing over 10, 15, 20 years, I do want to
16 know, if you take the medication for 18 months, does it
17 give you an advantage over the placebo? Then the
18 primary clinical outcomes are significant, which allows
19 me to say, "Well, now, I have a validation to start
20 looking at secondary outcomes." And they're at least
21 consistently favorable.

22 So I thought overall, on a dark night, even a

1 small sliver of the moon is better than no moon at all,
2 so I voted yes.

3 DR. MIELKE: Michelle Mielke. I voted no,
4 based on the evidence of one trial and the not
5 extremely highly significant p values.

6 DR. LOGIGIAN: Eric Logigian. I voted no.
7 This is a devastating disease. It's a terrible axonal
8 neuropathy. I don't think the study was flawed so much
9 as just a very challenging problem. And in some ways,
10 I'm amazed. I've seen some of these patients
11 completely paralyzed from the knee down. I'm amazed
12 that we saw a signal at all.

13 The problem was that even if you use the
14 sample without the liver transplants, your p values
15 were not quite as robust. And then we had the nagging
16 problem that most of the benefit was really from one
17 site.

18 DR. GOOCH: Clifton Gooch. I voted yes for
19 some of the same reasons that have been elucidated.
20 Number one, I agree strongly with the statement that's
21 been discussed, that this is an unusual circumstance
22 and the validity of looking at the evaluable endpoint

1 population is quite relevant here, given the whole
2 issue of liver transplantation.

3 So really, there are two parts to this. One
4 is, do we have the reproducibility? And one is, do we
5 have the core data? I think, with the evaluable
6 efficacy, we do have significance, which is the 005
7 study. With the 006 study, of which the data was
8 presented, we didn't talk too much about that. With
9 the crossover from placebo to open label, I thought
10 there were further signals of significance, which was
11 sufficient for me in this particular unique
12 circumstances to vote yes. And I usually also go with
13 intent to treat, but here I believe it's appropriate to
14 take this different approach.

15 DR. ROSENBERG: I'm Paul Rosenberg. I voted
16 no because I don't think it was robust results for the
17 clinical endpoints.

18 DR. ENSRUD: Erik Ensrud. I voted no. We
19 have a series of questions here that are set at
20 different bars. This question is a very high bar, and
21 I didn't feel the study, although I agree with Eric
22 Logigian that I don't see it as a flawed study, I

1 actually think it's a commendable study, but it didn't
2 meet this particular question.

3 DR. FOUNTAIN: That's all of our voting
4 members. Part B now is just a perfect follow-up to your
5 comments.

6 In the context of the above discussion, are
7 the findings of Study 005 sufficiently robust to
8 provide substantial evidence of efficacy, similar to
9 that usually provided by two supportive studies for a
10 biomarker rather than a clinical endpoint, that is
11 reasonably likely to predict a clinical benefit?

12 So we will begin voting now in exactly the
13 same manner.

14 DR. COHEN: Dr. Katz, can you just clarify
15 biomarker?

16 DR. KATZ: Clarify biomarker? Yes. Again,
17 maybe it was an inelegant word. We are looking for
18 surrogate. So again, usually it's some sort of a lab
19 test or something like that. It can be a clinical
20 endpoint that you feel is not the real clinical
21 endpoint you care about, but one that predicts a
22 clinical endpoint that you care about.

1 (Voting.)

2 DR. FOUNTAIN: So has everyone voted? Yes,
3 no, or abstain.

4 [Voting.]

5 DR. JOHNSON: I will now read the vote into
6 the record. We have 13 yeses and 4 nos.

7 DR. FOUNTAIN: Let's start on this side with
8 Dr. Ensrud this time.

9 DR. ENSRUD: I'm Erik Ensrud. I voted yes. I
10 felt, based on the wording of this question, the sigma
11 3 sum score, including the small fiber and the TTR
12 stabilization, met the query.

13 DR. ROSENBERG: I'm Paul Rosenberg. I voted
14 yes, same reason as he did.

15 DR. GOOCH: Clifton Gooch. I voted yes, also
16 not only because of the significance of the small fiber
17 QST results, but also because of the significance when
18 the muscle strength testing was assessed, which I think
19 both are very relevant measures clinically to patients
20 with this particular form of neuropathy.

21 DR. LOGIGIAN: Erik Logigian, weak yes for
22 muscle strength.

1 DR. MIELKE: Michelle Mielke. Weak yes for
2 muscle strength as well. I think there are some
3 weaknesses in the main positivity at one site that
4 worries me a little bit, but I think the positives
5 certainly outweigh the negatives.

6 DR. CLANCY: Robert Clancy. I voted yes also
7 for the same reasons already discussed.

8 DR. FOUNTAIN: Nathan Fountain. I voted yes.
9 I'd also add that the more traditional biomarker of
10 measuring the effect of the protein on the tetramers
11 was convincing to me, although we didn't discuss that
12 much or its methodology.

13 DR. KATZ: Can I go first? I'm sorry. Those
14 folks who voted yes and have said for the same reasons,
15 could you just be explicit as to which of the endpoints
16 you are considering the surrogate, for purposes --

17 DR. FOUNTAIN: If I could summarize, I think
18 it's the small fiber neuropathy, particularly part of
19 the sigma 3, muscle strength testing, as part of the
20 NIS-LL. And I added even the convincing but admittedly
21 unknown methodology of actually testing the tetramer in
22 binding and kinetics, the blood test.

1 DR. KATZ: Right. I understand that, though,
2 as an aggregate of what the people are voting yes for,
3 but it would be useful for us to know just specifically
4 what each person considered in their yes vote.

5 DR. FOUNTAIN: Should we begin again with Dr.
6 Ensrud?

7 DR. KATZ: Some people said it. I think Dr.
8 Clancy.

9 DR. ENSRUD: As I mentioned, TTR
10 stabilization and then the sigma 3 small fiber sum
11 score.

12 DR. ROSENBERG: Same for me.

13 DR. GOOCH: Small fiber subscore and
14 strength. Although I am intrigued by the physiologic
15 data from the TTR assay, I'm not sure that there's a
16 direct clinical link there in terms of its clinical
17 effects. It makes sense, of course, but these other
18 measures, small fiber function and strength, are
19 clearly validated as having direct clinical impacts on
20 a patient's function.

21 DR. LOGIGIAN: Muscle strength.

22 DR. MIELKE: All three.

1 DR. CLANCY: Yes. The muscle strength, the
2 sigma 3 scores, and the very sexy TTR assay, whatever
3 it means.

4 DR. FRANK: Samuel Frank. I voted yes. And
5 what was most convincing to me was the TTR
6 stabilization. And getting back to this being a
7 lifelong disease, it also raises the question of
8 whether genetic testing should be done in kids and
9 whether that should start as early as possible, based
10 on that stabilization, too, if that's truly the
11 mechanism of the disease.

12 MS. HOUSE: Tiffany House. I voted yes for
13 the TTR analysis and for the muscle weakness.

14 DR. MARDER: Ellen Marder. I voted yes for
15 two reasons. One is the muscle strength and the other
16 is the small fiber measurement, which seemed to keep --
17 let's see, the treated versus the controls seemed to
18 preserve a distance even when the controls started to
19 take the medication. They still seemed to do better in
20 the 006 study as time goes on.

21 DR. BAGIELLA: Emilia Bagiella. I voted no
22 because, although there is an effect, a possible effect

1 of the drug on this marker, it was not clear to me that
2 this marker are really surrogate endpoints for the
3 clinical outcome. There was no evidence of that.

4 DR. OAKLANDER: Anne Louise Oaklander. I
5 voted yes on the basis primarily of the outstanding
6 results for the tetramer stabilization. I would
7 comment also that the measures used to evaluate small
8 fiber function are not the ones identified as optimal
9 by the American Academy of Neurology and the European
10 Federation of Neurological Societies.

11 So I would suggest consideration in future
12 studies of the addition of skin biopsy and of other
13 small fiber measures in AFT. The sweat test, actually,
14 has been shown to be more sensitive in many cases. So
15 I'd like to see these small fiber measures expanded in
16 future study.

17 DR. VERMA: Ashok Verma. I voted yes. Number
18 one, good basic science, molecular basis with the TTR
19 analysis, and motor strength.

20 DR. PRESTON: David Preston. I voted yes. In
21 regards to the muscle strength and the small fiber
22 testing, I was actually not impressed at all by it, and

1 I think it has the problems of multiple testing. But
2 the TTR stabilization was so robust and the fact is
3 that it makes sense.

4 So I actually do believe that this is the
5 mechanism of the amyloid deposition. So this drug was
6 so convincing as far as stabilizing that tetramer so it
7 wouldn't break down, it makes so much sense, it fits
8 together, that I think maybe a longer trial will show
9 clinical efficacy.

10 DR. CHAUDHRY: I'm Vinay Chaudhry. I voted
11 no. I wasn't convinced with the muscle strength or the
12 small fiber data. And for the reasons that were
13 mentioned, the 006 study did not pan out with small
14 fiber. And I was more convinced with that being noise
15 and the muscle strength testing suffered from the
16 multiple testing issue. It did not form a length-
17 dependent pattern of muscle weakness.

18 TTR is clearly robust, but I still am not
19 convinced that that leads to a clinical benefit, since
20 the quality of life did not change in any of these. So
21 I'm not sure how to relate this to the clinical
22 benefit. Therefore, I voted no.

1 DR. SHEFNER: I'm Jeremy Shefner. I voted
2 no. I think all of the clinical endpoints, either in
3 aggregate or broken down, are not particularly robust,
4 didn't reproduce when the study was looked at without
5 that single site.

6 I am completely convinced that there's an
7 effect on the TTR stabilization, but I don't think
8 there is a strong argument to be made at this point
9 that, that has a particular implication on the clinical
10 disease. And I also want to note that some of our
11 microphones are still flashing and some of them aren't.
12 I don't know if that's a problem.

13 DR. COHEN: Jeffrey Cohen, a tortured no. I
14 think, again, because of the way this study was
15 constructed, that those data from the Portugal study
16 were so different from the others. Also, just
17 clinically, some of the results being positive in some
18 measures and others being negative, as we said, about
19 sensory testing, some of the small fiber function, just
20 doesn't make sense clinically to me.

21 DR. FOUNTAIN: Thank you. Next is question
22 3.

1 Given our response to questions 2A and 2B, do
2 you still want us to answer question 3? Dr. Katz?

3 DR. KATZ: We're discussing it. I think our
4 intention was, if you didn't think there was
5 substantial evidence for anything, clinical, or
6 biomarker, or surrogate, do you think Study 005 could
7 be one study contributing --

8 DR. SHEFNER: I'd like to vote on it.

9 DR. FOUNTAIN: So we're resolving whether or
10 not we're going to change the wording of question 3,
11 since as written, it's --

12 DR. KATZ: I don't think it's necessary to
13 vote on that question.

14 DR. FOUNTAIN: Okay.

15 So that means we'll move over to question 4
16 on the back side and projected on the screen, regarding
17 Study 006. Study 006 does not have the characteristics
18 of an adequate and well-controlled trial, but may
19 provide supportive evidence of effectiveness for
20 tafamidis.

21 Please discuss the strengths and weaknesses
22 of Study 006 as a source of supportive evidence,

1 including the effect of the following factors. And
2 some of these, we have discussed, but why don't we go
3 down the line and see if there is issues we need to
4 discuss further? And then we may need to clarify some
5 issues even if we don't agree on them.

6 First is analysis of many endpoints without
7 control for multiple testing.

8 DR. KATZ: Again, you have voted as a
9 committee that there is substantial evidence of
10 effectiveness for an effect on a surrogate. I think
11 that your views specifically with regard to the
12 regulatory implications of Study 006 are less important
13 at this point.

14 DR. FOUNTAIN: Would you like us just to move
15 to question 5 and vote or skip it?

16 DR. KATZ: We can go to 5. It's also sort of
17 moot. Right. I think it's not necessary to vote on 5.
18 It would be nice to have a little discussion about 6, I
19 mean, if there's anything else that maybe you want to
20 throw some comments in about, 006 or something.

21 DR. FOUNTAIN: It seems to me there's a topic
22 we haven't discussed that's come up now as kind of a

1 recurrent theme, and that is the TTR testing that we
2 haven't talked about so much.

3 If you have another comment, Dr. Logigian?

4 DR. LOGIGIAN: With regard to that, I don't
5 know if Dr. Kelly is still here. But with regard to
6 the TTR testing, I was wondering, is there a way to
7 measure in serum the toxic monomer? That you could
8 then use -- first of all, that's closer to the
9 stabilization issue, is closer to the toxic compound.

10 DR. FOUNTAIN: Dr. Kelly?

11 DR. KELLY: That's an excellent question. I
12 know at least two independent organizations that are
13 trying to develop antibodies to do that, and my lab is
14 trying to use a subunit exchange experiment. So we're
15 working on that, but it's not available today that I'm
16 aware of.

17 DR. LOGIGIAN: Can I ask a follow-up
18 question?

19 DR. FOUNTAIN: Yes.

20 DR. LOGIGIAN: Is it true that this is
21 actually a heterogeneous compound in someone with FAP?
22 That is that they would have a mixture of wild type and

1 mutant monomers, and that there could be five different
2 potential -- I don't know -- five or six combinations,
3 three of one, one of another, two and two, et cetera?
4 And do you think the drug has equal effect on all of
5 those different compounds, that is, in terms of
6 stabilizing them or are some potentially less bound?

7 DR. KELLY: It's an excellent question. I
8 think each different mutation and each heterotetramer
9 will have a slightly different binding constant. Now,
10 that said, the KD at the first site is 2 nanomolar and
11 the plasma concentration is 4 micromolar. So the issue
12 came up earlier about albumin binding, too. I mean,
13 basically, 99 percent of the tafamidis in plasma is
14 going to be bound to transthyretin unless the sites are
15 saturated. Then we'll go to albumin for sure. So your
16 question is a really good one and that's the answer.

17 DR. FOUNTAIN: Dr. Katz?

18 DR. KATZ: Yes. I have a question. Again,
19 part of the issue for us is where in the chain of
20 events this surrogate falls. So for TTR, it's
21 obviously very, very early in the chain, presumably
22 perhaps the inciting event. But the end of the chain

1 is the deposition of amyloid, which presumably is
2 what's doing the damage to the tissues.

3 So is there any in vivo data that looks at
4 amyloid deposition in a model or in people? I gather
5 there are no biopsies in people on treatment versus no
6 treatment?

7 DR. KELLY: As you probably know, Dr. Katz,
8 there have been two recently approved amyloid imaging
9 agents, both based on PET. To my knowledge, they've
10 never been attempted for transthyretin amyloidosis.

11 In the early days of FoldRX, we purposefully
12 avoided that for the following reason, that patients
13 who respond to light chain amyloidosis therapy and our
14 observations in this study as well with regard to
15 cardiac function, suggest that the wall thickness of
16 the heart doesn't change even in the responders,
17 suggesting that the amyloid doesn't change.

18 Now, I know there are many reports to the
19 contrary. But if you actually read those papers, the
20 title is opposite to the data. That is, there's very
21 weak evidence for amyloid clearance over five years.

22 So I personally think it would be a mistake

1 to look at amyloid load because the emerging theme in
2 the literature is that probably what our body does to
3 protect us from these terrible diseases is to make
4 amyloid, ironically. It's sort of like building a moat
5 around the cell to keep all the crap on the outside,
6 but that's still a hypothesis.

7 DR. FOUNTAIN: While you're up there, can I
8 ask you to clarify one other thing? And that is, you
9 might imply from the results, as they're listed, that
10 the drug works 100 percent or zero, but the percent is
11 actually a change in the rate constant or something
12 like that. Could you clarify the percent change that is
13 listed as the outcome from the study?

14 DR. KELLY: Without trying to make this too
15 complicated, I'm happy to work with you folks
16 afterwards.

17 Can we call up slide CP5?

18 DR. FOUNTAIN: The nature of my question,
19 just to clarify, not so much the basic chemistry, just
20 so we can put in perspective, if something can change
21 200 percent or 300 percent, then 100 percent has less
22 meaning.

1 DR. KELLY: So the bottom line is that, under
2 physiologic conditions -- so this is a subunit exchange
3 experiment. So Dr. Farkas and Dr. Katz didn't see
4 this. This is actually accepted for publication in P&S,
5 and it's been reviewed by Science and other published
6 articles.

7 What we do here is to take two tetramers. One
8 has a tag and one doesn't. And the idea is, how fast
9 can they exchange subunits, reflecting the rate of
10 dissociation?

11 As you can see, the rate of dissociation at
12 Cmin and Cmax is incredibly slow for the wild type
13 tetramer at drug concentration. So what Dr. Farkas
14 brought up in the briefing document is correct, that
15 is, that there's roughly a two- to threefold slowing in
16 the presence of drug. But you have to realize that's
17 in a 4.8-molar urea, where the binding constant takes a
18 huge hit and the rate of dissociation is dramatically
19 accelerated. So the only reason we use that assay is
20 we can measure it in a couple of days.

21 You can see here we're already out to eight
22 days and we only have 5 percent exchange. Right? So

1 this protein is really kinetically stable. I hope that
2 answers your question. So it's virtually 100 percent
3 under physiologic conditions. That's what makes it so
4 hard to measure.

5 DR. FOUNTAIN: Dr. Rosenberg? Dr. Clancy?

6 DR. CLANCY: He just answered it.

7 DR. FOUNTAIN: So we're on the theme of
8 additional aspects of efficacy that might be measured.
9 And the one we just talked about was TTR. Any other
10 questions about it or clarifying issues? Dr. Frank?

11 DR. FRANK: This is in regard to question 6.
12 Yes?

13 DR. FOUNTAIN: Yes.

14 DR. FRANK: So something that Dr. Coelho said
15 in passing -- and I hope I heard her correctly -- is
16 that 41 of the 44 patients removed themselves from the
17 liver transplant list when they were on this longer
18 term. Is that correct?

19 So I also want to raise the question of the
20 efficacy of liver transplant. I mean, we assume that
21 it works, but what's really the evidence? And right
22 now, that's the gold standard. There are many surgical

1 procedures that we assume work. And then when we do
2 more controlled studies, it turns out they don't.

3 So I think that we have more for this drug
4 than we do for liver transplant, especially if there's
5 longer- term evidence that could follow up on it.

6 DR. FOUNTAIN: Any more discussion about
7 question 6? Question 7 is, "Please discuss if there
8 are any particular concerns about safety," which we
9 approached to some degree before. And our conclusion
10 was, it's a small end, but there are no particular
11 concerns.

12 DR. GOOCH: I have a question about the
13 bladder issues. And I know that a neurogenic bladder
14 can be a part of this disease process. And I wonder if
15 the sponsors could comment on that particular adverse
16 event that came up in the safety data.

17 DR. FOUNTAIN: What comment would you like
18 them to make? Is that mechanistically, or if it's
19 coincidence, or other?

20 DR. GOOCH: Just comment on that particular
21 side effect in the treatment group versus placebo
22 group. It did kind of show up among the top four

1 adverse events in the study. Does the data support
2 that primarily as an issue related to the underlying
3 disease process alone, which we know it can be? Was
4 there any indication that the drug itself might
5 exacerbate a neurogenic bladder in a patient with this
6 condition?

7 DR. LOMBARDO: So I think, if I understand
8 you correctly, you're speaking about the UTIs that were
9 recorded?

10 DR. GOOCH: Yes.

11 DR. LOMBARDO: I'm actually going to ask Dr.
12 Susan Mather from our safety group to come up and speak
13 to that specifically.

14 DR. MATHER: Hi. I'm Dr. Susan Mather from
15 worldwide safety at Pfizer. And yes.

16 Let me see if we can pull up -- we might want
17 to pull up -- yes, slide 26. So this is just a brief
18 summary of some features of the patients who had
19 urinary tract infections, which as you rightly pointed
20 out, wouldn't be unexpected in this patient population.

21 Before I get into it, I might have to call my
22 colleague, John Davis, up to talk a little bit about

1 mechanism, but I will say that the number of serious
2 UTIs we saw was very, very small, even in this small
3 population of patients studied. There were two. And
4 by and large, the UTIs were treatable, didn't result in
5 patients discontinuing from the study, and may have had
6 something to do with the fact that some patients,
7 because of their urinary retention, were self-
8 catheterizing themselves.

9 So by and large, the adverse event itself is
10 an unexpected, but that imbalance in the groups was
11 something that definitely made us make note of this as
12 an adverse drug reaction in the proposed labeling.

13 Does that get at your question?

14 DR. GOOCH: That's a good summary of the
15 data. Any ideas, mechanistically, as to why -- or is
16 there any hint that this might in some way functionally
17 cause poor bladder emptying, or some kind of problem
18 with the immune protection of the bladder, or anything
19 of that nature?

20 DR. MATHER: I will say that, looking at the
21 white blood cells, and absolute neutrophil, absolute
22 lymphocyte counts, we were glad to see no evidence of

1 immunosuppression. As far as the other factors that
2 you mentioned, I don't think there's any evidence that
3 would explain it.

4 DR. FOUNTAIN: Dr. Clancy?

5 DR. CLANCY: Yes. Regarding the UTIs, do we
6 know, were all the patients self-cathetering or were they
7 more likely to be in this infection group?

8 DR. MATHER: No. Not all of the patients
9 were self-cathetering. About a third of the patients on
10 tafamidis -- no. Less than a third of the patients on
11 tafamidis were and a few on placebo were self-cathetering,
12 who had UTIs. But no. Not all of the patients were.

13 DR. CLANCY: But if it's a third in the
14 treated group and only a handful in the placebo, that
15 might be the mechanism, that you're more likely to get
16 an infection if you self-cath.

17 DR. MATHER: Yes. Definitely. That would
18 definitely introduce the mechanism, but it wasn't quite
19 a third. So in the UTIs we saw, only a small number of
20 patients on tafamidis and a small number of patients on
21 placebo were self-cathetering. So sorry if I confused.

22 DR. FOUNTAIN: Are there more comments about

1 that? So if we summarize, then, question 7, discuss
2 the particular safety concerns.

3 Dr. Chaudhry, do you have something to say
4 before I summarize?

5 DR. CHAUDHRY: Yes. I mean, I generally
6 don't bring this up as an adverse event, but I do think
7 about it as an adverse event. Is there a cost
8 estimated? Is there a yearly cost of this drug, say,
9 in Europe, which is being used or is it not fair game
10 to talk about it on this panel?

11 DR. KATZ: The cost? The question was, is it
12 fair game to talk about the cost? Not here. That is
13 not a consideration from the point of view of making a
14 decision about approving.

15 DR. FOUNTAIN: I think we'd summarize
16 question 7 by saying there are no particular safety
17 concerns.

18 Anymore comments from the panel? Or would
19 Dr. Katz like to make any summary comments?

20 DR. KATZ: I'd just like to thank everybody.
21 It's obviously been a very difficult set of data and
22 decisions, so it's really been extraordinarily helpful.

1 And again, thanks to the folks who spoke in the public
2 session. This was very helpful, and we appreciate it.

3 DR. FOUNTAIN: Thank you. And I think this
4 really illustrates the difficult job you have because
5 all of us here on the panel, of course, especially
6 after hearing such compelling stories, want to do all
7 we can to help people with an inexorably fatal
8 condition, but yet want to do what's right to find
9 drugs that are effective and safe. So that's your
10 mission that I think we can appreciate.

11 Thank you, everyone, for coming. Please
12 remember to drop off your name badge at the
13 registration table on your way out so they may be
14 recycled. The meeting is adjourned. Thank you.

15 (Whereupon, at 4:33 p.m., the meeting was
16 adjourned.)

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