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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
  
PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS  
ADVISORY COMMITTEE

MONDAY, OCTOBER 17, 2011

7:30 a.m. to 4:30 p.m.

FDA White Oak Campus  
White Oak Conference Center  
10903 New Hampshire Avenue  
Building 31, The Great Room  
Silver Spring, Maryland

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1       **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**

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P R O C E E D I N G S

**Call to Order**

1  
2  
3 DR. FOUNTAIN: Good morning and welcome.  
4 We'd first like to remind everyone to please  
5 silence your cell phones, Blackberrys, and other  
6 devices if you've not already done so. I would  
7 like to identify the FDA press contact, Sandy  
8 Walsh.

9 If you're present, could you please stand?

10 Okay. We'll point her out when she comes  
11 in.

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

22 In the spirit of the Federal Advisory

1 Committee Act and the Government in the Sunshine  
2 Act, we ask that the advisory committee members  
3 take care that their conversations about the topic  
4 at hand take place in the open forum of the  
5 meeting. We are aware that members of the media  
6 are anxious to speak with the FDA about these  
7 proceedings, however, FDA will refrain from  
8 discussing the details of this meeting with the  
9 media until its conclusion. Also, the committee is  
10 reminded to please refrain from discussing the  
11 meeting topic during breaks or lunch.

12 Thank you.

13 Now, I'll pass to Dr. Philip Bautista, who  
14 will read the conflict of interest statement.

15 **Conflict of Interest Statement**

16 DR. BAUTISTA: Thank you.

17 The Food and Drug Administration is  
18 convening today's meeting of the Peripheral and  
19 Central Nervous System Drugs Advisory Committee  
20 under the authority of the Federal Advisory  
21 Committee Act of 1972. All members and temporary  
22 voting members of the committee are special

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

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

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

21 Under Section 712 of the FD&C Act, Congress  
22 has authorized FDA to grant waivers to special

1 government employees and regular federal employees  
2 with potential financial conflicts, when necessary,  
3 to afford the committee essential expertise.

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

15           At today's meeting, the committee will  
16 discuss supplemental New Drug Application 21641013  
17 for Azilect, rasagiline mesylate tablets,  
18 manufactured by Teva Neuroscience, Incorporated,  
19 for the following proposed indication: treatment  
20 of patients with idiopathic Parkinson's disease to  
21 slow clinical progression and treat the signs and  
22 symptoms of Parkinson's disease as initial

1 monotherapy and as adjunct therapy to levodopa.

2           This is a particular matters meeting during  
3 which specific matters related to Teva  
4 Neuroscience's rasagiline will be discussed. Based  
5 on the agenda for today's meeting, and all  
6 financial interests reported by the committee  
7 members and temporary voting members, no conflict  
8 of interest waivers have been issued in connection  
9 with this meeting. To ensure transparency, we  
10 encourage all standing committee members and  
11 temporary voting members to disclose any public  
12 statements that they have made concerning the  
13 product at issue.

14           With respect to FDA's invited industry  
15 representative, we would like to disclose that Dr.  
16 Roy Twyman is participating in this meeting as a  
17 non-voting industry representative, acting on  
18 behalf of regulated industry. Dr. Twyman's role at  
19 this meeting is to represent industry in general  
20 and not any particular company. Dr. Twyman is an  
21 employee of Johnson & Johnson.

22           We would like to remind members and

1 temporary voting members that if the discussion  
2 involves any other products or issues not already  
3 on the agenda, for which an FDA participant has a  
4 personal or imputed financial interest, the  
5 participants need to exclude themselves from such  
6 involvement, and their exclusion will be noted for  
7 the record. FDA encourages all other participants  
8 to advise the committee of any financial  
9 relationships that they may have with the firm at  
10 issue.

11 Thank you.

12 DR. FOUNTAIN: We'll now proceed with  
13 Dr. Katz's introductory remarks.

14 **FDA Introductory Remarks**

15 DR. KATZ: Thanks, Dr. Fountain.

16 Let me extend my welcome to the members of  
17 the public who are attending, and to the sponsor,  
18 and particularly to the committee, and especially  
19 to the several invited guests that we have asked to  
20 come here to help us. I think we have a very  
21 distinguished panel of clinicians and statisticians  
22 to help us with today's very interesting issue.

1           Also, I'd like to thank everybody for their  
2 flexibility in agreeing to start the meeting at  
3 7:30. I recognize it's very early, but we have a  
4 very full agenda, a fair amount of which will be  
5 taken up with formal presentations and questions to  
6 the presenters. And in the interest of trying to  
7 maximize the time the committee has to discuss  
8 these issues, these very complicated issues, and  
9 deliberate on the questions we've asked them to  
10 vote on, we thought it was best to try to start a  
11 little earlier. So I appreciate everybody's  
12 indulgence in that matter.

13           Before I make my introductory remarks about  
14 today's issue, I've been given the task of, as this  
15 happens from time to time, recognizing the service  
16 of several of the committee members whose terms are  
17 coming to an end.

18           Serving on an advisory committee is  
19 difficult. There's a lot of work and preparation.  
20 And as we have more and more advisory committees,  
21 it becomes more and more time consuming for the  
22 folks on the committee, who obviously have many

1 other commitments. It's difficult in preparation.  
2 It can be difficult in the actual meeting. It can  
3 even require a bit of courage to take positions  
4 that may not be popular in a very public forum. So  
5 we very much appreciate folks agreeing to serve.

6 As I say, two folks are rotating off -- you  
7 know, committee members serve for several years,  
8 and two are rotating off basically today. And so  
9 we just wanted to recognize -- as we typically do,  
10 as I have said in the past, instead of money, we  
11 give plaques.

12 So the first plaque goes to Dr. Jason Todd,  
13 whose, I think, official service ends in January of  
14 next year, but we are not planning on having any  
15 advisory committees before then, other than today.  
16 But if we do, you'll have to give the plaque back,  
17 but we'll ask you to come back.

18 So if I could ask Dr. Todd to come up,.  
19 Dr. Todd's been on the committee for several years.  
20 His input has always been very useful, very  
21 helpful.

22 Let me just read the plaque. I think what

1 it says is very true. It says, "U.S. Food and Drug  
2 Administration Advisory Committee Service Award  
3 presented to Jason W. Todd, M.D., in recognition of  
4 distinguished service to the people of the United  
5 States of America." And I think that actually is a  
6 very true statement, and we very much appreciate  
7 it. So, Dr. Todd, thank you very much.

8 DR. TODD: Thank you.

9 [Applause.]

10 DR. KATZ: The second person  
11 whose -- actually, I think his last official day on  
12 the committee is at the end of this month -- is  
13 Dr. Roy Twyman, who you have heard is the industry  
14 representative and has always brought a very  
15 important perspective and very insightful comments  
16 to the meetings that he's been present at.

17 Again, "U.S. Food and Drug Administration  
18 Advisory Committee Service Award presented to Roy  
19 E. Twyman, M.D., in recognition of distinguished  
20 service to the people of the United States of  
21 America." And again, it's very true.

22 In Roy's case, not only don't we pay him

1 very much, we don't even let him vote.

2 [Laughter.]

3 DR. KATZ: But your service has been very  
4 distinguished, and thank you very much.

5 [Applause.]

6 DR. KATZ: So I'll move onto what I hope  
7 will be relatively brief formal introductory  
8 comments. Today, you know we're here to consider  
9 supplement to NDA21641, submitted by Teva  
10 Pharmaceuticals. And this is the first serious  
11 attempt that we've had from a sponsor to attempt to  
12 establish an effect of a drug, not just on the  
13 symptoms of a condition but on the underlying  
14 progression of the disease. As you know, this  
15 particular application proposes that rasagiline be  
16 indicated for slowing clinical or disease  
17 progression in patients with Parkinson's disease.

18 Rasagiline, as you know, is a monoamine  
19 oxidase B inhibitor and has been approved in this  
20 country since 2006 for the treatment of the signs  
21 and symptoms of Parkinson's disease. The current  
22 label makes no statements about the basis for the

1 effects seen in those patients. It doesn't say  
2 anything about progression of the disease. Like  
3 all drugs that we've approved, the assumption has  
4 been that the effect has been a symptomatic one and  
5 not an effect on disease progression. And, again,  
6 that's what we're here to talk about today.

7 But for various reasons, based on the  
8 pharmacology, and the mechanism of action, and even  
9 on some preliminary clinical results, which we'll  
10 talk about in one study, the sponsor believed that  
11 rasagiline could have an effect not only on the  
12 symptoms, but on the underlying progression of the  
13 disease itself.

14 In support of this claim, they've submitted,  
15 as you know, the results of two clinical trials,  
16 named TEMPO and ADAGIO. These trials incorporate  
17 elements of a study design term. They randomized  
18 or delayed-start design, a design that was first  
19 described in the literature by Dr. Paul Leber in  
20 the 1990s. You've presumably read a great deal  
21 about this. You've seen pictorial representations  
22 in the briefing documents. You will see a great

1 deal more of that this morning in the slides. But  
2 just briefly, in this design, patients are  
3 initially randomized to drug or placebo, followed  
4 for an appropriate period of time.

5           This first phase of the study is essentially  
6 identical to the typical sort of parallel group  
7 studies that we see all the time. After this first  
8 phase, in which there is an expectation that there  
9 will be a divergence of slopes on whatever outcome  
10 measure we're talking about -- in this case, it's  
11 the UPDRS, which is a sort of standard Parkinson's  
12 outcome measure -- we expected there would be a  
13 divergence of slopes in this first phase. And at  
14 the end of this first phase, when this difference  
15 emerges, patients originally randomized to drug  
16 continue on drug for another pre-determined period  
17 of time. These patients are called early-start  
18 patients because they started on drug from the  
19 beginning of the study. And patients originally  
20 randomized to placebo are in this second phase,  
21 called the so-called active phase, are now switched  
22 to active drug. And these patients are called

1 delayed-start patients for the obvious reasons that  
2 they start on placebo and their start on the drug  
3 was delayed.

4 We expect, for a drug that modifies the  
5 disease, the delayed-start patients would never  
6 really catch up by the end of this active phase,  
7 the presumption being patients treated  
8 early -- treating patients early fundamentally  
9 alters the course of the disease, so that if you  
10 start treating them later, they can never really  
11 catch up to the patients who started treatment very  
12 early.

13 If the delayed-start patients do catch up at  
14 the end of the study, the interpretation of that  
15 finding would be that there really has been no  
16 effect of the drug on the underlying progression of  
17 the disease because it didn't matter if you treat  
18 it early or late, they all ended up in the same  
19 place at the end of the study.

20 So it's critical, therefore, in the  
21 interpretation, the analysis, and the  
22 interpretation of this design that in order for a

1 conclusion -- or a preliminary conclusion about  
2 disease modification, that the patients actually be  
3 different; the early-start patients and the  
4 delayed-start patients be different at the end of  
5 the study.

6 But even if there was a difference or is a  
7 difference between the early- and delayed-start  
8 patients at the end of the study, it's possible  
9 that, in the active phase, the patients actually  
10 started to approach each other, and had the study  
11 been a little longer, they might have actually been  
12 the same at the end of the study. And so in that  
13 instance, if that were the case, seeing a  
14 difference by itself at the end of the study  
15 wouldn't be adequate to truly define a disease-  
16 modifying treatment.

17 So in order to prevent that spurious  
18 conclusion in this active phase, we require that  
19 the patients -- the slopes, in this case the UPDRS,  
20 be parallel to each other in the active phase.  
21 And, again, you will see pictorial representations  
22 of this throughout the day.

1           These studies are complicated. They've  
2 rarely been conducted adequately. Many of the  
3 issues that complicate the design, and the conduct,  
4 and the interpretation of this study design have  
5 been discussed in the literature. For example,  
6 when we're talking about calculating slopes in the  
7 first phase, where do we start counting data? Do  
8 we start from the very first datapoint, or do we  
9 wait -- do we exclude some of the early data in the  
10 calculation of the slopes?

11           Drugs that have disease-modifying effects  
12 can certainly also have symptomatic effects, and we  
13 wouldn't want the symptomatic effects to  
14 contaminate the interpretation of disease  
15 modification. So a decision is made to exclude  
16 some of the early data, on the presumption that  
17 that might reflect an entirely symptomatic effect.

18           But the question is, should we do that? If  
19 so, when we should start counting data in that  
20 first phase? Other questions are, for example, how  
21 long should the treatment phases be? And, in  
22 particular, how long should the active phase be, so

1 as to give the delayed-start patients sufficient  
2 time to actually catch up to the early-start  
3 patients, if that's possible.

4 How do we operationalize the quality of  
5 slopes in the active phase that the design seems to  
6 require in order for us to be able to conclude that  
7 the lines are actually not approaching each other,  
8 and that they are, in fact, for all intents and  
9 purposes, parallel? What if the data are not  
10 linear in either phase, and does that preclude an  
11 adequate assessment of whether or not -- a  
12 comparison of slopes? How would we do that in that  
13 case?

14 What if not all patients enter the active  
15 phase? And that's almost always probably going to  
16 be the case and was the case here. This can result  
17 in a comparison of the data in that phase of non-  
18 randomized groups, with the attendant possibility  
19 of the introduction of biases, either identified or  
20 non-identified. So there are many methodologic and  
21 conduct issues with regard to these studies.

22 So to talk a little bit about the studies,

1 one of the studies you'll hear about, as I  
2 mentioned, is called TEMPO, which was the first of  
3 the studies that the company actually did. And in  
4 this study, patients were randomized to placebo,  
5 1 milligram a day or 2 milligrams a day, for  
6 26 weeks in this first phase. And in the active  
7 phase, which was a similar duration, patients who  
8 received placebo in the first phase would switch to  
9 2 milligrams, but patients who had received  
10 1 milligram in the earlier phase continued on  
11 1 milligram. So there was no real delayed-start  
12 group for the 1-milligram patients.

13 In fact, the first phase of this study,  
14 which the protocol specified as being the primary  
15 phase for analysis, was relied upon in part to  
16 support the approval of rasagiline for its current  
17 indication. But the results of the entire study,  
18 including the active phase, were not really  
19 evaluated at that time or reviewed in detail. But  
20 when we looked at it and when the sponsor looked at  
21 it, there was a suggestion, based on the  
22 2-milligram early and delayed patients, that there

1 might be an effect on disease modification for the  
2 2-milligram dose.

3           So for this reason, the sponsor was  
4 motivated, encouraged to perform another study,  
5 which would be adequately and prospectively  
6 designed to establish whether or not, in fact,  
7 there really was a disease-modifying effect for  
8 some dose. And we subsequently worked closely with  
9 the sponsor to design and come up with an analysis  
10 plan for ADAGIO, which is the primary source of  
11 evidence that you'll hear about today.

12           We did tell the sponsor, at that time, that  
13 the results of the TEMPO study, by itself, although  
14 we hadn't fully analyzed it, would not likely  
15 support approval and that a second such study,  
16 adequately designed to look at this question, if it  
17 were sufficiently robust, together, those studies  
18 might support an approval for a disease-modifying  
19 claim.

20           So, as you know, the ADAGIO evaluated, in  
21 both phases, in the first phase and the active  
22 phase, both 1 milligram and 2 milligrams. And as

1 I've already described, there are three tests that  
2 need to be applied to the data in this study, and  
3 these tests have to be applied in a specific order,  
4 and this was agreed to in the protocol, and the  
5 performance of any subsequent tests relied on the  
6 fact that the previous test had to have reached  
7 statistical significance for that dose.

8 So, again, just to go over that, first, the  
9 slopes of the drug and placebo had to be  
10 significantly different in the first phase. We  
11 called that Hypothesis 1. And if this was true for  
12 either or both doses, then the change from baseline  
13 in the scores at the end of the study, at week 72,  
14 had to be significantly superior on the early  
15 versus delayed patients for any given dose. And  
16 that was called Hypothesis 2. And Hypothesis 2,  
17 again, could only be made by protocol if  
18 Hypothesis 1 was positive for either of the doses.

19 Then we compared the slopes of the curves in  
20 the active phase, early to delayed-start patients,  
21 and those had to be parallel. And that test for  
22 parallelism, defined by the imposition of a non-

1 inferiority margin for slopes, was called  
2 Hypothesis 3. And Hypothesis 3 was only to be  
3 tested if Hypothesis 2 was statistically  
4 significant for either of the doses.

5           It's important to note that the protocol-  
6 specified analysis permitted the possibility that  
7 either dose, as well as, of course, both doses,  
8 could have been considered positive. In a typical  
9 case, where we have two or more doses, we  
10 ordinarily look at the highest dose versus control  
11 first, and if that's significant, we move to the  
12 next highest dose and all the way down. But this  
13 protocol was not written that way. Either dose  
14 could have been significant on its own. So the  
15 1-milligram dose could have been significant by  
16 itself. The 2-milligram dose could have been  
17 significant by itself. Either would be considered  
18 positive. Of course, if the 1-milligram dose  
19 turned out to be positive and the 2-milligram  
20 didn't, there might be questions raised about the  
21 biological meaning of such an outcome. But,  
22 nonetheless, the protocol allowed for that outcome.

1           So, as you've seen the results, and, of  
2 course, you'll hear about in much more detail later  
3 this morning, the 1-milligram appeared on initial  
4 analysis as being positive. That is, the slopes  
5 diverged between 1-milligram placebo. As reported  
6 by the sponsor, there was a significant difference  
7 between the 1-milligram early- and delayed-start  
8 patients at week 72. And the slopes for those two  
9 groups were paralleled by test in the active phase.

10           However, there is agreement, I think, that  
11 although the slopes of the 2-milligram dose versus  
12 placebo diverge in the first phase -- in other  
13 words, Hypothesis 1 was positive with a 2-milligram  
14 dose -- there was no difference seen at week 72  
15 between the early- and delayed-start patients for  
16 the 2-milligram dose.

17           So the 2-milligram dose failed Hypothesis 2.  
18 And by protocol, of course, Hypothesis 3 really  
19 can't be tested for 2 milligrams, because, as I've  
20 discussed, the whole purpose of testing for  
21 parallelism is to see that the difference that you  
22 saw at week 72 wasn't diminishing and wouldn't

1       diminish shortly after the study was done. But of  
2       course, if there is no difference at week 72 for a  
3       particular dose, in this case the 2-milligram dose,  
4       it really makes no sense to test for parallelism.  
5       So the results for 2 milligrams were negative by  
6       protocol.

7               This finding, the negative result for the  
8       2-milligram dose, is a fundamental issue, in our  
9       view, in considering the question of whether or not  
10      the study really does provide evidence that  
11      rasagiline is disease modifying. It's not the only  
12      issue, but it is a fundamental issue.

13             The sponsor has proposed an explanation for  
14      the finding, which relates to the possibility of a  
15      floor effect in the patients studied under UPDRS,  
16      such that an effect really could only be seen in  
17      the sickest patients. And to support this, they  
18      presented analyses that examined the effects of the  
19      treatment based on baseline quartile scores,  
20      ostensibly showing that the patients in the worst  
21      quartile who did in fact actually have an effect.

22             We will show additional quartile analyses

1 that we believe are more appropriate and that raise  
2 questions about this conclusion, and you'll see  
3 those. But as I said before, the protocol did  
4 permit any dose to be positive independently. And  
5 as submitted by the sponsor, the analysis seemed to  
6 support the conclusion that the 1-milligram dose  
7 met the protocol-specified requirements for all  
8 three hypothesis.

9           However, our analyses of the 1-milligram  
10 dose outcomes suggest that the sponsor's conclusion  
11 about the 1-milligram dose meeting protocol-  
12 specified requirements is at least questionable.  
13 For example, a close examination of the first  
14 phases suggests that, in fact, the data are not  
15 linear, and the data in the latter part of that  
16 phase may not be consistent with a disease-  
17 modifying effect.

18           But much more important, however, is the  
19 observation that the sponsor did not present, as  
20 primary, the actual protocol-specified analysis of  
21 Hypothesis 2 for the 1-milligram dose, in other  
22 words, the change from baseline at week 72, at the

1 end of the study. They actually performed a non-  
2 protocol-specified analysis because they identified  
3 various interactions that they considered  
4 undermined the primary protocol-specified analysis.  
5 However, the post hoc analysis that they did do and  
6 presented the results for, in our view, the similar  
7 interactions were also observed for that analysis.

8 So, of course, that raises questions about  
9 the appropriateness of relying on the post hoc  
10 analysis as primary, and it's important to note  
11 that the results of the protocol specified primary  
12 analysis did not reach statistical significance,  
13 even for the 1-milligram group, for Hypothesis 2.  
14 And, of course, that would preclude the testing of  
15 Hypothesis 3. So by protocol, then both groups  
16 would be considered to have been negative.

17 As I also noted earlier, one of the  
18 potential complications of the design is that  
19 patients who enter the active phase may not be  
20 randomized groups, given the dropouts along the  
21 way. These studies are fairly long. And, indeed,  
22 in the ADAGIO study, a close look at the data

1 suggests that this was the case, raising questions  
2 about the interpretation of the study.

3 For example, we've already seen there was a  
4 significant change at the end of the study between  
5 the 1-milligram early- and delayed-start patients.  
6 That's the positive finding in the study. However,  
7 when you look at the results by sex, there was  
8 absolutely no effect in men. All of the effect  
9 seems to come from a very highly significant effect  
10 in women. But it also turns out that there was  
11 significant baseline differences in women, not in  
12 men, in the populations studied for Hypothesis 2.

13 For the 2-milligram group, there was no  
14 differences, we know, between the early and the  
15 late patients at the end of the study, and there  
16 were no baseline differences in the populations  
17 studied for that Hypothesis 2, for that group.

18 So the ostensibly positive findings for  
19 Hypothesis 2, for the 1-milligram group, seemed to  
20 arise from the one group that had significant  
21 baseline differences; that is, women.

22 Now, we understand that these analyses are

1 post hoc analyses. And often you can find apparent  
2 statistical significance where it doesn't exist  
3 when you do many post hoc analyses. But,  
4 nonetheless, this finding raises the question that  
5 there may have been other imbalances that we  
6 haven't tested for, given that the groups being  
7 compared are non-randomized groups.

8 Another concern, although I'm not sure it's  
9 an absolute critical concern for this study -- but  
10 another concern relates to the choice of a non-  
11 inferiority margin used to establish parallelism in  
12 the active phase. We've already seen it doesn't  
13 really make sense to test for parallelism for the  
14 2-milligram dose in that group because there was no  
15 difference between early and late patients at the  
16 end of the study. But such a test was done, and it  
17 turns out that, despite the fact that, very  
18 clearly, the slopes clearly approach each other and  
19 actually meet at week 72 for the early and late  
20 start patients, those two curves actually pass the  
21 test for parallelism. So, by protocol, they would  
22 have been considered parallel, even though, in

1 fact, they clearly are not parallel.

2 So this raises the question about the  
3 appropriateness of the choice of the non-  
4 inferiority margin; in other words, the choice that  
5 allowed two lines that are very clearly not  
6 parallel to be called parallel.

7 Finally, the TEMPO study was re-analyzed  
8 using the methodology that was adopted for the  
9 ADAGIO study. Again, the ADAGIO study had a very  
10 clear prospective plan for analysis. The TEMPO  
11 study didn't really have a clear plan for the  
12 analysis of that active phase, so we went back and  
13 analyzed the TEMPO study, using the methodology  
14 applied to the ADAGIO study. And we recognize that  
15 TEMPO was not designed to be analyzed that way,  
16 underpowered and that sort of thing.

17 The study reports the results of the  
18 2-milligram analysis in TEMPO as positive, but when  
19 you analyze, according to our view, in a more  
20 appropriate way using the ADAGIO methodology, there  
21 was no statistical significance for any of the  
22 hypotheses.

1           So, in summary, the results of the  
2           2-milligram group in ADAGIO appear to be clearly  
3           negative. The sponsor proposes an explanation  
4           based on quartile analyses. Our various quartile  
5           analyses suggest otherwise.

6           Again, although the protocol did permit  
7           either dose to be considered positive and the  
8           sponsor presents the result of the 1-milligram dose  
9           as having met the protocol-specified rules, our  
10          analyses suggest that this finding is, at best, not  
11          robust and not, obviously, correct.

12          Just to recap, in particular, the protocol-  
13          specified analysis of Hypothesis 2 for the  
14          1-milligram dose failed to achieve statistical  
15          significance. The alternative, unplanned analysis  
16          for Hypothesis 2, as presented by the sponsor,  
17          appeared to suffer from the same problem of  
18          interactions that the protocol-specified analysis  
19          suffered from.

20          There were baseline -- or there appeared to  
21          be baseline imbalances in the population analyzed  
22          in the active phase that appeared to importantly

1 affect the results, raising questions about whether  
2 or not they were other imbalances that we don't  
3 know about. There are questions about the non-  
4 linearity of the data, how that might affect the  
5 analysis and interpretation of the trial. And  
6 there are questions, at least in our mind, about  
7 the choice of the non-inferiority margin used to  
8 determine parallelism in the active phase. And,  
9 finally, a re-analysis of TEMPO using the ADAGIO  
10 methodology didn't reveal any significant findings.

11           So taken together, in our view, these data,  
12 these questions, suggest that there may not be a  
13 robust finding for disease modification for either  
14 the 1-milligram or 2-milligram doses. So our  
15 questions to you actually begin with asking you to  
16 discuss the elements of the design that was  
17 employed, to see what you think about that and  
18 whether it is capable of detecting a  
19 disease-modifying effect, if one exists. And then  
20 the other questions we ask you relate to the issues  
21 that I've discussed and that you will hear in great  
22 detail. Of course, if there are any other issues

1 that the committee wishes to discuss and address,  
2 that are relevant, that we have not asked about, of  
3 course, we are very interested in your comments on  
4 those.

5 So with that, let me just say, again, thank  
6 you very much for the work that you've done in  
7 preparation for the discussion and for the work  
8 that you are about to do today. And with that,  
9 I'll hand it back to Dr. Fountain.

10 DR. FOUNTAIN: Thank you.

11 **Introduction of Committee**

12 DR. FOUNTAIN: Now, I'd like to take this  
13 time to introduce the members of the committee, if  
14 we could go around the table, this way. I'll  
15 start, and we'll go around this way, so everyone  
16 knows who's here. I'm Nathan Fountain, professor  
17 of neurology at the University of Virginia.

18 DR. TODD: I'm Jason Todd. I'm a  
19 neurologist in private practice in Concord, North  
20 Carolina.

21 DR. RODNITZKY: Bob Rodnitzky, professor of  
22 neurology at the University of Iowa.

1 DR. BLACK: My name is Kevin Black. I'm a  
2 professor of psychiatry, and neurology, and  
3 neurobiology at Washington University in St. Louis.

4 DR. AHLKOG: I am Eric Ahlskog. I'm a  
5 full-time clinician at the Mayo Clinic in  
6 Rochester, Minnesota.

7 DR. HINSON: I'm Vanessa Hinson. I'm an  
8 associate professor of neurology at the Medical  
9 University of South Carolina in Charleston.

10 DR. ROSENBERG: Paul Rosenberg. I'm  
11 associate professor of psychiatry and behavioral  
12 sciences at Johns Hopkins University.

13 DR. MASSIE: Tristan Massie, FDA biometrics,  
14 reviewer.

15 DR. PODSKALNY: Dave Podskalny, medical team  
16 leader, Division of Neurology Products, FDA.

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

19 DR. UNGER: Ellis Unger. I'm deputy  
20 director of the Office of Drug Evaluation I, FDA.

21 DR. TWYMAN: Roy Twyman. I'm with Johnson &  
22 Johnson. I'm the industry rep.

1 DR. ZIVIN: Justin Zivin, University of  
2 California, San Diego.

3 DR. KHATRI: Pooja Khatri, associate  
4 professor of neurology at University of Cincinnati.

5 DR. FLEMING: Thomas Fleming, department of  
6 biostatistics, University of Washington.

7 DR. D'AGOSTINO: Ralph D'Agostino,  
8 statistician at Boston University.

9 DR. ELLENBERG: Susan Ellenberg,  
10 biostatistician, University of Pennsylvania.

11 DR. ZHAO: Hongyu Zhao, Yale School of  
12 Public Health, biostatistics.

13 DR. MARDER: Ellen Marder, neurologist,  
14 Dallas VA and UT Southwestern.

15 MS. CHRISTENSEN: Jackie Hunt Christensen,  
16 Minneapolis, Minnesota, patient representative.

17 DR. CLANCY: Robert Clancy, professor of  
18 neurology and pediatrics, the Children's Hospital,  
19 Philadelphia, at the University of Pennsylvania,  
20 School of Medicine.

21 DR. FRANK: Samuel Frank, associate  
22 professor of neurology at Boston University, and

1 I'm the consumer representative.

2 DR. BAUTISTA: Philip Bautista, designated  
3 federal officer for the FDA.

4 DR. FOUNTAIN: Thank you. Thank everyone.  
5 And I'd remind you that I should have said before  
6 to turn on the microphone, obviously, you push the  
7 button. But please remember also to turn it off,  
8 or else, we'll hear all your private conversations  
9 as well.

10 Now, let's turn to the industry  
11 presentation. Both the Food and Drug  
12 Administration and the public believe in a  
13 transparent process for information gathering and  
14 decision making. To ensure such transparency at  
15 the advisory committee meeting, FDA believes it is  
16 important to understand the context of an  
17 individual's presentation.

18 For this reason, FDA encourages all  
19 participants, including the sponsor's non-employee  
20 presenters, to advise the committee of any  
21 financial relationships that they may have with the  
22 firm at issue, such as consulting fees, travel

1 expenses, honoraria, and interests in the sponsor,  
2 including equity interests and those based on the  
3 outcome of the meeting.

4 Likewise, FDA encourages you, at the  
5 beginning of your presentation, to advise the  
6 committee if you do not have such financial  
7 relationships. If you choose not to address this  
8 issue of financial relationships, though, at the  
9 beginning of your presentation, it will not  
10 preclude you from speaking.

11 We'll now proceed with the sponsor's  
12 presentation.

13 **Sponsor Presentation - Dennis Ahern**

14 MR. AHERN: Good morning. My name is Dennis  
15 Ahern, with Teva Branded Pharmaceutical Products  
16 Regulatory Group, and I'd like to thank the FDA, as  
17 well as members of the committee, for the  
18 opportunity to present our data today.

19 Teva's branded divisions are focused on  
20 diseases of the central nervous system, women's  
21 health, respiratory, oncology, as well as pain.  
22 Our established brands in neurology are copaxone

1 for multiple sclerosis, as well as Azilect, which  
2 is the subject of today's meeting. Azilect, or  
3 rasagiline, has been approved in the United States  
4 since 2006. It's indicated for the symptomatic  
5 treatment of idiopathic Parkinson's disease, both  
6 as monotherapy at the 1-milligram dose and as  
7 adjunct therapy to levodopa at the 0.5-milligram  
8 dose of rasagiline.

9 The product is available in 41 countries  
10 worldwide and has a well-documented safety profile  
11 of over 500,000 patient-years of exposure. As you  
12 can see on screen, we are proposing to amend the  
13 current indication for the 1-milligram dose of  
14 Azilect to include the slowing of clinical  
15 progression.

16 I will now provide a brief overview of what  
17 you will hear in the sponsor's presentation, as  
18 well as some context around this area of scientific  
19 inquiry.

20 As you know, Parkinson's disease is a major  
21 public health problem and there is a clear need for  
22 a disease-modifying therapy. The numerous

1 therapies that are available today are all labeled  
2 and approved only for symptomatic treatment. While  
3 unlike demonstrating symptom relief, which has  
4 straightforward, clear, long-established  
5 approaches, historically, there has been no  
6 established pathway to demonstrate disease  
7 modification. However, as you'll hear in the  
8 presentation today, you'll hear about the  
9 delayed-start trial design, which was developed  
10 specifically to address the challenge of separating  
11 both the symptomatic and the disease-modifying  
12 components.

13 As Dr. Katz mentioned, we have two trials  
14 that we're presenting today, which are randomized,  
15 well-controlled delayed-start clinical trials,  
16 again, the ADAGIO and TEMPO trials. These trials  
17 are the first to undergo regulatory review for a  
18 disease-modifying claim for Parkinson's disease.

19 As you will see, ADAGIO provides consistent  
20 data, demonstrating efficacy of the 1-milligram  
21 dose of rasagiline for slowing clinical  
22 progression, and our TEMPO data support those

1 findings. Both studies show that early treatment  
2 with rasagiline provides better outcomes for  
3 patients than delaying that same exact treatment.  
4 Thus, these complementary trials provide  
5 independent substantiation of efficacy for this  
6 indication. They also confirm the favorable safety  
7 profile seen in worldwide marketing of rasagiline.  
8 By including these data into the prescribing  
9 information, we will now have the opportunity for  
10 physicians and patients to have a discussion about  
11 the disease-modifying therapy.

12 Here now is our agenda for the rest of the  
13 presentation. Dr. Warren Olanow, from Mount Sinai  
14 School of Medicine, New York, will provide  
15 background on Parkinson's disease, medical need, as  
16 well as describe the delayed-start trial design.

17 Dr. Cheryl Fitzner-Attas from Teva will  
18 present both the TEMPO and ADAGIO trial designs, as  
19 well as the results.

20 Dr. Olanow will be back to provide his  
21 clinical interpretation and perspective of the  
22 data, and its relevance to patients.

1           We also have a strong panel of experts in a  
2 number of relevant disciplines. All of our experts  
3 that have helped us prepare for this meeting today  
4 have been compensated for their time and costs.

5           I will now turn the lectern over to Dr.  
6 Olanow.

7           **Sponsor Presentation - C. Warren Olanow**

8           DR. OLANOW: Thank you very much. I  
9 appreciate the opportunity to be able to speak to  
10 you today. I've been asked to provide some  
11 preliminary comments about Parkinson's disease and  
12 attempts to develop therapies that slow clinical  
13 progression. As indicated, I have served as a  
14 consultant to Teva, and here are my additional  
15 conflicts of interest, noting that I consult to  
16 many different companies.

17           As you've heard, Parkinson's disease is an  
18 age-related disorder. It affects 500,000 to  
19 750,000 persons in the United States, and it is the  
20 second-commonest neurodegenerative disorder after  
21 Alzheimer's disease. It can affect basically  
22 anyone, men and women of all races and all

1 occupations. And, importantly, with the aging of  
2 the population, it is expected that the frequency  
3 will increase dramatically in the coming decades.

4 The classic description of Parkinson's  
5 disease by James Parkinson provided an assessment  
6 of the cardinal or classical features of the  
7 disease, hallmarks being bradykinesia or slowness  
8 of movement, rigidity or stiffness, tremor, usually  
9 resting, and gait disturbance.

10 The classic pathology of the disease, which  
11 was recognized perhaps 100 years later involved a  
12 degeneration of nerve cells in the substantia nigra  
13 pars compacta. It was recognized that these cells  
14 contain dopamine and that a dopamine depletion in  
15 the striatum, which is one of the main targets of  
16 these nigra projections, is the hallmark finding  
17 that is responsible for the classic motor features  
18 of the illness. In addition, pathology is  
19 characterized by proteinaceous inclusion bodies  
20 within the cell and within nerves, axons, which are  
21 known as Lewy bodies and Lewy neurites, an  
22 important area for current and future research.

1           What we've learned in the past several  
2 decades is that Parkinson's degeneration is not  
3 simply limited to dopamine neurons in the  
4 substantia nigra, but it involves norepinephrine  
5 neurons in the locus coeruleus, cholinergic neurons  
6 in the nucleus basalis of Meynert, serotonin  
7 neurons in the Dorsal Raphe, and degeneration in  
8 the olfactory systems, specific regions of the  
9 cerebral cortex, upper and lower brain stem, spinal  
10 cord, and even peripheral autonomic nervous system.

11           This, in turn, results in patients having  
12 the potential to develop additional what we call  
13 non-dopaminergic features that include postural  
14 instability, freezing, falling with fractures,  
15 autonomic disturbances, mood disorders, cognitive  
16 impairment, and in the majority of individuals,  
17 frank dementia. And it is these latter problems,  
18 particularly the falling and the dementia, that  
19 represent the main source of disability for  
20 patients as they advance.

21           Current therapies are largely based on a  
22 dopamine replacement strategy, largely using

1 levodopa. Other agents that we use include  
2 dopamine agonists, which act directly on dopamine  
3 receptors, COMT inhibitors, which block the  
4 peripheral breakdown of levodopa, allowing more to  
5 get into the brain, and MAO-B inhibitors, which  
6 block central metabolism of dopamine, allowing  
7 increased levels at the synapse.

8           These treatments are very effective for the  
9 classic motor features of Parkinson's disease, and  
10 they have provided benefit for millions of patients  
11 around the world. The problem is that they are  
12 associated with side effects. Levodopa has motor  
13 complications. Dopamine agonists are associated  
14 with impulse control disorders and sedation with  
15 sudden onset of sleepiness. COMT inhibitors are  
16 associated with diarrhea and hepatotoxicity.

17           Perhaps even more importantly, they do not  
18 control these non-dopaminergic features, which I  
19 have indicated are the major sources of disability  
20 for Parkinson's disease patients, and they don't  
21 stop progression or the development of disability.

22           So as you've heard, the treatment

1 intervention that slows, stops, or reverses this  
2 clinical progression is the most important unmet  
3 need in the therapeutics of Parkinson's disease. We  
4 have over the years that I've been working in this  
5 area come up with different names to try and define  
6 this. We originally used the term  
7 "neuroprotection," but since you can't count nerve  
8 cells, we moved to the term "disease modifying."  
9 But since we can't really measure the disease,  
10 either, we think a better term is "slowing clinical  
11 progression" because that, at least, gives us the  
12 opportunity to measure what it is we think we are  
13 affecting.

14           There have, however, been numerous obstacles  
15 in our attempts, over the last decade or two, to  
16 find a therapy that slows progression. Firstly, we  
17 don't know the exact cause of Parkinson's disease,  
18 and, therefore, we don't know exactly what to  
19 target. We lack an animal model that completely  
20 replicates the features of Parkinson's disease and  
21 that we know reflects the ideology and  
22 pathogenesis. So positive or negative results in

1 such a model don't necessarily translate into what  
2 one might see in Parkinson's disease. And perhaps  
3 the most important of all of these problems is the  
4 lack of a clinical trial design or biomarker that  
5 allows us to tell that we are influencing the rate  
6 of clinical progression.

7           This study is the classic DATATOP study that  
8 we performed 20 years ago. It seems like such a  
9 long time, but it's still a very important study.  
10 In this study, patients were randomized to deprenyl  
11 or its placebo, as well as to vitamin E in a two-  
12 by-two factorial design. This study clearly showed  
13 that patients who were randomized to deprenyl had a  
14 delay in their time to reach a milestone of disease  
15 progression, namely, disability requiring levodopa  
16 treatment. The problem is, we couldn't tell if  
17 that delay in reaching a milestone of progression  
18 was because we had slowed clinical progression or  
19 we had simply introduce a symptomatic therapy that  
20 masked ongoing progression of the disease.

21           We tried numerous other markers, as you can  
22 see, and we ran into the same problem, studies

1 being confounded by symptomatic or pharmacologic  
2 effects of the study intervention. Most of the  
3 agents we used, and the ones you will hear coming  
4 forward, utilized the unified Parkinson's disease  
5 rating scale as a method of measuring the state of  
6 Parkinson's disease. This is the standard scale  
7 that we use to assess Parkinson's disease in our  
8 trials, and it is basically divided into three  
9 components, as you can see, mentation, activities  
10 of daily living, and motor examination. It is made  
11 up of 44 different components, each of which is  
12 rated on a 0-to-4 scale, reflecting no disability  
13 to maximal disability.

14 This just simply illustrates the components  
15 in each of these sections, illustrating that most  
16 of these components are motor in nature, but some  
17 of the non-dopaminergic features, if you will, are  
18 captured as well, such as in mentation,  
19 intellectual impairment and mood are captured. We  
20 look mostly at motor functions for daily living,  
21 but we also look at things like sensory complaints  
22 and falling. And under motor, which is based on

1 examination, we gained focus primarily on motor,  
2 but we look at some non-dopaminergic features as  
3 well, such as postural stability.

4           The problem, then, is how to look at how  
5 this scale deteriorates over time and to separate  
6 out deterioration that occurs as part of the  
7 natural progression of the illness, that which  
8 occurs in the face of an agent that has symptomatic  
9 effects, what one might see if we had a disease-  
10 modifying effect, and the most complex, where there  
11 is both a disease-modifying effect and a  
12 symptomatic effect.

13           As you've heard, Dr. Paul Leber, when he was  
14 with the FDA, suggested the randomized withdrawal  
15 and delayed-start designs as ways of trying to  
16 possibly accomplish this goal. The randomized  
17 withdrawal involves randomizing patients to active  
18 treatment and then withdrawing them, and that  
19 requires maintaining patients off therapy entirely  
20 for relatively long periods of time. And from a  
21 practical point of view, that's just not possible  
22 or practical in Parkinson's disease. So where

1       there are active therapies that are available,  
2       perhaps, it's better suited for Alzheimer's  
3       disease.

4               Therefore, most of the interest in  
5       Parkinson's disease has focused on the delayed-  
6       start design, which you heard Dr. Katz describe for  
7       you. I'll just go through it again and show it to  
8       you pictorially.

9               Here is an example of period 1 of this two-  
10       period study design. In the first period, patients  
11       are randomized to active treatment or to placebo.  
12       And if there is a difference at the end of  
13       period 1, as you can see here, one doesn't know if  
14       this difference is because of a disease-modifying  
15       effect, a symptomatic effect, or both. So what was  
16       proposed is that, for period 2, patients in both  
17       treatment groups would be put on the same study  
18       intervention and then followed for a period of  
19       time.

20               If, in period 2, the delayed intervention  
21       group comes together with the early intervention  
22       group, and there is no difference between the two

1 groups in change from baseline at the end of the  
2 study, then one might consist that this is  
3 consistent with a symptomatic effect. I apologize  
4 for the error. That should say "symptomatic  
5 effect."

6 In contrast, if the two groups separate, and  
7 even though active treatment is introduced in the  
8 second period, the two groups still don't come  
9 together. And if there is no evidence that the two  
10 groups are converging on repeated follow-up  
11 evaluations, that suggests that the benefit that  
12 you see cannot be explained by an early symptomatic  
13 effect, and something that occurred in that early  
14 period of time accounts for this difference. This,  
15 then, might be consistent with slowing of clinical  
16 progression.

17 Now, in designing a delayed-start study, as  
18 you've already heard, there are a number of issues  
19 that must be considered in order to perform this  
20 type of study. The first period has to be long  
21 enough that any effect that you hope to see on the  
22 underlying disease process that slows clinical

1 progression can occur. And period 2 must be long  
2 enough so that the symptomatic effects of the drug  
3 can be seen and that there are enough periods  
4 afterwards so you can see that the two groups are  
5 not coming together. But at the same time, periods  
6 1 and 2 can't be so long that an unacceptable  
7 number of patients withdraw because they need  
8 therapy.

9 In this study, dropouts must be minimized  
10 because information from both periods is required  
11 in order to do a proper analysis. And to the  
12 extent there is missing data, it should be  
13 addressed prospectively with pre-defined  
14 sensitivity and imputation analyses.

15 One also has to consider what patients we  
16 will enter into this sort of trial. Do we take  
17 patients who are really early in the disease? If  
18 we do, then there is a greater chance that if an  
19 agent has an effect on the ongoing  
20 neurodegenerative process, we will be able to see  
21 it. And with early patients, we can keep them  
22 longer without needing to introduce a symptomatic

1 therapy. But on the other hand, data now shows  
2 that for patients with early disease, the rate of  
3 progression is extremely slow, probably because of  
4 ongoing compensatory responses, and it becomes very  
5 difficult to see any benefit.

6 Or should we use more advanced patients?  
7 They have a faster rate of progression, so if  
8 there's a benefit in the drug and a difference  
9 between early- and delayed start, we will have the  
10 opportunity to see it. But now, we have a greater  
11 risk of dropouts and it may be too late to obtain  
12 an effect on the underlying neurodegenerative  
13 process, which recent data suggests comes to a  
14 rather abrupt conclusion early in the disease  
15 process.

16 Finally, how should we analyze a delayed-  
17 start study? And, again, you heard Dr. Katz refer  
18 to this, and I'll just show you the same thing  
19 pictorially. It has generally been agreed that  
20 three methods of analysis should be applied to  
21 determine if a drug is slowing clinical  
22 progression.

1           The first is to demonstrate that after  
2 symptomatic benefits have been achieved, the rate  
3 of deterioration of the UPDRS score in the active  
4 treatment group is slower than that in the placebo  
5 group, consistent with an ongoing slowing of  
6 clinical progression.

7           Secondly, the change from original baseline  
8 in the delayed-start group should be greater than  
9 that in the early-start group, indicating that it  
10 was never able to catch up.

11           And thirdly, there has to be evidence that  
12 this benefit is enduring and that there is no  
13 evidence that the slopes of UPDRS progression,  
14 after symptomatic effects have been achieved, are  
15 coming together. And, if anything, the early-start  
16 has to be non-inferior or superior to the delayed-  
17 start group.

18           So you can see that this is a complex trial,  
19 but we believe it is the first study that allows us  
20 to separate out the differences between early  
21 symptomatic effects and ongoing slowing of clinical  
22 progression.

1           In summary, I've told you that Parkinson  
2 patients have disability that we cannot adequately  
3 control with our current therapies. We desperately  
4 need a method of slowing clinical progression. The  
5 trials we've used to date have not been able to  
6 differentiate slowing progression from symptomatic  
7 effects. But as I've said, I believe that the  
8 delayed-start design does permit us that  
9 opportunity.

10           Now, to discuss the results of the TEMPO-  
11 and ADAGIO-style studies, rather, where rasagiline  
12 was studied in delayed-start designs, it's my  
13 pleasure to introduce Dr. Cheryl Fitzer-Attas, who  
14 is director of scientific and medical affairs at  
15 Teva.

16           **Sponsor Presentation - Cheryl Fitzer-Attas**

17           DR. FITZER-ATTAS: Good morning. So, as  
18 we've heard from both Dr. Katz and Dr. Olanow,  
19 disease modification in Parkinson's disease is a  
20 very challenging area of research. And Teva has  
21 worked for many years, together with the FDA, in  
22 order to forge a development pathway for this

1       indication. In my role at Teva, I've had the honor  
2       of working with leading movement disorder  
3       specialists from around the globe, some of whom  
4       aren't with us today, in order to best understand  
5       our data and what it means to their patients.

6               So today, I am proud to be presenting the  
7       data from our two studies, TEMPO and ADAGIO, that  
8       together provide evidence of effectiveness for  
9       rasagiline in slowing the clinical progression of  
10      Parkinson's disease.

11              So, first, let me remind you about the  
12      rasagiline molecule itself. Rasagiline is a  
13      potent, selective, and irreversible MAO-B inhibitor  
14      that increases the level of androgynous striatal  
15      dopamine, as well as dopamine produced from the  
16      breakdown of exogenous levodopa. In both cases,  
17      this results in more dopamine and improved symptoms  
18      for the patient.

19              Rasagiline also contains a propargylamine  
20      structure. And in a laboratory, it has been shown  
21      that this structure has antiapoptotic and  
22      neuroprotective properties. And, in fact, in a

1 variety of cellular models, rasagiline was shown to  
2 protect dopaminergic and other types of neurons  
3 when they are exposed to a variety of insults. M  
4 Similarly, in animal models, rasagiline has also  
5 shown protective properties against a variety of  
6 insults, working through different cytotoxic  
7 mechanisms.

8           When we began seeing these protective  
9 effects in the lab, it was logical to then consider  
10 whether rasagiline might have similar effects in  
11 humans, and we initially did so in the TEMPO study.

12           TEMPO was designed and conducted in  
13 collaboration with the Parkinson's Study Group, the  
14 PSG, an independent group of U.S. and Canadian  
15 physicians and healthcare providers. TEMPO had two  
16 objectives. The main objective of ADAGIO was to  
17 evaluate the safety and efficacy of rasagiline in  
18 patients with early Parkinson's disease. And this  
19 was a pivotal study which led to the approval of  
20 rasagiline for the monotherapy indication. To  
21 investigate rasagiline's effect on clinical  
22 progression, the TEMPO protocol also pre-specified

1 an exploratory endpoint, which would compare the  
2 changes in UPDRS scores in patients assigned to  
3 early versus delayed treatment.

4 TEMPO employed a double-blind, randomized  
5 delayed-start design. It was a three-arm trial.  
6 Patients were randomized to either rasagiline 1- or  
7 2-milligram for 52 weeks or placebo for 26 weeks,  
8 followed by rasagiline, 2 milligrams, for 26 weeks.  
9 There was no 1-milligram delayed-start arm in the  
10 TEMPO trial; 404 subjects were randomized in the  
11 United States and Canada, and 380 of those entered  
12 the active phase.

13 TEMPO was designed to recruit early and mild  
14 Parkinson's disease populations for two reasons.  
15 First, when Parkinson's disease patients present in  
16 the clinic, they often have quite a substantial  
17 amount of neurodegeneration. An intervention as  
18 early as possible would be most beneficial for the  
19 patient. Moreover, in a delayed-start design,  
20 there are some ethical issues since patients won't  
21 be getting therapy; some of those won't be getting  
22 therapy until the active phase.

1           In TEMPO, patients had to be at least  
2   35 years old with early idiopathic Parkinson's  
3   disease, confirmed at screening by the presence of  
4   at least two cardinal signs, without any other  
5   known or suspected cause of Parkinsonism. Patients  
6   also had to have scored three or less on the Hoehn  
7   and Yahr scale, which is a commonly-used  
8   Parkinson's rating score, and scoring less than 3  
9   is considered mild disease.

10           Patients that required dopaminergic therapy  
11   were not enrolled in the TEMPO study and no other  
12   anti-Parkinsonian agents were allowed during the  
13   placebo-controlled phase, except for stable doses  
14   of anti-cholinergic medications. Subjects that  
15   needed additional anti-Parkinsonian therapy in the  
16   placebo-controlled phase proceeded to the active  
17   phase, where additional Parkinsonian agents were  
18   allowed. Importantly, the efficacy analysis did  
19   not include those UPDRS measurements so that any  
20   assessment of rasagiline on disease progression  
21   would not be confounded by the effects of other  
22   drugs.

1           TEMPO had a relatively low dropout rate of  
2 just under 11 percent. Of the 404 patients  
3 randomized in the placebo-controlled phase, 380, or  
4 94 percent, entered the active phase; 6 percent  
5 dropped out during the placebo-controlled phase;  
6 between 10 and 15 percent transferred early to the  
7 active phase; and 5 percent withdrew early from the  
8 active phase. And, finally, 360 or 90 percent of  
9 randomized patients completed the study.

10           There were similar baseline characteristics  
11 across the three groups studied in TEMPO. And as  
12 is typical in Parkinson's disease, the TEMPO  
13 population included patients with a mean age of 61,  
14 with more males. Patients in TEMPO had a mean  
15 diagnosis of 12 months and a mean total UPDRS score  
16 of 25.

17           The efficacy cohort for the 52-week analysis  
18 included all patients with at least one UPDRS  
19 measurement in the active treatment phase, and, of  
20 course, before the onset of additional anti-  
21 Parkinsonian therapy. So the analysis was based on  
22 371 or 92 percent of patients who entered the

1 active treatment phase.

2 So let's look at the endpoint used to show  
3 the efficacy of rasagiline in slowing progression  
4 in TEMPO. As you've heard already, the most  
5 important outcome of a delayed-start design is that  
6 the group of patients started later on the drug  
7 does not catch up with those started earlier. So  
8 the basic question in TEMPO was, will there still  
9 be a difference between the groups in UPDRS score  
10 after all patients have been on rasagiline for a  
11 full 26 weeks? Thus, the TEMPO endpoint, the  
12 superiority of early-start versus delayed-start  
13 rasagiline in mean UPDRS change from baseline to  
14 week 52.

15 So looking at the results for the  
16 1-milligram dose, mean changes in UPDRS scores in  
17 the first 26 weeks of the study showed that  
18 patients started early on rasagiline, 1 milligram,  
19 did better than those that started on placebo. And  
20 as I mentioned already, TEMPO did not include the  
21 delayed-start group for the 1-milligram dose in the  
22 second half of the study. However, when compared

1 to the 2-milligram delayed-start group, the early-  
2 start 1-milligram group deteriorated less at 52  
3 weeks. And as reported in the main publication of  
4 TEMPO, in the archives of neurology, the difference  
5 between the groups in change from baseline and  
6 UPDRS was 1.8 units.

7 Now, looking at the 2-milligram results,  
8 again, changes in mean UPDRS scores show that  
9 patients started earlier on the 2-milligram did  
10 better than placebo in the first half of the study,  
11 and this difference was maintained after an  
12 additional 26 weeks, when both groups were on drug.  
13 The difference between the groups at 52 weeks for  
14 the 2-milligram dose was 2.3 UPDRS units. Patients  
15 started later on rasagiline did not catch up to the  
16 early-start group.

17 These results led the Parkinson's Study  
18 Group to conclude that the differences observed at  
19 the final visit could not be fully explained by the  
20 symptomatic effects of rasagiline alone. One  
21 potential explanation of these results, according  
22 to the publication authors, is that rasagiline

1 slows the progression of disability in Parkinson's  
2 disease.

3 Patients from the 52-week TEMPO study were  
4 then followed in an extension phase, which was  
5 designed to assess the long-term efficacy and  
6 safety of rasagiline, 1 milligram. So although  
7 patients were all taking the 1-milligram dose now,  
8 patients and investigators remained blinded to the  
9 original treatment assignments.

10 Roughly three-quarters of the patients that  
11 began the TEMPO study participated in this  
12 extension phase. Patients could also be treated  
13 with other Parkinson's medications as needed, and  
14 they were followed for up to six and a half years.  
15 Of course, these long-term data must be considered  
16 in light of their limitations, including patient  
17 attrition over time and no restrictions on  
18 concomitant medications. However, we do see that  
19 patients started on rasagiline earlier did maintain  
20 their a head start over patients in the delayed-  
21 start arms for more than six years. And there was  
22 an adjusted mean difference in the percent change

1 from baseline and total UPDRS of 16 percent in  
2 favor of the early-start groups.

3 So because of encouraging findings from  
4 TEMPO indicating that rasagiline's activity may  
5 extend beyond a symptomatic effect, Teva, with FDA  
6 input, designed the ADAGIO study.

7 So ADAGIO was prospectively designed, with  
8 its main objective to investigate the effect of  
9 rasagiline on clinical progression in Parkinson's  
10 disease. ADAGIO was a randomized, placebo-  
11 controlled four-arm trial. It was designed to  
12 compare the effects of rasagiline, 1-milligram and  
13 2-milligram, in patients started earlier on drug  
14 versus those started later. Half of the patients  
15 were randomized to rasagiline 1- or 2-milligram for  
16 a full 72 weeks. These are the early-start  
17 patients. The other half was randomized to placebo  
18 for 36 weeks, followed by rasagiline, 1- or 2-  
19 milligram, for 36 weeks. These are the delayed-  
20 start patients.

21 So, essentially, there were two substudies  
22 in ADAGIO. Each dose had its own placebo group in

1 ADAGIO; 1,176 subjects were randomized in 29  
2 countries, and these were evenly divided between  
3 the four treatment arms. Almost 1,100 subjects  
4 entered the active phase of the study. Patients  
5 included in ADAGIO were men and women, aged 30 to  
6 80, with idiopathic Parkinson's disease, and this  
7 had to be confirmed by screening for the presence  
8 of at least two cardinal signs without any other  
9 known or suspected cause of Parkinsonism.

10 Patients also had to have scored less than 3  
11 on the Hoehn and Yahr scale. And, again, it was  
12 important to recruit an early population. And in  
13 ADAGIO, there were specific inclusion criteria that  
14 addressed this point and restricted the population  
15 even further than that in TEMPO.

16 So patients in ADAGIO had to have been  
17 diagnosed within the previous year and a half, and  
18 they could not require anti-Parkinsonian therapy  
19 either at enrollment or for the next nine months  
20 during the placebo-controlled phase.

21 Unlike TEMPO, ADAGIO did not permit the use  
22 of anti-Parkinsonian medications other than

1 rasagiline. However, of course, it was understood  
2 that some patients may need additional anti-  
3 Parkinsonian therapy. So if during the placebo-  
4 controlled phase an investigator determined that a  
5 patient needed additional therapy, that patient  
6 immediately proceeded to the active phase and would  
7 now receive rasagiline. However if additional  
8 anti-Parkinsonian therapy was required in the  
9 active phase when patients were already on drug,  
10 that patient was prematurely withdrawn from the  
11 study.

12 ADAGIO had a relatively low dropout rate of  
13 19 percent over 18 months of the study. Of the  
14 1,176 patients randomized in the placebo-controlled  
15 phase, 1,091 or 93 percent of the patients entered  
16 the active phase; 7 percent of all randomized  
17 patients dropped out during the placebo-controlled  
18 phase, usually because of an adverse event.

19 A higher proportion of patients in the  
20 delayed-start group, nearly 20 percent, transferred  
21 early to the active phase as compared to about 10  
22 percent in the early-start groups. The need for

1 additional anti-Parkinsonian therapy was the most  
2 common reason for premature termination from the  
3 active phase, about a hundred patients. And  
4 finally, 81 percent of randomized patients  
5 completed the ADAGIO study.

6 Now, the ADAGIO design and analyses evolved  
7 during numerous discussions with the FDA, as well  
8 as with relevant academicians and other  
9 stakeholders in this field. And I will discuss the  
10 evolution of the ADAGIO endpoints, where there have  
11 been changes that impacted study power and  
12 potentially the interpretation of the results.

13 So in the initial ADAGIO protocol, there  
14 were only two primary endpoints or hypotheses on  
15 which study power was based. The first hypothesis  
16 was that the UPDRS change from baseline across  
17 weeks 48 to 72 would be lower in the early-start  
18 group than in the delayed-start group. The second  
19 hypothesis was that the slopes of the UPDRS change  
20 over those weeks, 48 to 72, would not be  
21 converging. The power of the study was 87 percent  
22 to detect the difference of 1.8 UPDRS units between

1 the two groups.

2 The FDA later recommended changes to these  
3 endpoints, which Teva adopted, mindful that there  
4 would be a loss of statistical power. And here I  
5 show you the three final endpoints, agreed upon  
6 between Teva and the FDA, for the ADAGIO study.

7 So first of all, there was an additional  
8 efficacy endpoint added for the placebo-controlled  
9 phase in which the slope or rate of disease  
10 progression should be lower in patients on  
11 rasagiline than patients on placebo.

12 Endpoint 2 now changed from its original  
13 form. Instead of assessing the UPDRS change from  
14 baseline across weeks 48 to 72, it now assessed the  
15 change from baseline to week 72 only. UPDRS scores  
16 should be lower in the early-start group than the  
17 delayed-start group at this time point. Endpoint 3  
18 remained the same. The delayed-start group should  
19 not be catching up to the early-start group. This  
20 change in endpoint 2 reduced the power in ADAGIO by  
21 15 percentage points, from 87 to 72 percent. And  
22 because this recommendation was made nearly a year

1 after enrollment closed in the ADAGIO study, there  
2 was no opportunity to add patients to compensate  
3 for that lost power.

4 For each of the three endpoints I just  
5 described, different cohorts were defined a priori  
6 for the statistical analyses. So the ITT cohort  
7 included all subjects randomly assigned to study  
8 treatment. The modified ITT cohort included all  
9 subjects who underwent evaluations at baseline and  
10 at week 12 or later. And the active efficacy, or  
11 what we've called the ACTE cohort, included all  
12 subjects who received at least 24 weeks of  
13 treatment during the placebo-controlled phase and  
14 who underwent an evaluation at the week-48 visit or  
15 later.

16 1,164 patients or 99 percent fit the  
17 criteria for the modified ITT cohort, which was  
18 used for the analysis of primary endpoint number  
19 one. 996 or nearly 85 percent of randomized  
20 patients fit the criteria for the ACTE cohort,  
21 which was used for the analysis of endpoints 2 and  
22 3. So only 12 patients were excluded from the

1 modified ITT cohort, and an additional 168 were  
2 excluded from the ACT analysis for endpoints 2 and  
3 3.

4 So now let's turn to the results, starting  
5 first with the baseline patient characteristics.

6 In ADAGIO, there were similar baseline  
7 characteristics across the four groups. All had  
8 early and mild Parkinson's disease. ADAGIO  
9 included patients with a mean age of 62 and more  
10 males. The mean time for diagnosis was four and a  
11 half months. And the mean baseline UPDRS score was  
12 20.4. So indeed, as determined by the inclusion  
13 criteria I mentioned earlier, the ADAGIO population  
14 was milder than TEMPO and earlier in the course of  
15 the disease.

16 Here we see the baseline characteristics of  
17 subjects in the cohorts defined for the three  
18 endpoints. The modified ITT and the ACTE were, on  
19 the whole, similar to that of the ITT cohort. And  
20 here are the baseline characteristics for the four  
21 treatment groups within the ACTE cohort. There  
22 were differences in baseline UPDRS of up to 1 and a

1 half points between the early- and delayed-start  
2 groups. And this was due to more dropouts and more  
3 early transfers in the delayed-start groups. The  
4 sensitivity analyses I will present later on will  
5 address this issue.

6 So now I will show you the data for the  
7 1-milligram dose of rasagiline. The graph you see  
8 here shows the observed mean changes from baseline  
9 in total UPDRS scores for the first 36 weeks of the  
10 study, the placebo-controlled phase, and also for  
11 the modified ITT cohort. And as you see here, the  
12 placebo and rasagiline 1-milligram curves diverge  
13 over this time period. These observed UPDRS scores  
14 were then introduced into the statistical model to  
15 generate the results for endpoint number 1. And  
16 there was a difference in slopes in favor of the  
17 1-milligram early-start rasagiline group over  
18 placebo, with a point estimate of minus 0.046 UPDRS  
19 units per week or 2.4 UPDRS units per year, and a p  
20 value of .013.

21 Now, going back to the observed mean changes  
22 from baseline in total UPDRS scores, this graph

1 shows you the actual measurements taken over the  
2 entire course of the study, but now, for the ACTE  
3 cohort, used for the analysis of endpoints 2 and 3.  
4 And, again, we see diverging curves in the placebo-  
5 controlled phase. In addition, now we see the  
6 difference between early- and delayed-start groups  
7 at the end of the study in curves that do not  
8 appear to be converging in the active phase. So  
9 the separation in UPDRS scores that was achieved in  
10 the first phase of the study is maintained  
11 throughout the course of the second phase, when  
12 both groups were receiving rasagiline at this time  
13 point.

14           Again, these observed UPDRS scores were  
15 introduced into the statistical model to generate  
16 the results for endpoints 2 and 3. However, before  
17 I show you the results, I will explain some changes  
18 that were made to the final statistical analysis  
19 plan, which was submitted to the FDA.

20           So to remind you, for endpoints 2 and 3,  
21 each of these doses had its own delayed-start group  
22 unless there were two separate components within

1 the ADAGIO study, a 1-milligram component and a  
2 2-milligram component. And in planning of ADAGIO,  
3 it was implicitly assumed that the effects of two  
4 model covariates, baseline UPDRS and treatment  
5 center, would be similar between these two  
6 components. Thus, it was planned to analyze,  
7 actually, a combined dataset in the statistical  
8 model. However, interactions were found between  
9 each of these parameters and the dose components,  
10 as shown here.

11 Teva decided, at the time, that the most  
12 appropriate way to address these interactions would  
13 be to analyze the 1- and 2-milligram components  
14 separately for endpoints 2 and 3. This alternative  
15 approach was also deemed appropriate by the  
16 principal investigators and the steering committee  
17 of the ADAGIO study. The data were subsequently  
18 submitted and published in the New England Journal  
19 of Medicine.

20 So, for clarity, I'd like to show you the  
21 results of for endpoint number 2 in three different  
22 ways; first, the endpoint as defined in the final

1 statistical analysis plan as submitted to the FDA;  
2 second, the alternative analysis, using separate  
3 datasets that was adopted by Teva due to those  
4 covariate effects I just described; and, finally,  
5 the analysis on which the study was in fact  
6 powered.

7           So the analysis of endpoint 2, as defined by  
8 the statistical analysis plan, showed a statistical  
9 difference between early- and delayed-start groups  
10 of 1.4 UPDRS units with a p value of 0.051. And  
11 although the primary analysis did not meet the pre-  
12 specified threshold for statistical significance,  
13 due to the interactions that I just described, the  
14 alternative analysis was deemed a more accurate  
15 representation of the trial outcomes.

16           So the analysis of endpoint 2, in which the  
17 1- and 2-milligram sets were analyzed separately,  
18 showed a difference between the early- and delayed-  
19 start groups of 1.7 UPDRS units. And, in addition,  
20 analysis by the original endpoint 2, for which the  
21 study was powered, showed a difference between the  
22 early- and delayed-start groups of 1.4 units,

1 similar to the final statistical analysis plan.

2 Recall there was no change to endpoint 3,  
3 and, therefore, we see here the results for this  
4 endpoint, as analyzed by either the combined or the  
5 separate datasets. And in both cases, the  
6 difference between the slopes in the early- and  
7 delayed-start groups in the active phase was zero,  
8 and the upper limit of the confidence interval was  
9 less than 0.04, which was well below the  
10 pre-specified threshold of 1.5.

11 So looking at the data from the model  
12 illustrated on this schematic diagram, we see that  
13 for endpoint number 1, there was a difference in  
14 slopes, in favor of the 1-milligram early-start  
15 rasagiline group over placebo. In other words,  
16 there was a difference in the rate of clinical  
17 progression, as reflected by the UPDRS score,  
18 between the 1-milligram and placebo groups.  
19 Importantly, this was assessed after week 12, when  
20 it was assumed that the full effect of rasagiline  
21 on symptoms had been established.

22 Now, using the separate datasets for

1 endpoints number 2 and 3, there was a smaller  
2 deterioration from baseline to week 72 for the  
3 1-milligram early-start group as compared to the  
4 delayed-start group, and this difference had a  
5 point estimate of 1.7. And when the dataset was  
6 analyzed for endpoint number 3, the difference  
7 between the early- and delayed-start groups in the  
8 active phase was zero, this indicates that the  
9 difference between those groups is in fact enduring  
10 and not diminishing.

11 So now let's turn our attention to one of  
12 the issues that Dr. Olanow described as important  
13 when designing a delayed-start study, and that is  
14 the need to properly address missing data.

15 In order to evaluate the robustness of the  
16 results for the rasagiline 1-milligram dose,  
17 including the impact of missing data, we conducted  
18 several sensitivity and additional supportive  
19 analyses for each of the three endpoints.

20 For endpoint number 1, all three specified  
21 sensitivity analyses shown here, the completer  
22 dataset, the per-protocol dataset, and a multiple

1 imputation method, all showed similar results to  
2 the primary analysis.

3           Now, for Hypothesis 1, it was assumed that  
4 the rate of change in UPDRS would be linear. And  
5 while there was a statistical deviation from  
6 linearity in the placebo-controlled phase, for a  
7 variety of reasons, including an evaluation of the  
8 active phase, we do believe that linearity is a  
9 reasonable approximation of changes over time in  
10 the ADAGIO study. In addition, we also see here  
11 the results of a model that treats time as  
12 categorical and, therefore, does not rely on any  
13 linear assumption. And this analysis, as well,  
14 showed results similar to the primary analysis.

15           Now for endpoint number 2, the primary  
16 analysis was performed on the ACTE cohort, and, by  
17 definition, that cohort included only a subset of  
18 the randomized patients. So, as a result, the  
19 comparability of baseline characteristics between  
20 the early- and delayed-start groups was potentially  
21 compromised.

22           To address this issue, we performed the

1 sensitivity analyses shown here. So the first two  
2 I would like to point out are the multiple  
3 imputation and repeated-measures analyses, which,  
4 in fact, now, use the ITT cohort, and therefore  
5 preserve the comparability of baseline  
6 characteristics that existed at randomization.  
7 Both of these analyses included all patients and  
8 all observed data in the study from week 12  
9 onwards.

10 Next, as recommended by Dr. D'Agostino in an  
11 editorial that he wrote to accompany the New  
12 England Journal of Medicine article, we performed a  
13 propensity score adjusted analysis using the ACTE  
14 cohort. In this method, differences between the  
15 early- and delayed-start groups in the distribution  
16 of the various baseline covariates are summarized  
17 into one measure, namely, the propensity score.  
18 And in the analysis, it is adjusted accordingly;  
19 and this is an attempt to mimic randomization.

20 Finally, we performed a very conservative  
21 strategy of imputing missing data in both groups by  
22 the means of the delayed-start group. This was

1 also a pre-defined sensitivity analysis, and we see  
2 a consistent treatment effect with this analysis as  
3 well.

4 So, in summary, all sensitivity analyses  
5 show results that were consistent with the primary  
6 analysis performed on the ACTE cohort and reinforce  
7 the minimal impact of missing data on the results  
8 for this endpoint.

9 Finally, for all four sensitivity analyses  
10 performed for endpoint number 3, we see that the  
11 difference between the slopes and the confidence  
12 intervals were all very similar to the primary  
13 analysis.

14 So to summarize the rasagiline 1-milligram  
15 efficacy in the ADAGIO trial, rasagiline,  
16 1-milligram -- this is the dose we are requesting  
17 for our expanded indication -- showed a beneficial  
18 effect in all three of the study endpoints. These  
19 results were further confirmed with various  
20 imputation strategies and sensitivity analyses, and  
21 what stands out is the consistency of the results.

22 So now we return to the 2-milligram dose in

1 the ADAGIO study. And as I showed you for the  
2 1-milligram dose, here you see the observed mean  
3 changes from baseline in total UPDRS scores for the  
4 2-milligram dose over the course of the placebo-  
5 controlled phase and for the modified ITT cohort.  
6 And similarly to the 1-milligram dose, the curves  
7 diverge over this time period. Thus, for endpoint  
8 number 1, there was a difference in favor of the  
9 early-start 2-milligram group, with a point  
10 estimate of minus 0.072 UPDRS units per week. That  
11 translates into a difference of 3.7 UPDRS units per  
12 year and a p value of less than .001.

13 This graph shows the observed mean changes  
14 from baseline in total UPDRS scores over the entire  
15 course of the study, and this time for the ACTE  
16 cohort. And as you see, very clearly, where the  
17 curves did diverge in the placebo-controlled phase,  
18 there was no difference between the early- and  
19 delayed-start groups at the end of the study.

20 Again, the results of the statistical model  
21 for the 2-milligram dose reflect what was seen with  
22 the observed data. And, in summary, although a

1       divergence in the placebo-controlled phase was  
2       shown, a positive effect for the 2-milligram dose  
3       could not be demonstrated in the ADAGIO study  
4       because of failure at the endpoint number 2.

5               Now, the failure of the 2-milligram dose in  
6       ADAGIO to meet endpoint number 2 was puzzling to  
7       us, of course, because of the separation of slopes  
8       that was seen in the first phase of the study, as  
9       well as the earlier benefits we had seen in the  
10       TEMPO study. And we have looked at these results  
11       in a multitude of ways in order to best understand  
12       and explain them, and several explanations can be  
13       considered.

14               These different results could have occurred  
15       simply by chance. The doses may have different  
16       pharmacological effects, and there is a discussion  
17       on this issue in our briefing book. And to  
18       summarize, from our current understanding of the  
19       data, we do not believe that there is a solid basis  
20       to expect any different pharmacological effects  
21       between the two doses after chronic administration.

22               The results could have been impacted by

1 differential early transfers into the active phase  
2 between early- and delayed-start groups. And, in  
3 fact, this has made it more challenging for either  
4 dose to demonstrate a benefit in endpoint number 2.  
5 And, finally, it may have been difficult to see an  
6 effect because of the lower sensitivity to detect  
7 changes in UPDRS in patients with milder disease.  
8 And I will go into this possible explanation in  
9 just a bit more detail.

10           So, as we've seen, the 2-milligram dose  
11 demonstrated efficacy in TEMPO, where patients had  
12 a higher baseline UPDRS score, with a mean of 25,  
13 compared to about 20 in ADAGIO. And due to lower  
14 sensitivity in milder patients, higher UPDRS scores  
15 might allow for more room for detection of  
16 responses. And one may expect that an effect on  
17 clinical progression may be detected in a subset of  
18 patients with more advanced disease. And for this  
19 purpose, we performed a post hoc analysis in the  
20 25 percent of ADAGIO subjects with the highest  
21 baseline UPDRS scores, those above 25.5. And,  
22 indeed, the 2-milligram dose demonstrated a benefit

1 in subjects with the highest baseline UPDRS scores.

2 When looking at the three endpoints on a  
3 schematic illustration, we see that for endpoint  
4 number 1, there was a difference in slopes of minus  
5 .2 UPDRS units, in favor of the 2-milligram early-  
6 start group over placebo. This translates into a  
7 difference of 10.4 UPDRS units per year.

8 For endpoint number 2, there was a smaller  
9 deterioration from baseline to week 72 for the  
10 2-milligram early-start group compared to the  
11 delayed-start group. And the difference was in  
12 favor of the early-start group, with a point  
13 estimate of minus 3.6.

14 Finally, for endpoint 3, the difference  
15 between the early- and delayed-start groups was  
16 essentially zero. This type of post hoc analysis  
17 was also done for the 1-milligram dose in subjects  
18 with the highest baseline UPDRS scores. And there,  
19 too, the results were very similar to what we see  
20 here with the 2-milligram.

21 Now, one piece of data that might bring  
22 additional insight into this issue stems from

1 looking at placebo patients only in the first phase  
2 of the study. Placebo patients with higher UPDRS  
3 scores at baseline had a much higher rate of UPDRS  
4 deterioration than the entire population, 13 versus  
5 7 UPDRS units per year, almost twice as much.

6 This faster deterioration may allow for an  
7 opening up or almost a magnification of the UPDRS  
8 scale so that analysis of the more advanced  
9 patients allows for improved detection when using a  
10 scale such as the UPDRS, and, therefore, better  
11 separation between the symptomatic effects and  
12 those affecting clinical progression. In the final  
13 analysis, however, we cannot know for certain why  
14 the 2-milligram dose showed efficacy in TEMPO and  
15 in the placebo-controlled phase in the endpoint  
16 number 1 of ADAGIO, but not in endpoint number 2.

17 So I will now turn to the safety data.  
18 Rasagiline has been on the market for five years in  
19 the United States, six years in Europe, and we now  
20 estimate greater than half a million patient-years  
21 of exposure, together with our clinical development  
22 program.

1           The current prescribing information in the  
2 U.S. reflects all safety information we have from  
3 this large body of data. For clinical trial data,  
4 now, I will focus on the larger ADAGIO population.  
5 And although we are requesting a label expansion  
6 for the 1-milligram dose only, I am presenting data  
7 for both doses in order to provide a more complete  
8 picture of the safety of rasagiline.

9           This table shows that the overall incidence  
10 of adverse events, as well as serious adverse  
11 events and discontinuations associated with adverse  
12 events, were all similar between the rasagiline  
13 1-milligram, 2-milligram, and placebo groups.

14           Looking at specific adverse events reported  
15 for greater than 4 percent of patients in either  
16 rasagiline group and at a higher frequency than the  
17 placebo group, the most common events observed were  
18 fatigue, constipation, arthralgia, dizziness,  
19 falls, and musculoskeletal pain. However, no  
20 apparent relationship between dose and rate of  
21 adverse events was noted. Looking at dopaminergic  
22 adverse events in ADAGIO, the incidence was low

1 overall and, again, similar in frequency between  
2 the rasagiline and placebo groups. There were no  
3 concerns raised in the ADAGIO study regarding  
4 melanoma, serotonin syndrome, or tyramine effect,  
5 three issues that were closely followed in our  
6 clinical development program.

7 So to summarize the safety of rasagiline in  
8 ADAGIO as well as in TEMPO, the safety profile was  
9 similar to placebo when looking at overall adverse  
10 events, serious adverse events, and dopaminergic  
11 adverse events, and selected safety issues were not  
12 of concern.

13 Finally, the current label for Azilect  
14 reflects all the safety information from the  
15 clinical trial program and from post-marketing  
16 data.

17 So to complete my presentation, I've shown  
18 you that the results from TEMPO and ADAGIO  
19 independently substantiate our claim for clinical  
20 effectiveness of rasagiline in the slowing of  
21 clinical progression of Parkinson's disease. And  
22 importantly, all the safety data we've collected to

1 date are favorable and similar to what is in the  
2 current prescribing information.

3 I will now turn the lectern back to  
4 Dr. Olanow, who will provide his personal clinical  
5 perspective on these important data.

6 **Sponsor Presentation - C. Warren Olanow**

7 DR. OLANOW: Thank you very much.

8 What I'd like to do now is give my own  
9 personal perspective on this data. I don't need to  
10 tell everyone here I'm not a statistician. I'm a  
11 clinician. I look after Parkinson's disease  
12 patients. And what I would like to do is give you  
13 my view of how I see these data in prospective.

14 I start by saying that I'm a clinician who  
15 has taken care of Parkinson's disease patients for  
16 more than 25 years. I see them come into the  
17 clinic and present with a tiny bit of tremor, maybe  
18 a little bit of rigidity. They're basically fine.  
19 They're independent. They maintain their  
20 activities of daily living. But I know from the  
21 time I make the diagnosis, they're going to  
22 gradually deteriorate. And over time, they're

1 going to develop disabilities that will be  
2 intolerable and that cannot be adequately  
3 controlled by current therapies.

4 The biggest unmet need we have in  
5 Parkinson's disease today is a therapy that can  
6 slow or stop this progression. I've worked in the  
7 laboratory, trying to find such agents. I've tried  
8 to understand why cells degenerate in Parkinson's  
9 disease and what agents might stop them that we can  
10 bring into the clinic.

11 I've been involved in many different  
12 clinical trials, including the original DATATOP  
13 study, to try to see if we could slow progression.  
14 And I was the PI of the ADAGIO study and lead  
15 author of the article that was recently published  
16 in the New England Journal of Medicine. This was  
17 the first prospectively designed delayed-start  
18 study whose main objective was to demonstrate  
19 slowing of clinical progression. It was one of the  
20 most rigorous and challenging studies that has been  
21 performed in Parkinson's disease.

22 We had to recruit 1,176 untreated

1     Parkinson's patients, and we had to follow them for  
2     18 months, with no additional treatment, no  
3     levodopa, no dopamine agonists, only placebo or  
4     rasagiline, according to their randomization. And  
5     we had to meet three primary endpoints. To my  
6     knowledge, no study in Parkinson's disease has ever  
7     had to meet these requirements.

8             The design of this study was a collaborative  
9     effort between movement disorder experts,  
10    statisticians, the FDA, and Teva. The specifics of  
11    the analytical approach were reviewed in a public  
12    meeting, cosponsored by the Parkinson's Study  
13    Group, the Michael J. Fox Foundation, and the FDA.  
14    And they were published in separate articles,  
15    written by members of the FDA and by myself.

16            Carrying out the ADAGIO study was an  
17    extraordinary effort that involved more than 100  
18    Parkinson's disease centers around the world and  
19    literally hundreds of Parkinson's disease  
20    investigators, who were specifically trained for  
21    their role in this study.

22            Despite the complexity and duration of this

1 study, we still managed to have 85 percent of  
2 patient data be evaluable, with only 19 percent  
3 dropout. This is better than I would have  
4 expected, and it reflects well on the many  
5 investigators who worked so hard to participate in  
6 this study.

7 Just to give you an example, the recently  
8 completed prami BID study, which was only 12 weeks  
9 in duration and had a much simpler and less complex  
10 design, had 12 percent dropouts, the ADAGIO study  
11 was a formidable achievement.

12 Now, I recognize that the ADAGIO study  
13 showed different results for the 1- and 2-milligram  
14 doses and that this has led to uncertainty as to  
15 what it means, as I reported in the article I wrote  
16 in the New England Journal of Medicine.

17 The rasagiline dose, to start with it first,  
18 had positive results with respect to all three  
19 primary endpoints. The first endpoint showed  
20 separation between the placebo and active treatment  
21 groups between 12 and 36 weeks. After the pre-  
22 defined time point, when we believed that

1 symptomatic effects would have been fully achieved,  
2 that separation at that time point is consistent  
3 with slowing of clinical progression.

4           The second endpoint showed that early  
5 treatment provided benefit that could not be  
6 achieved with delayed treatment, using the exact  
7 same drug. This means that even though the early-  
8 and delayed-start groups were on the exact same  
9 treatment for nine months, early treatment provided  
10 benefits compared to delayed treatment.

11           To me, this difference must be due to  
12 something that happened during the early treatment  
13 phase. It cannot be readily explained by a short-  
14 term symptomatic effect. And in my mind, it's  
15 consistent with slowing clinical progression.

16           Finally, the third endpoint showed that the  
17 slopes of the UPDRS deterioration in the early- and  
18 delayed-start groups don't come together between  
19 weeks 48 and 72, even after nine months of active  
20 treatment for patients in both groups. It's hard  
21 for me to imagine that additional symptomatic  
22 effects of rasagiline could still emerge after nine

1 months, and the slope analysis provides no evidence  
2 of convergence.

3           These findings argue against the difference  
4 between early- and delayed-start being due to a  
5 delayed symptomatic effect. In addition, each of  
6 these three primary endpoints was supported by all  
7 of the sensitivity analyses that were performed,  
8 those that were pre-specified, those that were  
9 suggested by the scientific advisory board, and  
10 those that were suggested by the New England  
11 Journal of Medicine.

12           They all showed consistent findings.  
13 Further, in the TEMPO study, early treatment with 1  
14 milligram showed some benefits with respect to  
15 delayed treatment with 2 milligrams, although,  
16 obviously, it was grossly underpowered, and this  
17 was not meant to be the primary goal of the study.

18           So how does one explain these findings in  
19 the 1-milligram dose? I don't really know for  
20 sure. It could be neuroprotection, disease  
21 modification, preservation of a compensatory  
22 mechanism, or maybe something else. But by

1       whatever mechanism, treatment with rasagiline,  
2       1 milligram, is associated with slowing of UPDRS  
3       progression in my mind. This is what we  
4       anticipated we would see in a delayed-start study  
5       that showed slowing of clinical progression, and  
6       this is what we found.

7               Now, the difference between the early- and  
8       delayed-start groups was 1.7 points. Now, you may  
9       think 1.7 UPDRS points may not seem like much, and  
10       some have questioned its clinical significance.  
11       But because of the slow rate of progression of  
12       Parkinson's disease in this early stage, it is  
13       important to appreciate this represents a  
14       38 percent reduction in the rate of UPDRS decline  
15       between the early- and delayed-start groups. And  
16       this reflects only nine months of treatment,  
17       because both groups were on the same treatment  
18       during the second nine months.

19               So 1.7 UPDRS points may seem small, but if  
20       its 38 percent reduction in rate of progression  
21       continues beyond the 18-month period, then this  
22       could be huge for a patient with Parkinson's

1 disease.

2           Finally, this benefit was achieved with a  
3 remarkably good safety profile, literally no  
4 important safety concerns. Even theoretical  
5 concerns, such as tyramine reactions and serotonin  
6 reactions, were not a problem.

7           Now, while the results of the 1-milligram  
8 dose are strong and consistent to me, the  
9 uncertainty arises because rasagiline,  
10 2 milligrams, failed to meet the second endpoint.  
11 We don't know why this higher dose failed to reach  
12 this endpoint, but perhaps there's more to the  
13 story.

14           Firstly, the 2-milligram dose did meet the  
15 first primary endpoint, separation of slopes after  
16 12 weeks. You will recall that the 2-milligram  
17 dose also demonstrated a benefit in the TEMPO  
18 delayed-start study for the endpoint that was  
19 assigned to it. And the 2-milligram dose  
20 demonstrated a benefit with respect to all three  
21 endpoints in ADAGIO for those patients with the  
22 highest baseline UPDRS scores, as we reported in

1 our article in the New England Journal of Medicine.

2 Now, our decision to analyze the upper  
3 quartile was made because we noted that patients in  
4 TEMPO had higher baseline UPDRS scores than those  
5 in ADAGIO, and we speculated that a UPDRS floor  
6 effect might have masked our ability to detect a  
7 difference between the early- and delayed-start  
8 groups with this higher dose in such a mild  
9 population of patients. While it was a post hoc  
10 analysis, our choice of the upper quartile was  
11 based on this hypothesis. It was not based on any  
12 pre-examination of the data.

13 The concept of a floor effect is well known  
14 in Parkinson's disease. For example, in the  
15 Step-Up study, which we published in JAMA a number  
16 of years ago, we saw minimal treatment effects in  
17 patients with low UPDRS scores but prominent  
18 effects in patients with high UPDRS scores with all  
19 doses. And, in fact, we recently published a paper  
20 in Lancet Neurology that showed similar effects in  
21 the ADAGIO study.

22 The change between the placebo and early

1 treatment groups at week 36 seen in the entire  
2 population was relatively small in comparison to  
3 that same change seen in patients in the upper  
4 quartile, the difference being 3 points in all  
5 patients and over 7 points in patients in the upper  
6 quartile, consistent with a floor effect that fails  
7 to allow you to see these kinds of differences.

8 Failure of lower quartiles to show a  
9 monotone pattern, as you've heard, is what you  
10 would expect to see if there is a floor effect that  
11 limits the change in UPDRS scores that you can see  
12 in patients with relatively mild disease, too much  
13 noise to see such an effect.

14 Now, we recognize that this was a post hoc  
15 analysis, but it provides what I believe is a  
16 reasonable explanation for why the 2-milligram dose  
17 may have failed to meet the second endpoint. And,  
18 by the way, when we did the same analysis with  
19 respect to the 1-milligram dose, we again found, in  
20 the upper quartile, it met all three endpoints,  
21 despite the small sample size, and it met it with  
22 greater levels of magnitude than what we saw for

1 the population as a whole. And there were no  
2 safety issues with the 2-milligram dose, and I  
3 remind you that no request is being made for an  
4 indication with the 2-milligram dose.

5 Now, the FDA, in its briefing book, outlined  
6 a number of concerns beyond the question of the  
7 failure of the 2-milligram dose to meet endpoint 2.  
8 These include the question of whether 12 weeks is  
9 sufficient to obtain the maximal symptomatic effect  
10 of rasagiline if the deterioration of UPDRS is  
11 linear, and whether rasagiline, 1-milligram early-  
12 and delayed-start cohorts were comparable, or if  
13 they were compromised by unequal dropouts.

14 These are perfectly reasonable questions,  
15 but they are also inherent issues in designing a  
16 delayed-start study. Week 12 was chosen as the  
17 time when maximal symptomatic benefit occurred,  
18 based on analyses in TEMPO, indicating that this  
19 was the time point when it appeared that full  
20 symptomatic effects of the drug had been achieved.  
21 And, in fact, data from TEMPO suggests a maximal  
22 effect at 4 to 8 weeks, and 12 weeks was chosen as

1 a conservative estimate, based on the  
2 recommendation of the FDA.

3 It was not known if UPDRS deterioration in  
4 Parkinson's disease was going to be linear when the  
5 study was designed, and it was appreciated that,  
6 biologically, this may not be correct. But this  
7 assumption was agreed upon, and a linear slope  
8 analysis was positive for both doses and supported  
9 by categorical sensitivity analyses.

10 Importantly, from my perspective, the more  
11 important issue in any event is not so much the  
12 slope, but that the groups are different at the end  
13 of week 36, so that one can examine whether that  
14 difference at the end of week 36 is related to  
15 differences caused by symptomatic effects and/or  
16 slowing of clinical progression.

17 Now, the problem with dropouts in a delayed-  
18 start study is also appreciated and was from the  
19 beginning of the study. We made great attempts to  
20 minimize dropouts by permitting patients to have an  
21 accelerated advance from period 1 to period 2,  
22 rather than being withdrawn from the study. This

1 approach permitted us to obtain evaluable data in  
2 85 percent of patients, despite the complexity and  
3 duration of this trial.

4 Further, a variety of sensitivity analyses  
5 were used to address potential problems that might  
6 have resulted from an imbalance dropout, imputation  
7 strategies, ITT analyses, worst-case analyses, and,  
8 in each case, they supported the primary findings.  
9 It is also likely that differential dropouts in  
10 early switchers, if anything, biased against  
11 achieving a positive result in Hypothesis 2. They  
12 make it harder.

13 It is important to appreciate that there is  
14 no way to do a delayed-start study without  
15 encountering these kinds of issues, and that the  
16 assumptions that were made in designing this study  
17 were based on the best opinions of Teva scientists,  
18 the steering committee, and independent  
19 consultants.

20 Now, I respect the FDA's concerns that they  
21 raised and their desire to see the best and most  
22 convincing clinical study. The problem is, this

1        may be the best study that we can do at the present  
2        time to determine if an agent slows clinical  
3        progression. It is already the most rigorous study  
4        performed in Parkinson's disease that I'm aware of,  
5        and I think it will be difficult to do a comparable  
6        study with fewer dropouts. Indeed, it may not even  
7        be possible to repeat this study because the  
8        movement disorder community no longer has  
9        equipoise, and it may be difficult to recruit  
10       untreated patients to such a study, given the  
11       present results.

12                Now, I respect the fact that the FDA sees  
13        statistical problems with these studies, and I,  
14        too, would like them to be even better and more  
15        convincing. But I see a different set of problems  
16        that I think need to be considered. I see  
17        Parkinson's disease patients who, from the time of  
18        their diagnosis, have an inexorably progressive  
19        neurodegenerative disorder that will lead to  
20        disability. I see patients who desperately need a  
21        new treatment that slows clinical progression and  
22        reduces the chances they will develop intolerable

1 disability.

2           Rasagiline is a drug that has  
3 neuroprotective effects in the laboratory. The  
4 ADAGIO study showed consistent benefits for  
5 rasagiline, 1 milligram, namely that early  
6 treatment gives you a benefit that cannot be  
7 achieved with delayed treatment. I can think of no  
8 other explanation for that, than slowing of  
9 clinical benefit. While the magnitude may seem  
10 small, I believe a 38-percent reduction in UPDRS  
11 decline with no important safety risk is very  
12 meaningful for Parkinson's patients. And as I say,  
13 the drug has a very good safety profile that is  
14 superior to any other drug we use in Parkinson's  
15 disease, no motor complications, no impulse control  
16 disorders, no sleep attacks.

17           So based on this body of information, if I  
18 have a patient or a family member with Parkinson's  
19 disease, I would recommend starting them on  
20 rasagiline, 1 milligram, and I believe that most  
21 movement disorder specialists would at least  
22 consider this treatment option and discuss it with

1 their patients.

2           However, most Parkinson's disease patients  
3 are not started on treatment by a movement disorder  
4 specialist or even a neurologist. Two-thirds of  
5 patients are started on treatment by primary care  
6 physicians or internists, who are typically not  
7 familiar with this information. Many still hold  
8 the old view that it is best to wait to start  
9 treatment for patients with Parkinson's disease,  
10 largely because they're afraid of levodopa-related  
11 complications.

12           The addition of this information to the  
13 label would provide them an opportunity to consider  
14 that patients might do better with earlier  
15 treatment. It would provide them an opportunity to  
16 discuss the risks and benefits of rasagiline with  
17 their patient in order to determine if this is the  
18 right treatment approach for them.

19           The FDA, reasonably, may want to wait for  
20 better studies, more information, more clarity,  
21 before they provide an indication for slowing  
22 progression. But how long can we wait? This is

1 the closest we have come to identifying a drug that  
2 slows clinical progression in a clinical trial.  
3 And we may not be able to do better, not for a long  
4 time.

5 The issue for the panel, then, is to decide  
6 whether more studies and more information are  
7 required before this information can be presented  
8 to physicians and patients or if this package is  
9 sufficient to provide the information in the label  
10 to physicians right now, so that the decision as to  
11 whether or not to take rasagiline, 1 milligram, to  
12 slow clinical progression, can be made by  
13 physicians in conjunction with their patients.

14 My own view is that while the study may not  
15 be perfect, we need to step back and take a broader  
16 look. We need to consider that patients are  
17 deteriorating. There are no other treatment  
18 options. The study was done rigorously. The  
19 intervention is safe. And clinical effects are  
20 supported by laboratory findings.

21 It is not that the statistic and analytic  
22 issues aren't important, but they need to be

1 considered in this broader context, in my view.  
2 The fact that there are subtle questions pertaining  
3 to complex statistical issues doesn't detract from  
4 the strength of the findings that we see, its  
5 remarkable safety profile, and the desperate need  
6 of patients for this type of therapy.

7 Thank you.

8 **Sponsor Presentation - Cheryl Fitzer-Attas**

9 DR. FITZER-ATTAS: So we thank you very much  
10 for your attention this morning and are happy to  
11 address any of your questions at this time.

12 **Clarifying Questions**

13 DR. FOUNTAIN: Are there any clarifying  
14 questions for the sponsor? Please remember to  
15 state your name before you speak.

16 Dr. Rosenberg?

17 DR. ROSENBERG: Yes. I was just trying to  
18 figure out a bit of jargon here, combined dataset  
19 versus separate datasets. I think you're trying to  
20 say that the combined dataset involves combining  
21 the two placebo groups, the one that was destined  
22 to get 1 milligram, the one that was destined to

1 get 2 milligrams.

2 Please clarify here because it's kind of a  
3 key question.

4 DR. FITZER-ATTAS: Yes. Certainly. And I  
5 would like to ask Dr. Paul Feigin to come to the  
6 microphone to clarify that for you.

7 DR. FEIGIN: My name is Paul Feigin. I'm a  
8 professor of statistics at the Technion Israel  
9 Institute of Technology and a consultant for Teva.  
10 The ADAGIO design and analysis in the active phase  
11 involves comparing the early-start and the delayed-  
12 start groups individually for each dose. It's  
13 based on the combined ACTE dataset. That was the  
14 pre-specified analysis. It provided strong  
15 evidence that there was a positive result for the  
16 1 milligram, but not for the 2 milligram. This  
17 discrepancy was unexpected and we looked for an  
18 explanation.

19 As a statistician, my suspicion was that  
20 there was a possible floor in the model that was  
21 being used for both parts of the study. The pre-  
22 specified model, as well as the treatment effects,

1 had covariate effects based on UPDRS and center.  
2 And it was assumed that those covariates were  
3 acting the same way in the patients treated with  
4 1 milligram and the patients treated with  
5 2 milligrams. So we checked this assumption and  
6 found that it did not hold. It was violated. And  
7 it could have led to a bias in the way that the  
8 treatment effects for the 1 milligram and the  
9 2 milligram were estimated.

10 So we decided to analyze that data  
11 separately. That means we took out the data for  
12 the 1 milligram early start and the 1 milligram  
13 delayed start, and analyzed that data with the pre-  
14 specified model structure, and then did that same  
15 thing on the 2-milligram data. That's the  
16 difference between the combined and the separate  
17 datasets.

18 DR. ROSENBERG: So was there a significant  
19 interaction between dose UPDRS and outcome? Was  
20 there also similarly between dose site and outcome?

21 DR. FEIGIN: There were significant  
22 interactions between the dose level and the center.

1           Slide on. That was the p value for that  
2 interaction. There was a significant interaction  
3 between the dose level and the UPDRS. And that was  
4 the basis for deciding that these two substudies  
5 should be analyzed separately.

6           DR. FITZER-ATTAS: Thank you, Dr. Feigin

7           DR. FOUNTAIN: Dr. D'Agostino?

8           DR. D'AGOSTINO: One of my questions  
9 actually follows up on that. When you say there is  
10 an interaction, interaction where? There's three  
11 different tests and so forth. Where's the  
12 interaction actually coming up?

13          DR. FITZER-ATTAS: Dr. Feigin, please, could  
14 you continue your response?

15          DR. FEIGIN: The interaction between the  
16 dose level and the baseline, for example -- slide  
17 on -- in the 1-milligram dose to the co-efficient  
18 was .047, positive. In the 2-milligram dose, it  
19 was negative. The difference of .1 was  
20 significant.

21                 Did I get the answer to that question or do  
22 you want to --

1 DR. D'AGOSTINO: I think we're struggling,  
2 at least two of us, on where the interaction is  
3 coming up. I mean, we tend to think the  
4 interaction is going to be in the final test and so  
5 forth. And you throw an interaction term, and it  
6 sort of destroys things.

7 You seem to be saying it has something to do  
8 with baseline, and I'm not sure. I think I'm with  
9 you, but I'm not completely sure I am.

10 DR. FOUNTAIN: Would you like anymore  
11 clarification about that or is that answer  
12 sufficient?

13 DR. FEIGIN: We're talking about time points  
14 48 to 72. We're talking about the active phase  
15 stage of the analysis. And we want to see whether  
16 the change in UPDRS was influenced by the baseline  
17 UPDRS.

18 That is interaction that was evaluated  
19 between the 1-milligram set of data and the  
20 2-milligram set of data. In other words, the  
21 baseline on patients treated with 1  
22 milligram -- remember, we're in the active

1 phase -- the baseline had a different impact than  
2 it did in the patients treated with 2 milligrams.

3 DR. D'AGOSTINO: This is at week 36 and  
4 week 72?

5 DR. FEIGIN: This is over the weeks 48  
6 through 72.

7 DR. D'AGOSTINO: Forty-eight through 72.  
8 Okay. Thank you. And I do understand it.

9 Then my question that follows on that, how  
10 did this unfold with the discussion with the FDA,  
11 or was there a discussion with the FDA after  
12 finding those? You said it was approved by the  
13 advisory committee. It's all post hoc. The data's  
14 been locked, and you're looking at the data, and  
15 you're finding this.

16 So how did the discussions unfold with the  
17 FDA when this was found and you decided these other  
18 analyses? And then just a question with that, that  
19 if I understand the presentation, that even if you  
20 go back to the original procedure of testing, the  
21 p values are all hovering around the same results,  
22 anyway.

1           So there's two questions there. What was  
2 the interaction with the FDA? And the second one  
3 is, while we're making a lot of statements about  
4 these splitting and what have you, the gestalt in  
5 terms of the results are not that much different.

6           DR. FITZER-ATTAS: Yes. Two questions. And  
7 to first respond to the interactions with the FDA,  
8 I'd like to ask Dennis Ahern to respond to that.

9           MR. AHERN: If I understood the question  
10 correctly, you were asking if that  
11 separate/combined was agreed with the FDA, and I  
12 think that was a misunderstanding. That was not.

13           DR. FITZER-ATTAS: Regarding the -- the  
14 second part of your -- sounded more like a comment  
15 than a question.

16           Is there a specific question there, Dr.  
17 D'Agostino?

18           DR. D'AGOSTINO: No. I think I have enough  
19 of that. Let me have one more question.

20           Could I ask another question, and then I'll  
21 step aside?

22           DR. FOUNTAIN: Why don't we come back to

1 you, if that's all right?

2 Dr. Clancy?

3 DR. CLANCY: I have a question that's  
4 probably directed to Dr. Olanow. So in the initial  
5 presentation, you gave an overview of the classic  
6 symptoms of Parkinson's disease, which were motor,  
7 the shuffling gait, tremor, bradykinesia, and so  
8 forth.

9 In fact, for a patient to be enrolled in  
10 either of these studies, the cardinal feature was,  
11 they had to have motor signs. And yet, the rating  
12 score, this UPDRS rating score, is a composite of  
13 looking at mental function, mood, activities of  
14 daily living, and motor exam.

15 So my question is, because the drug is  
16 targeting mono A B inhibition, was there any  
17 attempt to do a subanalysis, simply looking at  
18 motor signs alone, to see if this is disease  
19 modifying, just for the motor system, not that the  
20 mental progression is not important or activities  
21 of daily living are not important, but to focus  
22 this as a disease modification for the motor

1       manifestations of the disease?

2               DR. FITZER-ATTAS:   So while this was  
3       addressed to Dr. Olanow, I will take the  
4       prerogative of the moderator and ask Professor  
5       Poewe from Innsbruck to respond to this question,  
6       who has looked at the different UPDRS subscores  
7       within the ADAGIO.

8               DR. POEWE:   Yes.   Thank you.   I'm Werner  
9       Poewe.   I'm a clinician, and one of the co-authors  
10       of the ADAGIO study, and also of the one that was  
11       referred to by Dr. Olanow, published in the Lancet.  
12       And that particular paper does contain some  
13       information that may be relevant to your question;  
14       what is the different contribution of the subparts  
15       of the UPDRS to the different outcomes that we're  
16       seeing at week 36, reflecting symptomatic effects  
17       mainly, at week 72?   And there was this difference  
18       that is indicating disease modification or slowing  
19       of clinical progression.

20               I would like to illustrate with that  
21       particular graph, where you can see that, indeed,  
22       the composition of the relative percentages of the

1 improvement that we're seeing at these two time  
2 points, week 36 and 72, is slightly different in  
3 terms of components of the UPDRS, in that at  
4 week 72, there is a greater proportion of  
5 improvement in the ADL subsection.

6 We felt that that was an interesting finding  
7 that adds weight to the assumption that the  
8 difference at the week 72 seen might indeed be  
9 particularly visible on patient-related outcomes,  
10 speaking to the fact of clinical relevance for  
11 patients.

12 The ADL subsection as opposed to the motor  
13 subsection, is more responsive, as has been  
14 suggested in some recent studies, to progression  
15 over time. And as compared to the motor section,  
16 it's less vulnerable to effects that may be related  
17 to observer variability at different time points,  
18 since it does look at a one-week perspective, while  
19 the symptomatic effect at week 36 is mainly due to  
20 the improvement on the motor subsection.

21 DR. CLANCY: Do you have this for the  
22 2 milligram?

1 DR. POEWE: I'm sorry. I didn't --

2 DR. CLANCY: Yes. You showed us results for  
3 the 1 milligram, and we understand that that was  
4 effective in stopping the course of progression,  
5 but within the 2-milligram dose, was there subset  
6 improvement?

7 DR. FITZER-ATTAS: Can I clarify?  
8 Obviously, for the 2-milligram at 72 weeks, there  
9 was no treatment difference, but, in fact, the ADL  
10 subscore was the only one that trended in the right  
11 direction.

12 But are you looking for the breakdown at 36  
13 weeks?

14 DR. CLANCY: No, at 72 weeks. So is the  
15 breakdown because there's no cognitive differences  
16 or because there were no motor differences in the  
17 2-milligram dose at 72 weeks?

18 DR. FITZER-ATTAS: Right. Please, Professor  
19 Poewe. Please.

20 DR. POEWE: There was no difference at  
21 week 72 that could have been analyzed in that  
22 particular fashion.

1 DR. FOUNTAIN: Thank you. I should have  
2 mentioned, also, that if the panel members will  
3 raise their hand, we'll keep track, and I promise  
4 we'll get to you in order. Next is Dr. Frank.

5 DR. FRANK: So even in the hands of the most  
6 experienced clinicians, the diagnosis of  
7 Parkinson's disease is a clinical one, and it's not  
8 perfect.

9 So, typically, in studies with Parkinson's  
10 disease, about 5 percent of patients or so turn out  
11 not to have Parkinson's disease. So do you have  
12 any information and follow-up on the patients in  
13 ADAGIO and the six years of follow-up in TEMPO of  
14 those that did not have Parkinson's disease and  
15 their response, and was there a difference in the  
16 different groups?

17 DR. FITZER-ATTAS: Perhaps, a piece of  
18 information that I could give you on that is that a  
19 subset of the ADAGIO patients are being followed in  
20 an extension follow-up study. We have about  
21 70 percent of the population and 680 patients who  
22 all retain the diagnosis of Parkinson's disease.

1 DR. FRANK: So none of the patients that  
2 have been enrolled have been found not to have  
3 Parkinson's disease?

4 DR. FITZER-ATTAS: I can't say for the  
5 entire population, but at least for the 70 percent  
6 that we are now following, continuing to follow.

7 Does that answer your question?

8 [Dr. Frank nods yes.]

9 DR. FOUNTAIN: Dr. Ellenberg?

10 DR. ELLENBERG: Thank you.

11 I'm still confused about the covariate  
12 interactions. The two interactions that were  
13 found, one of them was with center. Now, as I read  
14 the material, there were 129 centers, which means  
15 that on average, there was maybe fewer than 10  
16 people, on average, treated at each center.

17 I would like to have some intuitive feeling  
18 about the interaction by center, what could have  
19 caused that. How were the patients distributed  
20 across centers? Were there a lot of centers that  
21 only saw one subject, and how was that incorporated  
22 into the analysis?

1 I would also like to know how the  
2 randomization was stratified and how many different  
3 covariates were looked at in stratification, and  
4 for how many you looked for these kind of  
5 interactions.

6 DR. FITZER-ATTAS: Dr. Feigin, may I ask you  
7 to come to the microphone again?

8 DR. FEIGIN: First of all, in the study  
9 design, the centers were randomized or stratified  
10 in a block stratification of the randomization. So  
11 they were balanced. And you're right. There are  
12 many centers, and it's very hard to interpret a  
13 treatment-by-center interaction.

14 I can show you a graph -- slide on -- that  
15 will show the treatment by center interaction,  
16 averaged over the 48 to 72 weeks. What we're  
17 seeing and what the treatment effects are showing  
18 is that, on average over the centers, the level is  
19 below zero, and that's one way of interpreting the  
20 treatment effect.

21 The question about which covariates we  
22 looked at, you have to understand that the pre-

1 specified model only had two covariates. It had  
2 the baseline UPDRS and the centers. That's the  
3 only model we checked. We just checked -- for that  
4 model, there was an interaction with the dosing.  
5 And that led us, when we found that, to say we're  
6 going to use this same model, the same way of  
7 estimating treatment effects. We use the same  
8 covariates as in the pre-specified model. We apply  
9 it separately to each dataset. That's the whole  
10 story.

11 DR. ELLENBERG: Well, that answered the  
12 second part of my question, but I would still like  
13 to know what the distribution was of subjects  
14 across the centers. How many?

15 DR. FEIGIN: The actual graph tries to  
16 depict that by showing the size of the circles  
17 represents the number of patients. So there were  
18 some centers with two patients. That is true. And  
19 in a large study like this with many centers, you  
20 would expect to have quite a variability in size.

21 DR. FITZER-ATTAS: We can try and get those  
22 exact numbers for you over the break, if you'd like

1 to see that.

2 DR. ELLENBERG: This is hard for me to  
3 interpret immediately, just by looking at it. So  
4 if I could see a copy of that later to stare at a  
5 little longer, I would appreciate it.

6 DR. FEIGIN: I think it's in our --

7 DR. ELLENBERG: Is in the documents?

8 DR. FOUNTAIN: That would be great, if you  
9 can get that later, and then we can follow up on  
10 that question. Thank you.

11 Dr. Zivin?

12 DR. ZIVIN: You seem to be acting as though  
13 the UPDRS rating scale is linear, and that makes an  
14 important point about making the analyses that you  
15 do later on. And I don't understand how a scale of  
16 176 points, that isn't even ordinal, could be  
17 considered to be linear at any point along the way.

18 DR. FITZER-ATTAS: You would like an  
19 explanation of why, in UPDRS, we are even  
20 addressing the issue of linearity?

21 DR. ZIVIN: Yes.

22 DR. FITZER-ATTAS: Yes. So for that

1 question, I'd like to ask Dr. Patrick Darken to  
2 respond.

3 DR. DARKEN: Hi. I'm Patrick Darken. I'm  
4 the head of statistics at Teva. I think each item  
5 is rated zero to 4 and then summed up, so there is  
6 some ordinal aspect to the scale. The linearity  
7 issue, though, is really related that's being  
8 discussed here is the changes over time.

9 So would you like me to address that  
10 question?

11 DR. ZIVIN: Yes.

12 DR. DARKEN: So there was a statistical  
13 deviation from linearity in the placebo-controlled  
14 phase. The real question is whether linear is  
15 still a reasonable approximation. And I believe  
16 that if we look at all the data, and in particular  
17 the active phase of the trial, which was  
18 prospectively designed to evaluate linearity, that  
19 we can be confident that that estimate that we're  
20 getting from the week 12-24-36 data is an accurate  
21 reflection of the rate of decline in UPDRS on  
22 1 milligram in this trial.

1           If I could have that slide on, please?

2           This is the plot of the observed data that  
3       Dr. Fitzer-Attas showed earlier this morning.  
4       Here's our estimate of the slope that we got in the  
5       placebo-controlled phase, so 093.

6           Now, if I turn to the active phase, here are  
7       the slopes that we fit both to the early-start  
8       patients on the bottom and to the delayed-start  
9       patients on the top, once the symptomatic benefit  
10      has presumably been realized by week 48.

11          I can say two things from this, one, that a  
12      line seems to fit the pattern of response fairly  
13      well, and, two, that those point estimates are  
14      consistent with what we saw in the 093 value from  
15      the 12-24-36 data.

16          On the next slide, I can actually fit a line  
17      to the entire 12 to 72 weeks for the early-start  
18      patients, since they received 1 milligram  
19      throughout. And once again, a line seems to be a  
20      reasonable approximation to that data, and the  
21      point estimate is consistent, if anything,  
22      numerically smaller, than the 093 value.

1           So, in summary -- next slide,  
2           please -- here's the 24-to-36 value, which has been  
3           concerning to some people. And this, I would  
4           caution to interpret too much, since it's only  
5           based on two points in time, only 12 weeks apart.  
6           And when you look at all these slopes together,  
7           really, to me, that's the outlier in all this  
8           analysis.

9           The second point I'd like to make is that we  
10          also did an analysis that didn't require linearity  
11          for getting from 12 to 36 weeks, and that's this  
12          categorical analysis that Dr. Fitzer-Attas just  
13          referred to. And there we just compared the  
14          difference at week 36 to the difference at week 12,  
15          and showed that the difference at 36 between early  
16          and delayed was, in fact, greater.

17          So if you're worried about how you get from  
18          12 to 24, we see a difference whether you're  
19          fitting a line or not in that value. So the  
20          summary is, we're confident that that difference we  
21          saw in slopes in the placebo-controlled phase is  
22          consistent with slowing of clinical progression in

1 the trial. Thank you.

2 DR. FITZER-ATTAS: Thank you, Dr. Darken.

3 DR. ZIVIN: But is it not possible that,  
4 considering the error bars that you see around the  
5 data at the various different points, you could  
6 not, in fact, fit a better type of line to the data  
7 using other points, and, therefore, getting  
8 different slopes? And as a matter of fact, the  
9 FDA, later on in a post hoc analysis, fitted a  
10 quadratic equation to the lines that seemed to fit  
11 better than anything that you showed.

12 DR. DARKEN: Yes. So if I could address  
13 that, please. We're talking about the active phase  
14 now.

15 DR. ZIVIN: Yes.

16 DR. DARKEN: Actually, I believe this is the  
17 plot you're referring to. So I do believe that you  
18 could make an argument that the quadratic model  
19 fits the data a little better than a simple linear  
20 model, but the real key point here is, it looks  
21 like railroad tracks. They're parallel. So even  
22 if you fit a quadratic model, it's not coming

1 together. They're still staying separate by  
2 approximately the same amount.

3 So I think we don't even have to be overly  
4 concerned about linearity from that standpoint,  
5 that even if we fit a quadratic model, we get the  
6 same answer. The groups are staying apart in the  
7 active phase.

8 DR. FOUNTAIN: Thank you.

9 Ms. Christensen?

10 MS. CHRISTENSEN: Thank you.

11 Two questions. In the pre-screening the  
12 patients, if I understood you correctly, there was  
13 no thought about the fact that patients may have  
14 symptoms for, in my case, 18 months before I was  
15 actually diagnosed, and you were going from date of  
16 diagnosis? And also when patients were evaluated,  
17 how did you account for the fact that Parkinson's  
18 patients have differing symptoms? I mean, you all  
19 can watch me throughout the day and you will see  
20 how my symptoms change. And that, I would think,  
21 could significantly affect the UPDRS scores.

22 I'm just asking, did you account for that?

1 DR. FITZER-ATTAS: Dr. Olanow, can I ask  
2 you, please, to take that question?

3 DR. OLANOW: So with respect to the first  
4 question you asked, namely, the time they may have  
5 had symptoms before they were diagnosed, one could  
6 use that as a time point for defining the duration  
7 of Parkinson's disease and just say when did you  
8 first have symptoms. But symptoms can be so  
9 variable, and some person has a little bit of,  
10 they're not feeling well one day; was that  
11 Parkinson's or was it not? Two years later, when  
12 they have Parkinson's disease, they look back and  
13 they say, maybe that was.

14 So what we have found over the years is the  
15 more reliable time point is the time when the  
16 actual diagnosis was made. But you're correct.  
17 One could use the time when symptoms first began.  
18 But by tradition, typically, studies use the time  
19 when the diagnosis is actually made.

20 Now, not all patients have exactly the same  
21 constellation of symptoms, so you're correct. Some  
22 may have tremors. Some may not. And one of the

1 ways we deal with that, of course, is with the  
2 randomization process so that, in theory, they  
3 should be randomly assigned to the different  
4 treatment groups in equal proportion.

5 But you are correct that it is possible that  
6 someone with tremor-dominant Parkinson's disease  
7 might progress at a slightly different rate than  
8 someone who had more axial symptomatology. And if  
9 we were to split them out, you can imagine, in  
10 subgroups, how would we ever recruit this many  
11 patients. So we recruit the lot, and we rely on  
12 randomization to take care of it for us.

13 DR. FOUNTAIN: Dr. Twyman?

14 DR. TWYMAN: Right. Changing an endpoint  
15 late in a study can be quite problematic,  
16 especially in a pivotal study. And so could you  
17 elaborate a little bit further on the rationale and  
18 why a change from two endpoints to three endpoints  
19 so late in the study, which could also impact the  
20 informed consent, how this conclusion is reached of  
21 changing from two to three?

22 DR. FITZER-ATTAS: In fact, that question

1 may be best proposed to the agency, but this was a  
2 discussion that went on together between Teva and  
3 the agency, with public forums, as Dr. Olanow  
4 alluded to. And their best understanding at the  
5 time was that the three endpoints would be a better  
6 representation, and they suggested that we change  
7 the study endpoints accordingly. And, as I said,  
8 we did, mindful that it did reduce the power by 15  
9 percentage points, and that was done. That  
10 occurred almost a year after the final patient was  
11 enrolled. So at that point, there was really no  
12 opportunity to enroll further patients.

13 DR. FOUNTAIN: Next is Dr. Fleming.

14 DR. FLEMING: Dr. Zivin had asked a question  
15 about the UPDRS, and linearity, and scale. And,  
16 actually, I'd interpreted your question to be  
17 whether it was linear in clinical relevance. I  
18 don't know if that was what you had in mind.  
19 That's a question I'm interested in, but given one  
20 question, I'd like to pursue the linearity in time  
21 issue.

22 I'd like to quickly flash through three

1 slides to ask my question. CO-30, by design, we're  
2 going to, in particular, look at trying to sort out  
3 symptoms from disease modification in weeks 36 to  
4 72 data. But if we look at them -- if the sponsor  
5 could show, quickly, CO-30.

6 DR. FOUNTAIN: Could you put up CO-30  
7 quickly

8 DR. FLEMING: So, essentially, as this is  
9 conveyed here, there's a sense that even in this  
10 first period, there's going to be a difference  
11 between what the effect is at the beginning and  
12 what the effect will have emerged to at week 36,  
13 with the concept that disease modification,  
14 hopefully, is already kicking in.

15 When you go to CO-67 and look at the actual  
16 data, and we see this same pattern -- if you can go  
17 to CO-67, what we see is evidence of the symptom  
18 benefit, potentially even continuing to emerge  
19 here. We see the same basic pattern when we look  
20 at the 2-milligram dose, but we see an increase of  
21 1.6 here against an increase of only 1.0.

22 If we could finally go to slide CO-74,

1 you're giving an estimate of the 12-to-36 week  
2 estimate of minus .04, in the right direction.  
3 But disease modification might actually-- there  
4 might be some clues about disease modification even  
5 in this first 36, particularly when you look at  
6 weeks 24 to 36.

7 Am I correct? My understanding is the point  
8 estimate of the difference in the slopes, when  
9 you're looking at weeks 24 to 36, is out here at  
10 plus .05 with a 90 percent confidence interval that  
11 actually excludes a quality p value, two-sided p  
12 value,.10. I don't believe in 90 percent  
13 confidence intervals, but in any event, there's  
14 some precision to that estimate.

15 Am I correct, that you're actually out here  
16 at .05 for the primary comparison over weeks 24 to  
17 36, .049, I think it is?

18 DR. FITZER-ATTAS: Patrick -- Dr. Darken,  
19 would you, please? Thank you.

20 DR. DARKEN: Yes. I believe that's about  
21 right. It would be right at about .05, if you just  
22 looked at the 24-to-36 values, which of course, are

1 subject to dropout and early transfer, don't  
2 forget.

3 DR. FLEMING: We're going to be even more  
4 subject to dropout and early transfer when we try  
5 to interpret the data between weeks 36 and 72. So  
6 you have less of that in the first 36 weeks.

7 DR. FOUNTAIN: So the answer is yes, I  
8 think. Is that right?

9 DR. FLEMING: The answer appears to be yes.

10 DR. FOUNTAIN: Okay. We'll have lots of  
11 time for discussion later today. I do want to make  
12 sure that everybody gets an opportunity to ask a  
13 question, so I'd like everyone to confine their  
14 comments to one question and to make it succinct if  
15 you can.

16 Dr. Hinson?

17 DR. HINSON: Dr. Olanow mentioned earlier  
18 that preservation of compensatory mechanisms at the  
19 brain level might be a potential explanation if  
20 there, indeed, were to be a beneficial disease-  
21 modifying effect of this drug.

22 My question relates to the delayed-start

1 design and how can we be sure that we're not seeing  
2 a positive effect of an early intervention in the  
3 non-specific sense versus how specific is this  
4 effect to the drug in question, namely rasagiline?

5 In other words, are we just better off  
6 treating our patients early because we do preserve  
7 compensatory mechanisms versus using this  
8 particular drug?

9 DR. FITZER-ATTAS: Yes. Thank you for that  
10 question. Dr. Olanow, I would like you to answer  
11 that.

12 DR. OLANOW: I think that's a very good  
13 question. If I understand you correctly, what  
14 you're saying is, how do you know, basically, that  
15 any symptomatic agent, given early, might not give  
16 you the same result? I think that's perfectly  
17 reasonable.

18 We considered that ourselves, and I think I  
19 even mentioned that in the paper, with the idea  
20 that that may not necessarily be bad, and it may  
21 still be consistent with preservation of a  
22 compensatory mechanism, which is something that I

1 think is underappreciated in Parkinson's disease  
2 and something many people are exploring further.

3           So that is very much in our mind, that it  
4 might be that early treatment itself has certain  
5 beneficial effects. It is interesting,  
6 though -- slide on. This is the result of the  
7 PROUD study, which was another delayed-start trial  
8 that was performed, this time using the drug  
9 pramipexole, which is a dopamine agonist.

10           Basically, it was a similar concept. The  
11 periods are a little different in length, and there  
12 aren't as many points. But I think you can see  
13 that the two groups really robustly come together,  
14 not showing any evidence of benefit. And an upper  
15 quartile analysis in that group, I understand, did  
16 not show benefit, either.

17           So you may be absolutely correct, and that  
18 has not been tested. I think it's an important  
19 issue. It doesn't change, in my mind, that you're  
20 still altering the way the disease is naturally  
21 progressing. What we're discussing, though, in my  
22 mind, here is what mechanism that might be

1 occurring by.

2 DR. FOUNTAIN: Thank you. I think we'll  
3 have Dr. Black's question, and then we might ask if  
4 there's any pressing questions for now. We'll have  
5 another opportunity later to have discussion among  
6 ourselves, also clarifying questions for the FDA.

7 So if there is something that really needs  
8 to be asked to the sponsor right now, then we can  
9 do that now, after Dr. Black's question.  
10 Otherwise, we'll take a break.

11 DR. BLACK: Some of these issues might be  
12 more clear if we had an outcome measure that was  
13 not affected symptomatically in the short run.

14 I'm just curious if the sponsor could  
15 enumerate for us what other outcomes are available.  
16 For instance, you probably have weight, or Beck  
17 Depression Inventories, or MMSE, or something, that  
18 began at 0 and 72 weeks.

19 What other data do we have from this study,  
20 other than the UPDRS, which was the primary  
21 endpoint?

22 DR. FITZER-ATTAS: From the ADAGIO study?

1 DR. BLACK: Yes.

2 DR. FITZER-ATTAS: Yes. I would like to ask  
3 Professor Poewe to respond to that.

4 DR. POEWE: What we have in terms of such  
5 data are analysis, really, that are restricted to  
6 the symptomatic effect at week 36. And there have  
7 been a number of measures that we used for the week  
8 36 analyses that included the non-motor scale, the  
9 novel MDS, novel multi-experience of daily living  
10 scale, whether it was significant differences in  
11 favor of rasagiline at 1 milligram.

12 There was a fatigue scale used, and the  
13 difference that was seen in the non-motor scale  
14 were very much on apathy, subitems for apathy, for  
15 depression, and cognition. But we don't have data  
16 that would differentially show, at week 72,  
17 different outcomes. We only have analyses for the  
18 week 36 outcome.

19 DR. BLACK: Can I just follow up briefly,  
20 please? So I was just asking, what other data were  
21 collected at 72 weeks?

22 DR. FITZER-ATTAS: At 72 weeks, it was only

1 UPDRS. There were a number of other endpoints, as  
2 Professor Poewe mentioned, in the first phase of  
3 the study only.

4 DR. FOUNTAIN: I realize that Dr. Rosenberg,  
5 Dr. D'Agostino, Dr. Zivin, and Dr. Ahlskog have  
6 questions. If there are some that we really need  
7 to ask the sponsor right now, we could ask them.  
8 Otherwise, if it's more commentary discussion among  
9 ourselves, we might save it for later.

10 Dr. Rosenberg, can we save your question for  
11 later or would you like to ask it now? Okay.

12 DR. ROSENBERG: Quick question to the  
13 sponsor, if you found an interaction between dose  
14 and UPDRS on outcome, why not -- instead of using  
15 separate databases, why not just include the  
16 interaction term in the models?

17 DR. FITZER-ATTAS: Dr. Feigin, please?  
18 Thank you very much.

19 DR. FEIGIN: Yes. You're right. There are  
20 two ways of handling an interaction effect. One is  
21 to include the interactions in the model.

22 The reason that we chose the simple approach

1 of just analyzing data separately is that, first of  
2 all, it uses the same format of the original pre-  
3 specified model, and, secondly, doesn't make an  
4 extra assumption that your error structure is the  
5 same in the two substudies.

6 I can show you the results of that analysis,  
7 if you want to see it. It gives a very similar  
8 result to the result that we got for the way we did  
9 it, with a p value of .019 or something like that.

10 DR. FOUNTAIN: Dr. Bautista, just to inform  
11 you, you can ask questions anytime. So maybe we'll  
12 take a break now, and we'll have another  
13 opportunity to ask questions after the FDA  
14 presentation or later. So right now, it's just  
15 after 10:00. Let's return in 10 minutes, at 10:12.  
16 Thank you.

17 (Whereupon, a recess was taken.)

18 DR. FOUNTAIN: I'd like to reconvene the  
19 meeting now, so if everyone could take their seats.  
20 I earlier identified the FDA press contact as Sandy  
21 Walsh, but, in fact, I believe it's Jeffrey  
22 Ventura.

1           If Jeffrey Ventura is present, can you  
2 stand?

3           Okay. We'll now proceed with the FDA  
4 presentations.

5                           **FDA Presentation - Tristan Massie**

6           DR. MASSIE: While the stragglers are coming  
7 in, I just want to shout out to my wife, who won a  
8 100-mile foot race on Saturday. And believe it or  
9 not, there were other competitors than her.

10                   As we've seen, the high-dose 2-milligram  
11 early group failed to show an effect at the end of  
12 the active phase and was even numerically worse  
13 than the 2-milligram delayed group. Are we to  
14 believe that the 2-milligram failure is a false  
15 negative, or perhaps, it's a true negative and the  
16 1 milligram is a false positive.

17                   The sponsor has proposed a possible  
18 explanation for the failure of 2 milligrams, in  
19 particular, arguing that there may have been a  
20 floor effect. They did post hoc analyses comparing  
21 the treatment effects in subgroups above and below  
22 the highest baseline UPDRS score quartile, that is,

1 the 75th percentile of the baseline score.  
2 However, I will provide reasons later why we  
3 believe this analysis is inconclusive and was  
4 unplanned.

5 The lack of the 2-milligram effect is  
6 troubling clinically and raises doubts about the  
7 1-milligram effect. I will go through similar  
8 issues we have identified with the 1-milligram  
9 results.

10 Let's review the ADAGIO study design. The  
11 first 36 weeks were placebo-controlled. 1,176  
12 patients were randomized equally to either  
13 1 milligram delayed, 1 milligram early,  
14 2 milligrams delayed, or 2 milligrams early. The  
15 UPDRS score was assessed at baseline as well as  
16 weeks 12, 24, and 36 in the placebo-controlled  
17 phase. After week 36, the delayed groups began to  
18 take their assigned active treatment in a double-  
19 blinded fashion. Further assessments of the UPDRS  
20 were made every six weeks up until the end of the  
21 study, at week 72.

22 This graph shows the profile of the mean

1 change from baseline in the total UPDRS for the  
2 1 milligram delayed, in early groups over the  
3 course of the trial. This is based on the active  
4 phase-eligible dataset, denoted ACTE, a subgroup of  
5 the randomized patients, which we will review later  
6 on.

7 This figure shows the corresponding result  
8 for the high dose, 2 milligrams early and delayed  
9 groups. Notice the separation at the end of the  
10 placebo-controlled phase, but the convergence of  
11 the profiles at the end of the active phase, at  
12 week 72.

13 There were three ordered hypotheses that had  
14 to be significant in order for a dose to win,  
15 according to the pre-specified analysis plan.  
16 Hypothesis 1 was a slope difference of the change  
17 from baseline in total UPDRS over the placebo-  
18 controlled phase. Specifically, the hypothesis  
19 test, one for each dose, compared the 1-milligram  
20 early slope versus placebo slope or 2-milligram  
21 early slope versus placebo slope. Note here, the  
22 placebo group is the pooled placebo group formed

1 from the two delayed groups, which should be  
2 comparable before the active phase.

3 This figure shows the pattern of least  
4 scores means over time for each group in the  
5 placebo-controlled phase. And, again, as  
6 mentioned, the two placebo groups are combined  
7 here, as dictated by the pre-specified analysis.

8 The primary analysis was a comparison of  
9 group slopes of change in UPDRS over time, as  
10 determined from the period weeks 12 through 36.  
11 The pre-specified hypotheses were significant for  
12 each early dose group, as compared to the placebo  
13 group. However, the data failed the pre-specified  
14 test of checking the constant slope-over-time  
15 assumption.

16 The alternative, non-linear model involved  
17 in the test was the basis for the pattern of the  
18 group means shown in the figure. This non-  
19 linearity calls the Hypothesis 1 slope difference  
20 results into question because the hypothesis  
21 presumes that a line represents the data well over  
22 a whole period, but the non-linearity test suggests

1 that this is not the case.

2           The best we can do with the out-of-constant  
3 slope over the entire period is look at the two  
4 available time segments, week 12 to 24 and week 24  
5 to 36. It first suggests divergent slopes, as we  
6 see in the figure. But the second segment, from  
7 week 24 to 36, suggests parallel slopes, or,  
8 equivalently, no slope difference. The average  
9 slope over the entire period is not valid, as the  
10 non-linearity test indicates that it does not  
11 adequately represent the data. Since the  
12 hypothesis required diverging slopes and there's  
13 evidence to the contrary in the second segment, it  
14 is not clear that Hypothesis 1 has been satisfied.  
15 But the active phase analysis is more directly  
16 relevant to the question of disease modification,  
17 so let us proceed to evaluate the active phase,  
18 based on the pre-specified nominally significant  
19 result for Hypothesis 1, though it is questionable.

20           Before we get to the active phase, we need  
21 to consider the multiple dose-testing issue.  
22 Basically, with two doses, there are two chances to

1 win. You can win on 1 milligram or win on  
2 2 milligrams. There is a need for an adjustment to  
3 the significance level to control the overall false  
4 positive rate for the study and to be comparable  
5 with the single-dose study, so that, from  
6 application to application, you have a level  
7 playing field.

8 The sponsor pre-specified the Hochberg  
9 method as the multiplicity adjustment approach.  
10 This approach does not require the high dose to win  
11 before looking at the low dose. It turned out to  
12 be the ideal choice for the ADAGIO outcome.

13 The method is as follows. Calculate the  
14 p value for each dose comparison. If both doses  
15 have p values less than or equal to .05, then we  
16 can conclude both doses are statistically  
17 significant. If, on the other hand, the larger of  
18 the two p values is greater than 0.05, then we  
19 cannot conclude that dose is significant, and we  
20 can only conclude the dose with the smaller p value  
21 is significant if that p value is less than .025.

22 Hypothesis 2 concerns the active treatment

1 phase at weeks 48 through 72. In particular, it is  
2 a test for superiority of the early group mean  
3 change from baseline in total UPDRS to the  
4 delayed-start mean at week 72, the end of the  
5 active phase. Because the hypotheses were  
6 hierarchical, this test was only to be performed if  
7 Hypothesis 1 was statistically significant.

8 The sponsor pre-specified the primary  
9 analysis dataset for this hypothesis as the dataset  
10 containing all four groups of patients that were  
11 eligible for the active phase, as outlined in the  
12 protocol. Using this dataset, a joint or  
13 simultaneous model of all four groups' changed in  
14 UPDRS permitted performing the two-dose comparisons  
15 of interest, 1 milligram early versus delayed, and  
16 2-milligram early versus 2-milligram delayed at  
17 week 72.

18 Analysis of Hypothesis 2 requires  
19 restriction to the subset of the ITT population  
20 because of dropouts. The pre-specified analysis  
21 dataset for Hypothesis 2 was the active efficacy  
22 data analysis set, noted ACTE. It consists of all

1 subjects entering the active treatment phase, with  
2 at least 24 weeks of treatment during the placebo-  
3 controlled phase, who also have at least 1 UPDRS  
4 measurement at week 48 or later during the active  
5 treatment phase.

6 In addition to ordinary dropouts, due to  
7 various reasons, the trial allowed early transition  
8 to the active phase for patients who, in the  
9 investigator's opinion, needed additional anti-  
10 Parkinsonian beyond the double-blind randomly  
11 assigned study treatment. However, if, based on  
12 this need, patients transitioned before the week 24  
13 assessment, the sponsor pre-specified that they  
14 were to be totally excluded from the active phase  
15 analysis. This exclusion of early, early switchers  
16 may not bias against the drug. It may bias for the  
17 drug. We don't know. We just know that excluding  
18 patients is a problem.

19 This was certainly in the patients' best  
20 interests, allowing them to switch early, but  
21 presents a real challenge for the use of this  
22 design. In particular, since these exclusions may

1       disturb the balance between treatment groups  
2       created by the initial randomization, and so may  
3       bias the analysis of the active phase, we will  
4       investigate this later on.

5               As we heard earlier, the sponsor changed the  
6       pre-specified analysis dataset to a post hoc  
7       analysis dataset, based on the separate dose  
8       datasets. We have concerns about the sponsor's  
9       post hoc change of analysis dataset from the  
10       combined four-group dataset to the two separate  
11       dose datasets.

12               The final analysis plan planned to analyze  
13       the processes, too, using the combined dataset  
14       containing all doses. The sponsor's rationale for  
15       the change of analysis dataset was that there were  
16       statistically significant interaction effects  
17       between baseline score and dose, and also between  
18       sites and dose, in the analysis model when the pre-  
19       specified combined dataset was used.

20               These interactions suggest the pre-specified  
21       model adjustments for the baseline UPDRS score, as  
22       well as for sites, are significantly different

1 between the 1-milligram dose and 2-milligram dose.  
2 However, the pre-specified final analysis plan had  
3 no provisions for checking significance of these  
4 interactions or alternative models in case they  
5 were found. Therefore, there is uncertainty if the  
6 primary analysis should be revised, and if so, how.

7 Let us examine why the analysis results may  
8 vary, depending on whether the pre-specified all-  
9 four-groups dataset or the separate dose-specific  
10 datasets are used. Here, we see, on the left, a  
11 representation of the analysis model when the  
12 combined dataset is used, and on the right, we see  
13 what the model looks like when the separate dose  
14 datasets are used on the top for 1 milligram and on  
15 the bottom for 2 milligrams.

16 It should be emphasized that although the  
17 sponsor calls the all-four-groups dataset the  
18 combined dataset, this does not actually combine  
19 the doses into one. Both doses exist in the  
20 dataset, and their identities are retained there,  
21 and the early versus delayed comparisons still made  
22 separately for each dose.

1           In the analysis model, regardless of the  
2 dataset use, we assumed the spread of the random  
3 deviations of the data from the model and effects  
4 of baseline score and sites are the same for early  
5 and delayed groups within a particular dose.

6           In the combined set with the associated  
7 four-group joint analysis model, we assume that  
8 these effects are the same for both doses as well.  
9 So baseline and site adjustment effects or some  
10 general effects with common values for all  
11 treatment groups in a particular dataset are  
12 estimated based on data from all groups in the  
13 dataset.

14           For example, in the 1-milligram separate  
15 dataset, 2-milligram has no influence on the  
16 common-effect estimates because the 2-milligram  
17 data is excluded. On the other hand, each group's  
18 pattern of mean change over time is essentially  
19 estimated based on that group's data alone after  
20 taking these common effects into account.

21           The common effects are estimated based on  
22 twice as much data when using the sponsor's term,

1 combined dataset, as seen here, and equals 996,  
2 shows that 996 patients are used to estimate these  
3 common effects when the combined dataset is used.  
4 And on the right, only 489 are used when the  
5 1-milligram separate dataset is used and 507 when  
6 the 2-milligram separate dataset is used. This can  
7 lead to differences between the all-four-groups  
8 model and the separate dose dataset models, and the  
9 common effect estimates, which then in turn lead to  
10 adjustments in the within-dose treatment group  
11 comparisons.

12 Here we see the results for the week-72  
13 analysis for each dose. First, it's pre-specified  
14 in the protocol, using the four-group joint  
15 statistical model. We see that the 2-milligram  
16 p value was greater than .05, so the 1-milligram p  
17 value needs to be less than or equal to .025 for  
18 significance, but it is not statistically  
19 significant at just over .05.

20 The sponsor presented a post hoc re-analysis  
21 based on using separate datasets for each dose,  
22 shown here. Here, again, the 2-milligram result

1 was above .05, so the 1-milligram p value needs to  
2 be less than or equal to .025. Using this post hoc  
3 method, the 1-milligram result was right at the  
4 significance limit for the p value.

5 Again, the sponsor justified this post hoc  
6 change to the dose-specific dataset because they  
7 added interaction effects between baseline score  
8 and dose, as well as between sites and dose, to  
9 their pre-specified statistical model. They found  
10 these interactions to be important, yet there was  
11 no mention in the analysis plan of testing these  
12 interactions, or whether, or how to alter the  
13 analysis if they were found.

14 These interactions suggest that the effect  
15 of the baseline score on the change in UPDRS  
16 differs between doses. Similarly, the dose-by-site  
17 interaction suggests that the side effects have  
18 different values for each dose, 1 milligram and  
19 2 milligrams.

20 Through the assessment of these  
21 interactions, the sponsor assumed that within each  
22 particular dose, that is, comparing early versus

1 delayed groups within a particular dose, there is  
2 no difference in these baseline score and side  
3 effects on change in UPDRS. However, there is  
4 equally compelling evidence that within dose,  
5 particularly for 1 milligram delayed versus  
6 1 milligram early, that the effects of baseline  
7 score as well as sites on the change in UPDRS are  
8 not consistent.

9           So, at best, if we accept the move to the  
10 post hoc 1-milligram separate dataset, the  
11 implication and the additional within-dose  
12 interactions is at the 1-milligram treatment  
13 difference, early versus delayed, is significantly  
14 inconsistent and variable across different baseline  
15 UPDRS scores, as well as across different  
16 investigational sites.

17           In summary, the only way to get significance  
18 at the required multiplicity-adjusted level for  
19 1 milligram at week 72 was not in the analysis  
20 plan.

21           Here we see a Forest plot of the baseline  
22 UPDRS for females, males, and overall in the ITT

1 and ACTE, the active phase population. The blue  
2 line segments represent the 95 percent confidence  
3 interval for the mean baseline UPDRS score  
4 difference, early minus delayed. And at baseline,  
5 we would expect all differences to be zero because  
6 of randomization, so the lines should intersect the  
7 vertical dash line that crosses the X axis at zero.

8 If the line doesn't cross this dashed line,  
9 the blue line doesn't cross this dashed line, then  
10 it suggests that there is a nominally significant  
11 baseline UPDRS score imbalance between the early  
12 and delayed groups.

13 For the ITT comparisons, all three crossed  
14 the vertical dashed line, suggesting balance  
15 between 1-milligram early and delayed groups within  
16 the ITT population. However, with the ACTE  
17 population, the lower three confidence intervals,  
18 the line for the overall, that is, males and  
19 females together, just touches the vertical line,  
20 with a corresponding p value of 0.056, and for  
21 females, the line is completely to the right of the  
22 vertical line with a corresponding p value of .014.

1 The males, however, still appear balanced within  
2 the ACTE population.

3 Now, if we look at the week-72 differences  
4 for overall, and females and males, we see that  
5 where we had a baseline imbalance in the ACTE  
6 population is where we see a difference at week 72,  
7 first for the overall ACTE population, and then in  
8 the female subgroup, which seems to account for all  
9 of the overall effect.

10 Let's summarize what we've just seen. We've  
11 just seen that the 1-milligram female subgroup,  
12 which had a large treatment group difference, early  
13 minus delayed at week 72 and UPDRS change, also had  
14 a significant imbalance at baseline, times zero, in  
15 UPDRS.

16 The problem is that the loss of dropouts,  
17 inactive and ineligible patients, has likely  
18 disturbed the balance between the treatment groups  
19 that was created by the initial randomization. We  
20 are unable to know if the baseline score imbalance  
21 partly accounts for the treatment difference at  
22 week 72, but it raises concerns that there could be

1 other baseline variables measured or unmeasured,  
2 with imbalances between the treatment groups, which  
3 could partly account for the week-72 difference.

4 The baseline score adjustment incorporated  
5 into the model is not perfect, nor can it correct  
6 for other imbalances if they exist. The amount of  
7 patients that were lost from the ITT and going from  
8 the ITT to ACTE was 16 percent, who dropped out or  
9 were otherwise not eligible for the active phase  
10 analyses. One may think that 16 percent is not  
11 high, but in most trials, patients missing the  
12 final assessment have at least some earlier post-  
13 baseline data that can be used in the analysis.  
14 Here, though, without any active phase-eligible  
15 data, the patients have to be totally excluded. So  
16 it's like having 16 percent with no post-baseline  
17 data in a single-phase study.

18 Viewed in this light, this percentage is not  
19 low. In addition, more troubling, we have seen  
20 that the loss of this group gives rise to a  
21 treatment group imbalance. For validity of the  
22 Hypothesis 2 analysis, we need to assume these

1 patients are missing completely random, but this is  
2 likely not the case, because some of these patients  
3 were rescued by allowing them to transition to the  
4 active phase early, due to their need, in the  
5 investigator's opinion, for additional Parkinson's  
6 treatment beyond the assigned study treatment.

7 The sponsor's pre-specified sensitivity  
8 analyses for missing data, for the most part, did  
9 not address the non-ACTE part of the ITT  
10 population, the loss of which appears to have  
11 created an imbalance.

12 Now, for completeness, let's just go back  
13 and do the corresponding assessment of balance  
14 between treatment groups for 2 milligrams in the  
15 baseline UPDRS score. Here, males, females, and  
16 both taken together, the early and delayed groups  
17 are reasonably well balanced in terms of baseline  
18 to UPDRS score in the ITT population.

19 For 2 milligrams, unlike 1 milligram, the  
20 same is true within the ACTE population, as all the  
21 blue lines cross the vertical dashed line at zero,  
22 suggesting no significant baseline UPDRS score

1 imbalance between 2-milligram early and delayed  
2 groups.

3 If we look at Hypothesis 2, the week-72  
4 difference analysis, as shown in the Forest plot on  
5 the right, there is no difference at week 72  
6 between early and delayed groups, since all the  
7 lines cross the dashed vertical line, representing  
8 no difference.

9 The lack of effect for 2-milligram, which  
10 had balanced UPDRS scores between early and delayed  
11 groups at baseline, also begs the question of  
12 whether the 1-milligram difference at week 72 was  
13 influenced by the 1-milligram's lack of baseline  
14 balance.

15 In the advisory committee briefing packets,  
16 the sponsor highlights the analysis based on their  
17 original proposal for Hypothesis 2, which was the  
18 average treatment difference over the period,  
19 week 48 through week 72; that is, to do this  
20 original analysis, we compute the early minus  
21 delayed difference for each of the five visits  
22 between week 48 and 72, and then average them.

1           They argue that the week-72-only analysis  
2 was underpowered because the FDA advised switching  
3 to it only after the study was under way. There  
4 may be some truth to this underpowering, however,  
5 the 2-milligram effect estimate here is just minus  
6 .27, and by either version of the hypothesis,  
7 original or final, it seems too small to be  
8 consistent with a slight underpowering issue.

9           In the new drug application for the claim  
10 under consideration today, the sponsor presented  
11 post hoc analyses by baseline UPDRS score  
12 quartiles, attempting to explain the failure of the  
13 high dose to show any benefit at the end of the  
14 study, week 72.

15           Note that the quartiles are the 25th, 50th,  
16 and 75th percentiles of the distribution of the  
17 baseline UPDRS score among patients in the trial.  
18 A total UPDRS score of 25.5 happens to be the 75th  
19 percentile of the UPDRS score for the ITT  
20 population in this trial, meaning that 75 percent  
21 of patients had baseline UPDRS total scores below  
22 this value.

1           The sponsor hypothesized, after the fact,  
2           that the lack of difference for 2-milligram at the  
3           end may have been caused by a floor effect, in  
4           which patients with more severe Parkinson's, as  
5           evidenced by their higher baseline total scores,  
6           showed greater responses, and below some threshold  
7           value of Parkinson's already, it's difficult to  
8           demonstrate a difference because patients are  
9           progressing too slowly.

10           The sponsor presented post hoc baseline  
11           UPDRS score quartile subgroup analyses in the NDA  
12           package. And the advisory committee, they are  
13           focusing on the highest quartile subgroup versus  
14           the lower three quartile subgroups combined; that  
15           is above and below the 75th percentile of the UPDRS  
16           total score at baseline.

17           The estimated treatment difference, early  
18           minus delayed, at week 72 for 2-milligram is shown  
19           here in the figure. Negative values below the  
20           horizontal line, near the middle of the figure,  
21           favor the early group. Therefore, we see that the  
22           highest quartile of the baseline UPDRS score does

1 favor 2-milligram early, but the lower quartile  
2 favors the delayed group, as we may expect, based  
3 on the negative overall result.

4 Note that quartiles are arbitrary split  
5 points of the baseline UPDRS score because they  
6 were not mentioned in the protocol. Other split  
7 points could have been specified there, but none  
8 were. In addition, these quartiles are not really  
9 quartiles for this analysis, because they were  
10 derived for the full ITT population, but the  
11 analysis population is the smaller ACTE population.  
12 These so-called quartiles did not always capture  
13 the right proportion of ACTE patients between them  
14 because of dropouts.

15 This is the picture we see if we break the  
16 lower subgroup, baseline UPDRS less than or equal  
17 to 25.5, up into its three quartile component  
18 subgroups. Notice that in each of the lower three  
19 quartiles, which is shown to the left, the week-72  
20 difference numerically favors the delayed group.

21 As just mentioned, the sponsor's break  
22 points for the UPDRS were based on the ITT

1 population, but the analysis was based on the ACTE  
2 population. If we derive the 75th percentile at  
3 baseline UPDRS score for the true analyses  
4 population on the sponsor's preferred separate dose  
5 dataset, we find the following for their post hoc  
6 upper quartile subgroup analysis. For 2-milligram,  
7 it turns out to be a fairly similar picture. We'll  
8 see later that there are differences for 1  
9 milligram. If we break up the subgroup below the  
10 ACTE-derived upper baseline score quartile so that  
11 we see all four quartiles, we get the following  
12 picture for the 2-milligram, week-72 treatment  
13 differences.

14 It's interesting to note that the third  
15 quartile subgroup just below the highest quartile  
16 subgroup is the most in the wrong direction for the  
17 early minus delayed comparison. We might expect a  
18 linear trend if we believe the sponsor's theory  
19 about floor effect, but the third quartile subgroup  
20 being the worst doesn't fit such a trend across the  
21 four quartiles. There's no obvious biological  
22 reason to believe this pattern.

1           As the sponsor had done in the NDA, we will  
2 now look at the corresponding baseline quartile  
3 analyses for 1 milligram. Here, the quartiles were  
4 derived from the ITT population overall, as the  
5 sponsor did. For the sponsor's highest quartile  
6 subgroup, the effect appears slightly bigger than  
7 below the highest quartile, 25.5, but both  
8 subgroups favor the early group, at least  
9 numerically.

10           Here is the picture if we subdivide the  
11 lower subgroup. Again, the fourth quartile  
12 subgroup has the best, most negative effect, but  
13 the third has the least negative.

14           Now, let's see what happens if we use the  
15 baseline score quartiles derived from the actual  
16 analysis dataset for the week-72 difference. That  
17 is the 1-milligram, separate ACTE dataset. In this  
18 case, the subgroup below the 75th percentile of the  
19 baseline UPDRS score has about the same effect as  
20 the effect in the group above the 75th percentile.

21           Here we see the real reason for going  
22 through all these various baseline post hoc

1        quartile analyses, which were initiated by the  
2        sponsor. When we base the quartiles on the actual  
3        Hypothesis 2 population and the 1-milligram dose  
4        separate dataset, we find a very consistent  
5        treatment effect pattern across the quartiles, and  
6        the fourth quartile is no longer numerically the  
7        best. This pattern really does not support a floor  
8        effect, and if there was such a floor effect for  
9        2 milligram, then we would expect it for the lower  
10       dose, 1 milligram, as well. These 1-milligram ACTE  
11       population-derived quartiles are more relevant to  
12       the 1-milligram separate dataset that the sponsor  
13       argued for and to the actual analysis population  
14       for the hypothesis under consideration for this  
15       analysis, week 72.

16                Let's summarize the sponsor's post hoc floor  
17        effect theory for the 2-milligram failure and the  
18        post hoc quartile analyses designed to support it.

19                The subgroup analysis of the ITT-derived and  
20        ACTE-derived quartiles with a UPDRS baseline score  
21        distribution give different pictures for  
22        1 milligram. The ITT-derived quartiles suggest a

1 possible floor effect, but the ACTE quartiles,  
2 which are more specific to the analysis in question  
3 since they are based on the actual population for  
4 the analysis, suggest no floor effect, since the  
5 distribution of the week-72 treatment differences  
6 is roughly constant across these latter baseline  
7 score quartile subgroups.

8           Also, when the patients with the baseline  
9 scores above the 75th percentile appear to have the  
10 best effect, the third quartile subgroup usually  
11 had the worst. So there's no evidence of a linear  
12 trend in the effects over the quartile subgroups,  
13 which might support the idea of a floor effect.

14           Therefore, if we are to believe this floor  
15 effect theory, then we need to assume the fourth  
16 quartile cut point of 25.5 is a special value of  
17 the UPDRS baseline score. Also, in the delayed  
18 group, the fourth quartile of baseline UPDRS score  
19 subgroup had a higher proportion of early switchers  
20 than in the lower three quartiles, who were still  
21 eligible for the active phase analysis. Early  
22 switching implies a poor response midway and it

1 also shifts the active phase assessments 12 weeks  
2 closer to time zero, compared to normal switchers.  
3 But this is not accounted for in the analysis.  
4 This could bias the quartile subgroup analyses.

5 Let's move onto Hypothesis 3, which is a  
6 comparison of slopes during the active phase weeks,  
7 48 through 72. This is a non-inferiority  
8 comparison, meaning that the early group need not  
9 be superior to the delayed group, in terms of  
10 slope. It can even be a little worse. We just  
11 want to be sure that the slopes are parallel, or  
12 nearly parallel, so we have some reassurance that  
13 the early group will not converge to the delayed  
14 group. This idea was quantified by requiring that  
15 the upper 90 percent confidence limit for the slope  
16 difference, early group minus delayed, should be  
17 less than 0.15 UPDRS change points per week.

18 Choosing an appropriate, clinically relevant  
19 margin is a difficult task. The sponsor's chosen  
20 margin of 0.15 points per week would allow the  
21 early group to lose up to 1.5 points of its  
22 advantage over the delayed group in a 10-week

1 period and still past the test of parallelism. We  
2 will investigate the chosen margin in more detail  
3 later.

4 As the three hypotheses were hierarchical,  
5 again, Hypothesis test 3 was only to be performed  
6 if Hypothesis 1 and 2 were both statistically  
7 significant before it. Note that the test of  
8 parallelism is irrelevant if there's no difference  
9 at week 72.

10 Although 2-milligram was not eligible for  
11 Hypothesis 3, based on the Hypothesis 2 outcome and  
12 their hierarchical ordering of the hypotheses, it  
13 can be used to evaluate the adequacy of the chosen  
14 non-inferiority margin of 0.15 points per week for  
15 the slope difference.

16 The figure here shows the fitted slopes for  
17 the 2-milligram early and delayed groups, as well  
18 as the least squares means for each visit in the  
19 active phase during the relevant period, weeks 48  
20 through 72. We find that the early group has a  
21 numerically larger slope, but is still non-  
22 inferior, according to this test, because the upper

1 confidence limit for the slope difference at .06 is  
2 well below the required limit of .15. In fact, we  
3 see that the early group line, the blue line,  
4 crosses over the delayed group line around week 60.  
5 Thus, it seems that the pre-specified margin of  
6 0.15 allows too liberal a definition of  
7 parallelism.

8 This figure shows the 2-milligram early and  
9 delayed group mean UPDRS changes for the whole  
10 trial. Focusing on the key period for  
11 Hypothesis 3, weeks 48 through 72, this figure also  
12 suggests convergence of the 2-milligram early and  
13 delayed groups' lines at the end. This is more  
14 visual evidence that the margin, which would allow  
15 calling these lines parallel at and beyond week 48,  
16 was too liberal in its definition of parallelism.

17 Here, we summarize the issue of the  
18 excessive pre-specified non-inferiority margin for  
19 the slope difference in the active phase. The  
20 2-milligram dose, although not strictly eligible  
21 for Hypothesis 3, provided a means of illustrating  
22 the issue. Visual inspection of the active

1 treatment phase shows slopes for 2-milligram early-  
2 start and delayed-start groups are not parallel,  
3 but statistical analysis using the 0.15 non-  
4 inferiority margin for the slope difference  
5 indicates that the 2-milligram early and 2milligram  
6 delayed group slopes are statistically parallel,  
7 despite the fact that the early group line actually  
8 crosses the delayed group line and is numerically  
9 worse at week 72.

10 Underlying the Hypothesis 3 comparison of  
11 group slopes of change in UPDRS over time in the  
12 active phase is an assumption that the group slopes  
13 are constant over the period under consideration,  
14 weeks 48 through 72. The non-inferiority margin  
15 also is dependent on this assumption since it is  
16 defined in terms of the slope difference. The  
17 sponsor's pre-specified tests of non-linearity was  
18 carried out on the combined dataset and tested for  
19 any non-linearity among the four groups. The test  
20 would reject the linearity assumption if the  
21 p value was less than or equal to 0.05.

22 The result was a p value of 0.089. One may

1 question why the 2-milligram dose should be  
2 involved in the test for non-linearity, since the  
3 2-milligram dose is not eligible for Hypothesis 3.  
4 Considering this, if we apply the non-linearity  
5 test to the 1-milligram separate dataset, which the  
6 sponsor used to perform the Hypothesis 3 test, we  
7 find a p value for non-linearity of .0435.

8 Stronger evidence of non-linearity was found  
9 using an exploratory test for non-linearity,  
10 involving a quadratic model for the UPDRS  
11 change-over-time relationship. This calls into  
12 question and complicates the interpretation of the  
13 Hypothesis 3 result for 1 milligram. Determining a  
14 margin in the case of non-linearity is a harder  
15 problem than the linear case because non-linearity  
16 has many different forms.

17 The sample mean plot over time shows  
18 arguable non-linearity, but the plot is a  
19 simplification of the actual, correlated patient-  
20 level data. We need to rely on a statistical test  
21 of non-linearity to be scientific and avoid  
22 eyeballing, which may make unjustified

1 simplifications. We have seen that such a pre-  
2 specified test rejects the linearity needed for the  
3 1-milligram Hypothesis 3 result of parallelism to  
4 be strictly valid.

5 Now, let's move onto the earlier study,  
6 TEMPO. This figure shows the TEMPO study design.  
7 TEMPO had a shorter overall duration than ADAGIO,  
8 52 weeks as compared to 72. Like ADAGIO, the  
9 switch of placebo to active treatment occurred at  
10 the midway point, but there was no 1-milligram  
11 delayed group, only a 2-milligram delayed group.

12 TEMPO had more UPDRS assessments, indicated  
13 by the downward directed arrows at the top, than  
14 did ADAGIO in the placebo-controlled phase. This  
15 is likely because TEMPO's primary objective was to  
16 demonstrate a standard symptomatic effect. The  
17 primary objective of TEMPO was to demonstrate an  
18 effect of rasagiline at the end of the placebo-  
19 controlled phase at week 26. The active phase was  
20 originally stated as primarily for obtaining safety  
21 information and to explore efficacy.

22 The statistical analysis plan for the end of

1 the active phase was not submitted by the sponsor  
2 for FDA review and comment prior to the unblinding  
3 of the data. There was no single primary efficacy  
4 endpoint nor single primary analysis population  
5 specified in the analysis plan.

6 This figure shows a pattern of the mean  
7 change from baseline in total UPDRS in TEMPO for  
8 each treatment group. The 2-milligram early group,  
9 the green line, looks promising compared to the  
10 blue line, the 2-milligram delayed group. However,  
11 the proportion of patients assessed drops to  
12 65 percent at week 52. The 1-milligram early  
13 group, represented by the brown line, looks less  
14 promising, especially in the last 10 weeks, where  
15 it looks to be converging to the blue line.

16 Of course, the 2-milligram delayed group is  
17 not the ideal control for the 1-milligram early  
18 group, but no 1-milligram delayed group was  
19 incorporated into the design. Though not  
20 definitive, this 2-milligram pattern seemed to  
21 encourage further study.

22 A preliminary review of topline results from

1 the active phase suggested a positive disease-  
2 modifying effect, though not definitive.  
3 Therefore, in a 2004 meeting, the FDA informed the  
4 sponsor of the following. Ordinarily, two trials  
5 are required to support efficacy. The TEMPO study  
6 post hoc analysis may not be sufficient for review  
7 because it is not the primary analysis. If the  
8 next study is robustly positive, then the TEMPO  
9 study may provide supporting evidence.

10 Here, we see the results for the TEMPO data  
11 after reanalyzing the TEMPO, according to the  
12 ADAGIO analysis plan. We acknowledge that this is  
13 an underpowered analysis, but we believe that it is  
14 more relevant than the original plan for the  
15 analysis of TEMPO, which FDA didn't get the  
16 opportunity to review prior to the unblinding of  
17 the data. Recall that the timing of the UPDRS  
18 assessments was different in TEMPO, and it had  
19 shorter overall duration than ADAGIO.

20 The results of the re-analysis, according to  
21 the ADAGIO plan, are shown here. The slope  
22 difference estimate for Hypothesis 1 in the

1 placebo-controlled phase was minus .08 for  
2 2-milligram early minus 2-milligram delayed, which  
3 didn't reach nominal significance, although it may  
4 be underpowered. The corresponding Hypothesis 2  
5 result for the week-52 difference was minus 1.93  
6 with a pvalue of 0.0768. Finally, the upper limit  
7 for the confidence interval of the slope difference  
8 over weeks 42 through 52, just two points, in the  
9 active phase was .03.

10 Below are the margins specified for ADAGIO  
11 of .15 points per week, but based on the timing of  
12 events, the choice of this value for the margin  
13 could have been influenced by the TEMPO data, so  
14 this hypothesis is hard to evaluate objectively for  
15 TEMPO.

16 The results of 1-milligram early are also  
17 shown here. Note again that 1-milligram early was  
18 compared to 2-milligram delayed because there was  
19 no 1-milligram delayed group in the design. The  
20 results here for 1-milligram, Hypothesis 2, suggest  
21 possible bias of the sponsor's pre-specified last  
22 observation carried forward analysis, in which they

1 found a significant effect of 1-milligram early,  
2 compared to 2-milligram delayed, at the end of the  
3 active phase, as the p value here is .50.

4 Here we discuss some issues with the  
5 original analysis of TEMPO. We consider the  
6 original analysis to be of secondary importance to  
7 the re-analysis, using the ADAGIO plan, although we  
8 acknowledge that the re-analysis is underpowered.

9 Considering the original analysis, while  
10 it's true that 92 percent of ITT were included in  
11 the analysis of the UPDRS mean change differences  
12 at the end, only 65 percent had the week-52  
13 assessment. The others had earlier assessments  
14 carried forward. This pre-plan last observation  
15 carried-forward imputation involved in the primary  
16 analysis is problematic for assessing disease  
17 progression because it treats times which are  
18 actually different as the same. In particular,  
19 observed week-52 UPDRS for those that had it  
20 measured and UPDRS at earlier times for those  
21 missing week 52 are treated as the same.

22 For example, if a delayed group patient

1 drops out at week 32, after only six weeks in the  
2 active phase, they had their treatment delayed for  
3 26 weeks, and then they may not have had the  
4 opportunity to have a full symptomatic effect  
5 before dropping out. This may bias the original  
6 analysis.

7           This last observation carried forward  
8 imputation could be expected to create a bias,  
9 favoring the early group. For example, we see a  
10 raw mean group difference, where raw indicates no  
11 modeling involved, of only minus 1.2 for the  
12 completers, but a larger magnitude of difference of  
13 minus 2.2 for LOCF imputation. This suggests bias  
14 for LOCF imputation. An exploratory repeated  
15 measures model produced a p value of 0.0501 for the  
16 2-milligram difference at week 52, but it's not  
17 conclusive, given its exploratory nature.

18           The sponsor presented long-term extension  
19 follow-up data for TEMPO, but the data that this  
20 provides is collected open label and is confounded  
21 by dropouts and concomitant Parkinson's treatments.  
22 Inclusion of the individual patients in the

1 follow-up data is not complete and is not  
2 randomized. For these reasons, it is difficult to  
3 interpret these data. This is why we rely on  
4 double-blind randomized trials instead.

5 Here are our summary and conclusions. The  
6 most troubling issue is the failure of the high  
7 dose, 2 milligrams, in ADAGIO to show a benefit at  
8 the end of the study, week 72. It was actually  
9 numerically worse, and the p value was 0.60.

10 We found several issues with the sponsor's  
11 results for ADAGIO, 1 milligram. 1 milligram was  
12 only significant at the required multiplicity-  
13 adjusted level after a post hoc modification to the  
14 primary analysis dataset. We also found treatment  
15 group imbalances in the baseline UPDRS score in the  
16 ACTE population, suggesting it may be a biased  
17 sample of the ITT population and suggesting there  
18 could be other imbalances within it, which could  
19 compromise the analysis.

20 We saw non-linearity of the UPDRS change  
21 from baseline over time, despite Hypothesis 1 and 3  
22 assuming linearity. There was a significant gender

1 difference in 1-milligram efficacy, suggesting that  
2 all of the effect was in females. This is  
3 particularly troubling with coupled with the  
4 observation that, in females, there was also an  
5 imbalance in the efficacy measure at baseline  
6 between early and delayed groups, yet males were  
7 balanced at baseline and had no effect at week 72.

8           There were also interactions between  
9 treatment at baseline score as well as site. These  
10 interactions within dose, between early and delayed  
11 groups, suggest that the 1-milligram effect, even  
12 for the separate dose dataset, is not consistent  
13 across these subgroups. Also, no observed effect  
14 at 2-milligram at the end raises questions about  
15 the biological plausibility of the 1-milligram  
16 effect.

17           The TEMPO 2-milligram result is not  
18 considered definitive. Its pre-specified analysis  
19 is not appropriate for assessing progression. And  
20 then the ADAGIO analysis was applied to  
21 2 milligrams in TEMPO, it did not meet the usual  
22 significance level for Hypothesis 1 for a slope

1 difference in the placebo-controlled phase or at  
2 the end of the active phase, week 52. Therefore,  
3 the issues we've discussed suggest there's no  
4 totally robust finding for any dose in either  
5 study.

#### 6 **Clarifying Questions**

7 DR. FOUNTAIN: I gather that's the end of  
8 the presentation.

9 Are there any clarifying questions for the  
10 FDA? Please remember to state your name as you  
11 begin to speak.

12 Dr. Fleming?

13 DR. FLEMING: Could we go back to the slide  
14 30? It could either be 30 or 5. I think it's the  
15 same slide. Really, as we get at an important  
16 point about what I might call a paradox, as you're  
17 coming to slide 30, what we see as we look at the  
18 2-milligram dose is that the difference that we see  
19 here at 48 weeks, which about 0.8, disappears at  
20 week 72.

21 So just clinical common sense would say, if  
22 there's any opportunity for disease modification,

1 there must be some difference remaining at week 72  
2 because, if anything, it would be symptom benefit  
3 and disease modification.

4           So it seems like a paradox, then, that the  
5 non-inferiority margin, if you actually computed  
6 that analysis, is met. What the analysis shows is  
7 if you look at the data as you go from week 48 to  
8 week 72, that the slopes, in fact, are, by  
9 estimate, higher in the early group than in the  
10 delayed group, by .03. But the confidence interval  
11 that you would get, you might compute a 90 percent  
12 confidence interval. The upper limit is .058. I  
13 would actually compute 95, or in fact, in this  
14 case, 97.5, where the upper limits are .06, .068,  
15 but it doesn't matter for purposes of this  
16 discussion.

17           Suppose the upper limit of the confidence  
18 interval is .06. That clearly lies below .15. So  
19 you're clearly establishing non-inferiority,  
20 according to that criterion. But if these slopes  
21 differed by .15 each week, over 24 weeks, there  
22 would be a shifting of 3.8. So what your non-

1 inferiority analysis is saying, just from clinical  
2 common sense, is, yeah, you're .8 better off here,  
3 and I can rule out that I'm 2.8 worse at week 72.

4           Okay. But that doesn't establish that I  
5 have disease modification. I clearly have to rule  
6 out even that they're the same. What you actually  
7 rule out with an upper limit of 6 is this plus .8  
8 is not worse than minus .8. But that still doesn't  
9 allow us to conclude disease modification.

10           I have to have the ability to rule out a  
11 quality. And so, in fact, just ruling out a  
12 quality, the margin that I would have to use there  
13 would be .033. Some of us would say you'd have to  
14 have a preservation of effect -- we'll talk about  
15 this maybe this afternoon -- in which case, the  
16 margin would have to be less than half that.

17           So the absolute biggest margin you could  
18 defend here for the 2-milligram dose would be  
19 somewhere in the range of .016 to .033, not .15.  
20 And so, just from clinical common sense, this  
21 paradox is totally obvious here. The problem is,  
22 the margin is totally unjustifiable.

1 Am I missing anything?

2 DR. FOUNTAIN: Perhaps, you'd like to state  
3 that in a question.

4 DR. FLEMING: Yes.

5 DR. FOUNTAIN: Such as, do you think that  
6 the margin is unjustifiable?

7 DR. FLEMING: So, Tristan, the margin of .15  
8 only allows you to conclude that this plus .8  
9 doesn't become minus 2.8. Far less slope  
10 differences would represent complete lack of any  
11 evidence of disease modification. So the margin  
12 here is an order of magnitude larger than you could  
13 clinically defend that it should be. And once you  
14 recognize that, the paradoxes all go away. There's  
15 no paradox here at all. The evidence is suggesting  
16 no possibility of disease modification with the  
17 2-milligram dose. Now, we'll come this afternoon  
18 to discussing what this means for the 1 milligram.

19 DR. FOUNTAIN: So perhaps the question  
20 is -- or is that all the statement you'd like to  
21 make?

22 DR. FLEMING: Are there any comments on what

1 I've said, Tristan?

2 DR. MASSIE: Yes. We tried to show in our  
3 presentation that the margins seemed to be  
4 excessive.

5 DR. FLEMING: And all I'm saying is,  
6 clinical common sense says, absolutely and  
7 obviously, way excessive.

8 DR. FOUNTAIN: Dr. D'Agostino?

9 DR. D'AGOSTINO: If you would go to slide 4,  
10 you raise a number of points with the analysis.

11 And one is in the first phase, you talk about the  
12 non-linearity. I don't want to be cute and ask,  
13 aren't you worried about the fact that you're doing  
14 post hoc analysis and running with them. But if we  
15 looked at this first phase and we said, the designs  
16 that fit straight lines, we get a significant  
17 result -- but even if you don't -- this is the  
18 question that I want to ask at this point, is  
19 what's happening at week 36? Isn't that also -- or  
20 shouldn't that be thought of as being compelling?

21 When you switched -- both the company and  
22 the FDA have switched to post hoc analysis. So if

1 you wanted to say was this an effect in the  
2 phase 1, I mean, you can spend all your time that  
3 you want on looking at linearity versus non-  
4 linearity, but isn't the week-36 difference  
5 compelling that something's going on, or is it not?

6 DR. MASSIE: I think it's compelling that a  
7 symptomatic effect is going on.

8 DR. D'AGOSTINO: Yes. That's fine. So is  
9 that something that you can hang on this  
10 1 milligram? I'm trying to figure out what's going  
11 on with it and what can be concluded. That's where  
12 I'm ultimately heading, later on today.

13 DR. MASSIE: Well, I think there may be some  
14 expectation to see divergent slopes if you have a  
15 disease-modifying drug, although if you see  
16 divergent slopes in the placebo-controlled phase,  
17 that doesn't necessarily imply disease modifying.

18 DR. D'AGOSTINO: No, but they got that, and  
19 then you do a sort of post hoc analysis that says I  
20 don't believe the straight lines.

21 Let me go on quickly because I don't  
22 want -- the other question I have in terms of this

1 missing data and so forth -- now, the  
2 sponsor -- and I'm not sure that you saw it. But  
3 the sponsor gave a number of analyses where they  
4 were trying to do sensitivity-type analyses, taking  
5 advantage of the repeated measure aspect and then  
6 also doing the propensity analysis.

7 Do any of those analyses add to the  
8 discussion that you've presented in a positive way?  
9 Do you think that the propensity score analysis has  
10 no merit to it? Do you think the other sensitivity  
11 analyses have no merit to them?

12 DR. MASSIE: I think they suffer from being  
13 unplanned. The choice of the baseline variables  
14 to --

15 DR. D'AGOSTINO: But everything you do is  
16 unplanned, also, so I mean, if you follow the rigid  
17 line of the analysis, you've done an awful lot of  
18 unplanned analyses, looking at subgroups and so  
19 forth, that weren't in there. And I don't have any  
20 objection to them, but they are all unplanned.

21 DR. MASSIE: Yes. I'm just saying that you  
22 have choices to make when you do a propensity score

1 analysis, such as which variables go into the  
2 propensity score model, how do you account for that  
3 in your model of UPDRS change. You can stratify  
4 the analysis, use it as a covariate. There are  
5 choices to be made, and we did some analyses which  
6 suggest that these choices make slight differences.  
7 So the fact that it's unplanned is not conclusive.

8 I think most of the sensitivity analyses for  
9 missing data didn't address the non-ACTE part of  
10 the ITT, and the loss of that subgroup we saw  
11 appeared to give rise to a baseline imbalance.

12 DR. D'AGOSTINO: And my last question. You  
13 talked about 16 percent went missing, but then when  
14 you went onto describe it, it sounded like some of  
15 that 16 percent were individuals who left the  
16 placebo group and went into the second phase, or  
17 left early in phase 1 and went into phase 2  
18 earlier.

19 Is that not true?

20 DR. MASSIE: The 16 percent are the ones  
21 that switched -- they switched, but they were  
22 excluded because they switched too early. The

1 sponsor had --

2 DR. D'AGOSTINO: They were switches, but  
3 they switched too early. Is that what you're  
4 saying?

5 DR. MASSIE: Yes.

6 DR. D'AGOSTINO: Is that why you can't count  
7 them?

8 DR. MASSIE: If you switch before week 24,  
9 then they excluded you from the active phase  
10 analysis.

11 DR. FOUNTAIN: Dr. Katz, did you have a  
12 comment that you wanted to make in regard to this  
13 question?

14 DR. KATZ: No. There's just the question of  
15 do we agree that there is -- that the first phase,  
16 if we look at weeks 12 to 24 and 24 to 36  
17 separately, the slopes, do we at least agree that  
18 there's a possible symptomatic effect? That's a  
19 given. The drug is approved at that dose, and so  
20 we absolutely believe there's a symptomatic effect.

21 DR. D'AGOSTINO: I thought there was  
22 something about confirming, that you wanted a

1 second study so you could confirm, because there  
2 was questions.

3 DR. KATZ: Well, not confirm that the drug  
4 has a symptomatic effect. We wanted a second study  
5 to confirm what appeared to possibly represent a  
6 disease-modifying effect for the 2 milligrams.

7 DR. D'AGOSTINO: So the question about  
8 linearity in the first phase is on the table, but  
9 nobody's interested in it?

10 DR. KATZ: The only reason it's potentially  
11 interesting is, I think, because you would expect a  
12 disease-modifying drug to result in divergent  
13 slopes, and that was one of the requirements for  
14 phase 1. As Tristan said, it doesn't mean that if  
15 you see divergent slopes, it's automatically  
16 disease modification. There are other  
17 explanations. That's why we had the active phase.

18 So we would expect the slopes for a disease-  
19 modifying drug to be divergent. If you look at the  
20 two portions of the slope for the 1 milligram in  
21 the first phase, the second portion is absolutely  
22 parallel to the placebo group. So it suggests that

1 that's not divergent.

2 Now, again, the protocol called for 12 to  
3 36 weeks, as the data to be used for calculating  
4 the slope. When you do that, if you assume it's  
5 linear, they do diverge, but the question is, it  
6 doesn't look like it's linear, and that was the  
7 issue.

8 DR. FOUNTAIN: Dr. Ahlskog?

9 DR. AHLKOG: I'm going to ask Dr. Massie  
10 for a simplification and clarification. As a  
11 clinical neurologist, Hypothesis 2 is most  
12 important to me, baseline versus end of study. And  
13 I think that's what Dr. Leber's intent was when he  
14 wrote his original paper. And the other two  
15 hypotheses were added to make certain that things  
16 made good sense, statistically, and also by  
17 eyeballing the data.

18 In the original publication of the TEMPO  
19 paper, both the 1- and the 2-milligram doses were  
20 significant -- and this is the one-year study, not  
21 the six-month study -- were significant at the end  
22 of the study, baseline to 52 weeks. And you had

1 recalculated the data and used a different  
2 statistical approach, so I'm not in a position to  
3 really judge which of the two is more appropriate.  
4 So I'm going to ask you to defend the approach that  
5 you took to re-analyze the data.

6 DR. MASSIE: Okay. Well, given the fact  
7 that we're in a delayed-start design, where one  
8 group gets treatment earlier than the other, if we  
9 have patients with missing data in the active phase  
10 and we carry forward their earlier data, then  
11 they've had less opportunity to have any drug  
12 effect, they've had a delay in their treatment; so  
13 it's going to bias against the drug or against the  
14 delayed group.

15 You can't determine progression. If you  
16 carry forward data -- say, suppose, all patients in  
17 the delayed group dropped out at week 32. You'd be  
18 carrying forward a straight line. And because you  
19 had a difference at week 26, you'd have parallel  
20 slopes. So if all the group dropped out, you would  
21 conclude disease modification, based on LOCF.

22 So I think that's why LOCF is not a useful

1 approach here.

2 DR. AHLKOG: I'll just comment. The TEMPO  
3 investigators were good enough to also publish  
4 their database of the 249 patients carried forward  
5 to the end of the study, and those were not  
6 statistically significant. I don't know if that's  
7 worthwhile noting, but it was in the published  
8 paper.

9 DR. FOUNTAIN: Dr. Zhao?

10 DR. ZHAO: Yes. I think you have done a  
11 very thorough study, looking at the gender effect  
12 for the second study. For the TEMPO study, did you  
13 look at a gender effect, or has anyone looked at  
14 gender effects in the first TEMPO study?

15 DR. FOUNTAIN: Was gender effect examined in  
16 the first TEMPO study, in the first study, TEMPO?

17 DR. ZHAO: Yes.

18 DR. MASSIE: For the week 52 analysis, I  
19 believe there was an effect in the opposite  
20 direction, although there was not a statistically  
21 significant difference in the week-52 effect  
22 between males and females. But the males had a

1 numerically bigger effect than the females in that  
2 study.

3 DR. ZHAO: This may be where my minor point  
4 is. For the 2-milligram dosage, for the TEMPO  
5 study, there are more females than males, that may  
6 account maybe for a little bit of difference  
7 between dosage and effect.

8 Also -- this maybe is going back too far.  
9 In terms of long-term follow-up, I'm still not  
10 really sure where is, really, a good place or time  
11 point to look at this issue of the modifying  
12 effects. So maybe we can talk about this more in  
13 the afternoon. Yes.

14 DR. FOUNTAIN: Okay. That'd be fine.

15 Ms. Christensen?

16 MS. CHRISTENSEN: I didn't conspire with  
17 Dr. Zhao, but my question actually follows up with  
18 that perfectly. I was wondering if the sponsor had  
19 thought about or would consider looking into  
20 estrogen or androgen receptors as a mechanism of  
21 action and having that be the reason that women  
22 have a more pronounced response than men, and if

1 the agency would require or ask that of the company  
2 in the future.

3 Also, were there any reproductive toxicity  
4 tests done? Because for a medication that is for  
5 patients, if we're going to consider that it's  
6 delaying the disease, younger patients, in  
7 particular, will want to take it. And a lot of  
8 women that I know, when they're diagnosed with  
9 Parkinson's -- I was diagnosed at 34 and had  
10 planned to try and have another baby. And the  
11 drugs were the reason I didn't, but there wasn't  
12 any information. But that's just maybe a little  
13 esoteric. But I think, with the growing young  
14 onset patients, that that would be something to  
15 look at.

16 DR. FOUNTAIN: So the question for the  
17 sponsor is, is, is there any anticipated follow-up  
18 on gender differences; and then, secondly, if they  
19 could have a brief comment on the genotoxicity or  
20 pregnancy effects.

21 DR. FITZER-ATTAS: Would you like us to  
22 respond to that?

1 DR. FOUNTAIN: Yes. If you could, yes.

2 DR. FITZER-ATTAS: Dr. McDermott?

3 DR. FOUNTAIN: So the question is, is there  
4 any anticipated follow-up on the gender  
5 differences?

6 DR. MCDERMOTT: So I'm Mike McDermott. I'm  
7 a statistician at the University of Rochester, and  
8 I'm not qualified to address all aspects of your  
9 question. The only thing I'll mention is that the  
10 effects seen in TEMPO, as was pointed out, were  
11 quite the opposite of what was seen in ADAGIO and  
12 were unanticipated.

13 On the surface, in ADAGIO, yes, effects  
14 might look interesting in men versus women, but  
15 there was no a priori, or that we can think of,  
16 post hoc reason, to believe that there would be  
17 systematic differences between gender and  
18 responses.

19 We've also not seen -- I should say the  
20 sponsor has not seen in other studies of rasagiline  
21 any differential effects by gender. So it's hard  
22 to explain those results. And I think it's at

1 least my view that this is likely due to chance,  
2 but it's interesting.

3 DR. FITZER-ATTAS: I'm sorry. To the direct  
4 question, we do not have anything planned at this  
5 time.

6 DR. FOUNTAIN: Okay. I'm sorry. The answer  
7 to the question, why there's no further planned  
8 analyses with regard to the gender differences,  
9 from the sponsor.

10 And moving to Dr. Fleming --

11 DR. FLEMING: Subgroup analyses are always  
12 hard to interpret. What was interesting, though,  
13 is that there are imbalances that are informative  
14 missingness that the FDA analysis is showing are  
15 predominantly in females, and that's what's driving  
16 the estimated effect. So that's partly the  
17 problematic issue.

18 Dr. Ahlskog and Dr. Katz, I just wanted to  
19 quickly comment on this issue. I concur. My  
20 understanding of what you're saying is, there's  
21 definite acceptance of the fact that there's  
22 symptom effects. And ADAGIO seems to confirm what

1 TEMPO shows, and they're symptom effects. The  
2 whole point here is, are there disease modification  
3 effects? And while it's not the only way to look  
4 at it, the point that I had asked the sponsor, was  
5 on this very slide, this slope is .4 more than that  
6 slope. So you were saying, in fact, it's not  
7 growing. It's parallel.

8 Well, it's actually a little worse than  
9 parallel. And, in fact, if that little bit worse  
10 than parallel persisted over here, it would wipe  
11 out the entire difference. So a .04 non-parallel  
12 is problematic.

13 The TEMPO analysis that was in place as the  
14 primary analysis, I'm not hearing anyone  
15 challenging, that the primary analysis of TEMPO is  
16 a symptom effect. A supported post hoc analysis  
17 is, does TEMPO tell us something about disease  
18 modification for which there is fuzziness, but some  
19 suggestiveness. And, of course, that's what we're  
20 about here is, is there a disease modification  
21 effect? And what the FDA was trying to do was  
22 re-analyze it according to the ADAGIO approach for

1 disease modification

2 That's my understanding. I didn't interpret  
3 they were trying to re-do what TEMPO analysis did,  
4 but in the context of now using TEMPO for a  
5 different purpose, which is, does it tell us about  
6 disease modification, analyzing it as ADAGIO was  
7 analyzed.

8 DR. FOUNTAIN: Dr. Katz, would you like to  
9 make a comment?

10 DR. KATZ: No. I think that Dr. Fleming  
11 made my points.

12 DR. FOUNTAIN: Dr. Clancy?

13 DR. CLANCY: So Dr. Massie's presentation  
14 started off with this dichotomy of 1 milligram  
15 seems to be protective and the other one doesn't.  
16 So which is true? Could they actually both really  
17 be protective or neither?

18 Then, in additional analyses, there was the  
19 use of the combined placebo group, but still  
20 keeping the identity of the 1-milligram versus the  
21 2-milligram subsets. It was that four-point  
22 analysis.

1           So just thinking that if they are both  
2           ineffective or are both effective, could there be a  
3           way of simply, truly combining -- with losing the  
4           identity, just did you get the early drug or did  
5           you get the late drug? Would that be something  
6           statistically valid or would that be an inaccurate  
7           way of approaching the problem?

8           DR. FOUNTAIN: The question is, if you  
9           combined the 1 milligram and 2 milligrams together,  
10          without regard to whether they got 1 or 2  
11          milligrams, would you increase the power to find a  
12          difference?

13          DR. CLANCY: Yes.

14          DR. FOUNTAIN: And was that the original  
15          analysis that was originally planned, before the  
16          hypotheses were changed?

17          DR. MASSIE: No.

18          DR. FOUNTAIN: Okay. So then that's the  
19          question.

20          DR. MASSIE: It was just the dataset --

21          DR. FOUNTAIN: Would there be value in that?

22          [No response.]

1 DR. FOUNTAIN: So the question is, would  
2 there be value in combining those groups, is I  
3 think Dr. Clancy's question.

4 DR. MASSIE: Well, there are assumptions you  
5 have to make when you do a combined dose analysis.  
6 That was done as, I think, a pre-plan sensitivity  
7 analysis. And I believe it didn't -- I think the  
8 p value was .1 or something for the combined, where  
9 you just compare early combined 1- and 2  
10 milligrams, and get your early group, combine  
11 1 milligram delayed and 2-milligram delayed to get  
12 your delayed group. Just compare those two.

13 DR. FOUNTAIN: Does the sponsor have  
14 anything else to add to that?

15 Do you have anything else to add to that?

16 DR. FITZER-ATTAS: Patrick?

17 DR. FOUNTAIN: The question is, was there an  
18 original analysis that combined the 1- and  
19 2-milligram groups, and was anything different  
20 found?

21 DR. DARKEN: I don't think I have anything  
22 to add to what Dr. Massie said. The result would

1 clearly be in between the two results we saw in the  
2 study.

3 DR. FOUNTAIN: Okay. Dr. Twyman?

4 DR. TWYMAN: Yes.

5 DR. FOUNTAIN: Sorry. Before you ask your  
6 question, I just wanted to make a comment that  
7 after this, we'll break for lunch in a few minutes.  
8 If there are other questions, please raise your  
9 hands now.

10 DR. TWYMAN: Yes. I'd like to follow up on  
11 my earlier question to the sponsor, because this  
12 has broad implications to the field. And what I  
13 was asking is, how did it come to be that the  
14 hypotheses were changed so late in the study,  
15 particularly relevant to a pivotal study, which was  
16 probably designed and agreed upon with the  
17 agencies, with regard to the hypothesis to be  
18 tested, and then changed. Not only one hypothesis  
19 was changed, another one was actually even added to  
20 make it now a triple-hypothesis approach.

21 So I just need to understand this, at least  
22 from the industry standpoint, is how does this come

1 about, and what are the implications of this as we  
2 move forward? And if this information that these  
3 hypotheses were important to be tested or the  
4 information was important to be known, why couldn't  
5 they be done as secondary analyses or secondary  
6 efficacy variables?

7 So if I can have the agency help me  
8 understand this.

9 DR. KATZ: Yes. I'll just give you from our  
10 point of view. I don't recall exactly, and I don't  
11 think we know exactly why things changed when the  
12 study was ongoing or that sort of thing. I think  
13 the final statistical analysis plan came in after  
14 the protocol. How long it took us to respond to  
15 it, I don't know. And we can get those dates, and  
16 perhaps the company even has those dates.

17 But I think the changing -- I agree with  
18 you, of course, that as a general matter, changing  
19 hypotheses, study design elements, that sort of  
20 thing after the study is well on its way is very  
21 problematic. I don't think, though, that in this  
22 particular case, it really affected very much.

1           For example, I think, if I remember the  
2 presentation of the company correctly, the phase 1,  
3 the Hypothesis 1 was added. But that didn't really  
4 change anything. I mean, that was clearly not an  
5 underpowering issue because both doses seem to have  
6 won in phase 1 or Hypothesis 1.

7           As far as, I think, sort of the main point  
8 about the analytic plan being changed had to do  
9 with the combined 48 to 72 week original proposal  
10 versus looking at the endpoint for Hypothesis 2,  
11 that being changed, apparently while the study was  
12 ongoing, that in our view didn't have any  
13 particular material effect on the outcome. It  
14 didn't seem to be -- it reduced the power, but the  
15 failure of the 2-milligram in Hypothesis 2 did not  
16 seem to be a power question. And as Tristan  
17 showed, if you actually look at the original  
18 analysis that the company proposed, that was  
19 ultimately changed, the 48-to-72-week analysis,  
20 that failed quite clearly at 2 milligrams.

21           So it's true, things might have changed  
22 during the course of the study, but I don't think

1 they had any material effect on any of the  
2 important outcomes.

3 DR. TWYMAN: Thank you, Dr. Katz. I'm just  
4 trying to understand. In this particular  
5 situation, it didn't really have any material  
6 impact because Hypothesis 1 was clearly not a  
7 problem. But for other programs -- and that's what  
8 I'm trying to understand, is what was the rationale  
9 that drove this change? Because, in fact, you've  
10 changed the hypothesis of the study late in the  
11 program. And this has broad implications to the  
12 field, for us, from an industry standpoint, because  
13 it could alter our decision making with regard to  
14 these types of studies.

15 DR. KATZ: I think -- if I can answer  
16 it -- this is a particularly, or has been, or was a  
17 particularly difficult issue to try and work out  
18 all the details, and we were continuing to look at  
19 what the best way to analyze such a trial would be.

20 That took a long time. We had a public  
21 meeting, as you heard. And I think the public  
22 meeting occurred after the protocol had been

1 submitted or well after the protocol had been  
2 submitted. Somebody can correct me if I'm wrong  
3 about the dates.

4 So this was an evolving process that  
5 pertained to this specific protocol design, because  
6 it was so new, because no one had ever done it  
7 before. No one had ever really worked out the  
8 specifics of what the analysis ought to look like.

9 So in this particular case, which I think is  
10 quite unusual, it took a long time for us, and the  
11 field I think, to come down on what the specific  
12 elements of the analysis ought to be. I think it  
13 was just an unusual circumstance.

14 DR. FOUNTAIN: Thank you.

15 Now, I'd like to ask a question or maybe  
16 make a comment.

17 Can you pull up slide 5? So I might just be  
18 restating what Dr. Fleming was stating, but not  
19 only do these not appear parallel, they look as  
20 though they're going to cross. And so you maybe  
21 entertain that notion that 2 milligrams makes you  
22 worse if you follow the logic forward. That's not

1 on a statistical basis, just on looking at the  
2 graph. And then going -- if we can have slide 4.  
3 Then again, here, eyeballing it, it looks as though  
4 the lines might even eventually approach each  
5 other.

6 So the nature of my brief question or  
7 unrelated question that either FDA or the sponsor  
8 could answer is that, if I understand right, the  
9 last observation carried forward was true for all  
10 patients who entered the treatment phase at week 48  
11 or after.

12 If that's true, which observation was  
13 carried forward, or is that not true?

14 DR. DARKEN: So the ADAGIO trial did not use  
15 last observation carried forward. That was from  
16 TEMPO.

17 DR. FOUNTAIN: They're just entirely ejected  
18 if they left at any time? They weren't counted at  
19 all if they left at any time in the initial phase?

20 DR. DARKEN: The data that was observed was  
21 included. So if we're looking at Hypothesis 1 that  
22 used all the data that was available in the

1 placebo-controlled phase before they left, but if  
2 they early-transferred, then the data after they  
3 early-transferred would then be potentially part of  
4 the ACTE if they early-transferred at 24 weeks or  
5 later. If it was before 24 weeks, Dr. Massie was  
6 correct; those patients were not included in the  
7 ACTE.

8 DR. FOUNTAIN: Okay. Thank you.

9 DR. DARKEN: Does that answer your question?

10 DR. FOUNTAIN: Yes. It does. Thank you for  
11 clarifying?

12 DR. FOUNTAIN: Let me ask Dr.  
13 Ellenberg -- okay.

14 DR. D'AGOSTINO: I was under the impression  
15 that they were using the repeated measure-type  
16 analysis for that. So you use as much information  
17 as the subject has, and you make some assumptions  
18 about missing at random, but you're not moving data  
19 forward.

20 DR. FOUNTAIN: The last question is for  
21 Dr. Ellenberg.

22 DR. ELLENBERG: So I don't work in

1 neurological diseases, so this may be a very naive  
2 question and easy to answer. But I noticed that in  
3 the ADAGIO data, in both the 1-milligram and  
4 2-milligram group, the slope reverses at 36 weeks.  
5 And there are two reasons that occur to me for  
6 that. One is that a lot of people have dropped  
7 out, and so maybe the people who weren't doing well  
8 dropped out, so the people who were left have a  
9 better score.

10 Another reason could be that it's a double-  
11 blind study. And so at week 36, if people would  
12 know that they were getting active treatment, there  
13 could be another possible bounce as a placebo  
14 response, which would mean that the early group  
15 would sort of get the benefit of two of those and  
16 not just the one that might be part of the  
17 reduction at the beginning.

18 So I wondered whether either the FDA or the  
19 sponsor had an explanation, and, in particular, for  
20 those who stayed in the study, to see whether there  
21 was any evidence of any kind of a sort of placebo  
22 response, that people who were starting to get

1 worse after week 24 somehow then got a little bit  
2 better after that.

3 I just noticed that was in both arms, and I  
4 would like somebody to -- I'm just curious as to  
5 what the explanation is.

6 DR. KATZ: Well, I guess we don't know for a  
7 fact, but we think it's the latter of the two that  
8 you described, which is that everybody knows that  
9 they're getting switched. So even people who are  
10 sort of getting worse, who have already seen drug,  
11 get a little bit of a bump, you know, was  
12 symptomatic, so called. But I hesitate to use the  
13 word "symptomatic" because we're here to try to  
14 figure out what's symptomatic and what -- but some  
15 early effect, knowing that this is happening.

16 DR. ELLENBERG: So it does make you wonder,  
17 in a real world situation, where that wasn't  
18 happening, what would happen to that line at  
19 week 36. Would it have gone -- sort of continued  
20 zooming up. We can't know, and there's reason we  
21 do double-blind studies. But in this case, it does  
22 seem that there's a possibility of a little extra

1 advantage. And I just wanted to see whether you  
2 agreed with that.

3 DR. FOUNTAIN: Thank you. We can continue  
4 with questions and further discussion after lunch  
5 break. And it'll be Dr. Rosenberg, D'Agostino,  
6 Zivin, Dr. Rodnitzky, and Dr. Ahlskog. So everyone  
7 will have an opportunity for discussion.

8 We'll now break for lunch and reconvene  
9 again in this room at 12:45. Please take any  
10 personal belongings you may want with you at this  
11 time. The room will be secured by FDA staff during  
12 the lunch break. You will not be allowed back into  
13 the room until we reconvene. And panel members,  
14 please remember that there should be no discussion  
15 of the meeting during lunch amongst ourselves or  
16 with any member of the audience.

17 (Whereupon, at 11:43 a.m., a luncheon recess  
18 was taken.)

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A F T E R N O O N   S E S S I O N

(12:45 p.m.)

**Open Public Hearing**

DR. FOUNTAIN: I'd like to resume the meeting, if everyone would like to take a seat.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationships that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

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

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

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

21           I believe we have eight speakers today.

22           Will speaker number one step up to the

1 podium? And please, introduce yourself.

2 MS. COMSTOCK RICK: Good afternoon. My name  
3 is Amy Comstock Rick, and I'm the chief executive  
4 officer of the Parkinson's Action Network. I'd  
5 like to thank the FDA for holding this advisory  
6 committee meeting today.

7 I am here, actually, on behalf of, in  
8 addition to the Parkinson's Action Network, the  
9 American Parkinson's Disease Association, and the  
10 National Parkinson's Foundation, the Parkinson's  
11 Disease Foundation, the Parkinson's Alliance, and  
12 the Michael J. Fox Foundation for Parkinson's  
13 research.

14 The Parkinson's community views the lack of  
15 anything, anything at all, that slows the  
16 progression of this degenerative disease as one of  
17 our most serious issues. It should go without  
18 saying that this is a major need in our community.  
19 As a community, we also respect and appreciate the  
20 significant effort that Teva is making in this area  
21 and are encouraged by the ongoing work that Teva is  
22 sponsoring, and we thank them for that.

1           Because of the importance and complexity of  
2 this issue, the organizations on whose behalf I am  
3 here today have chosen to not make individual oral  
4 statements on whether adequate evidence has been  
5 presented to show that the 1-milligram dose of  
6 Azilect slows clinical progression of Parkinson's  
7 disease and should be relabeled accordingly.

8           Rather, we have prepared one, joint, written  
9 statement that we ask you to read, and I suggest to  
10 all of you in the room, it is no small thing for  
11 six large national organizations to prepare one  
12 joint statement. But given the importance of this  
13 issue and this meeting, we chose to do that.

14           I understand that our written statement was  
15 not available for your pre-prepared packets, but I  
16 do believe it has been distributed to you this  
17 morning, and I have extra copies if anyone should  
18 need one.

19           I do acknowledge that it is actually  
20 somewhat awkward for me to stand up here and make  
21 an oral statement that simply asks you to read our  
22 written statement. But I ask that you appreciate

1 that we have chosen this route to be absolutely  
2 clear that we are speaking definitively and with  
3 one voice on behalf of all the organizations.

4 Thank you. And, again, I have extra copies  
5 if anyone would need one. Thank you.

6 DR. FOUNTAIN: Thank you.

7 If open public hearing speaker number 2 is  
8 here, please make yourself known and approach the  
9 podium if you'd still like to give your  
10 presentation.

11 [No response.]

12 DR. FOUNTAIN: If speaker number 2 appears  
13 later, we can entertain that as well.

14 Now, let's move onto speaker number 3.  
15 Could you step up to the podium?

16 MS. OBERDORF: Thank you. My name is Joyce  
17 Oberdorf. I'm president and CEO of the National  
18 Parkinson's Foundation. I'd like to thank this  
19 committee for holding today's session and also for  
20 taking public comments. Our statement is intended  
21 to further elucidate one central question posed in  
22 the joint statement signed by the six Parkinson's

1 organizations.

2 Starting in 2009, the National Parkinson's  
3 Foundation created a large database of detailed  
4 information about people with Parkinson's in our  
5 Quality Improvement Initiative, or QII, which is  
6 based on a model used in cystic fibrosis.

7 We would collect information about  
8 medications and therapies patients receive, in  
9 order to begin to measure what treatments produce  
10 the best outcome. We are following 4,259 patients  
11 and over 1200 have had at least one year's follow-  
12 up. QII is deployed at 17 of the top movement  
13 disorder centers in four countries. Recognizing  
14 that many clinical trials do not include the  
15 sickest patients, our goal is to create a real-  
16 world measurement of Parkinson's.

17 This database, a multi-center aggregate of  
18 patient demographics, therapies, and outcomes, is  
19 creating normative data to inform our understanding  
20 of PD. We track a spectrum of outcome variables,  
21 including motor function and mobility, mood and  
22 memory, activities of daily life, and plan to

1 follow as many as 10,000 patients throughout the  
2 course of their disease.

3           When we compare Parkinson's outcomes in  
4 1967, or pre-levodopa, to just one datapoint, which  
5 is the Hoehn and Yahr's stage, it confirms what  
6 other studies have shown; namely, over the last 45  
7 years, medication advances and best care may have  
8 improved the quality of life for the average PD  
9 patient, but only for a time. In fact, roughly  
10 seven years of quality of life is added.

11           In this cohort, levodopa is used by  
12 87 percent of the patients, and Azilect and other  
13 MAO-B inhibitors are used by 22 percent alone or in  
14 combination. The latter group of patients in this  
15 cohort consistently report better outcomes,  
16 compared to controls matched for age, disease  
17 duration, and severity, with significant p values.  
18 But looking overall at this chart, the need is  
19 clear for some intervention that would add many  
20 more years of functionality and slow clinical  
21 progression, especially for those with advanced  
22 disease.

1           Clinical progression remains the gold  
2 standard for measurement and every drug available  
3 today received approval based on clinical  
4 measurement. What we would benefit from and what  
5 we would ask the FDA to supply as part of its  
6 review in this hearing are definitive guidelines as  
7 to what constitutes an appropriate measurement of  
8 Parkinson's progression.

9           We believe clarity is needed in four  
10 essential areas. What time period is essential to  
11 measure? What stages of disease are important to  
12 consider? Parkinson's does not progress in a  
13 linear fashion, most likely. We know that  
14 Parkinson's is far more than a motor disease. So  
15 is progression only measured for motor or must  
16 other symptoms of the disease be addressed as well?  
17 And what do we do should they diverge? Finally,  
18 how should progression be measured when clinical  
19 and biological assessments diverge, as is likely  
20 the case in future trials?

21           Were we to have these questions answered, we  
22 and others could harmonize our approach to your

1 guidance. With this insight, we could generate  
2 much more significant information. Indeed, our QII  
3 database is designed to be a ready-made,  
4 comparative test bed for new treatments and  
5 therapies.

6 In summary, our hope is that your  
7 deliberations here will not only address the issue  
8 at hand, but will also address the issue of the  
9 relevance of clinical progression to your  
10 evaluation of Parkinson's disease therapies. This  
11 will provide our broad community with an  
12 understanding of the bar we must pass and also help  
13 industry to know that their efforts to change the  
14 course of Parkinson's will be recognized.  
15 Ultimately, the people who benefit are the  
16 1 million Americans with Parkinson's. Thank you.

17 DR. FOUNTAIN: Thank you.

18 Will speaker number 4 approach the podium?

19 DR. PAGAN: Hello. My name is Fernando  
20 Pagan. I'm a physician at Georgetown University  
21 Hospital. I do have disclosures. I have served as  
22 a consultant and received educational grants from

1 Teva Neuroscience.

2           The main reason -- actually, can I get the  
3 next slide, please? The main reason why I'm here is,  
4 I'm in the trenches, treating Parkinson's disease,  
5 treating our patients, and too often I see patients  
6 who are coming for care, who have been diagnosed with  
7 Parkinson's disease one, two, four, ten years,  
8 without receiving any medications whatsoever. And  
9 it's still poorly understood that what we do for  
10 clinical care to improve the quality of life for  
11 our Parkinson's patients does change their quality  
12 of life. It does change the disease, by being able  
13 to do so.

14           If you take a look at this particular slide  
15 here, prior to 1967, before levodopa was available,  
16 Parkinson's disease was considered a fatal  
17 disorder. In fact, when Parkinson's patients did  
18 not receive treatment, their life expectancy was  
19 well below what we see in that of the general  
20 population.

21           Now, we've had certain studies, but none  
22 have been so well-studied as far as rasagiline

1       today. But levodopa, for example, does help  
2       improve the quality of life. The UPDRS of  
3       disability continues to increase without treatment.  
4       At 150, 300, 600 milligrams, patients do a lot  
5       better in terms of the progression of the disease,  
6       but the side effects, especially with the  
7       600-milligram group, is much greater than that  
8       which you see with the 150 or 300. But this is the  
9       first signs of inclination that there is something  
10      being done by the medicines that we give our  
11      patients.

12                I think the TEMPO study, especially a long-  
13      term TEMPO study, when you take a look at the fact  
14      that patients who were delayed in their treatment,  
15      their disability was much greater over 5.5 years in  
16      its extension label, compared to the patients who  
17      received it from the early get-go.

18                We are changing the disease progression when  
19      we're giving this medicine, so slowing the  
20      progression of disease by starting treatments  
21      earlier, I don't disagree with the organizations  
22      that we need further studies, but I think we're

1       doing a harm to patients by not giving them  
2       medicines when we make the diagnosis. And  
3       symptomatic benefit is not always the main goal,  
4       but also where the disease is going.

5               I think you've spent a lot of time probably,  
6       today talking about the ADAGIO study, but I think  
7       here, you see the rate of progression of the  
8       disease in the first nine months, compared to what  
9       you see with the people who received their  
10      treatment from an early get-go.

11             So the reason why we need this indication  
12      for patients, I think is so our patients see that  
13      there is an alternative to the watch-and-wait  
14      approach. The watch-and-wait approach is one that  
15      will end up with progression of disease with a poor  
16      quality of life. And I think that's really what  
17      the take-home message of this. Can we be offering  
18      this treatment to our patients for quality of life,  
19      knowing that there's something going on? Further  
20      studies are definitely still necessary, but I  
21      think, with the ADAGIO and the TEMPO study, this is  
22      pretty darn good data that we've seen here,

1 compared to studies like the coenzyme Q10 studies,  
2 selegiline studies.

3 This has been very well-studied for the  
4 first time, so I do applaud Teva Neuroscience for  
5 the great work that they've done. I still think  
6 further studies are needed. But we do need to let  
7 other physicians and patients know that there is  
8 something else besides levodopa that we can offer  
9 to our patients, and something that will enhance  
10 their quality of life until we find something that  
11 ultimately stops progression of the disease.

12 Thank you for allowing me to speak. Thank  
13 you.

14 DR. FOUNTAIN: Thank you.

15 Would speaker number 5 approach the podium?

16 DR. ISACCSOON: Hi. I'm Stuart Isaccson.  
17 Thanks for giving me the opportunity to come and  
18 speak with you all today. I should disclose, I've  
19 received payments from pharmaceutical companies,  
20 including Teva, for research, consulting, and  
21 speaking activities.

22 I'd like to speak from three distinct

1 perspectives. One is treating, as a busy  
2 clinician, Parkinson's disease in New York City,  
3 and now, in this elderly demographic of south  
4 Florida for the past over 20 years; as the director  
5 of one of the busiest clinical research trial  
6 sites, including being a site for the ADAGIO and  
7 the ADAGIO extension trial, as well as being the  
8 medical director of the Parkinson's Research and  
9 Education Foundation, directing the education and  
10 wellness programs, and overseeing the Project  
11 Sunshine database of over 15,000 clinical visits  
12 and 5,000 patients.

13           Specifically, though, I'd like to discuss a  
14 little bit of the inherent value of the prescribing  
15 information label in treating the day-to-day  
16 patient and making treatment decisions. There's an  
17 increasing awareness of the utilization and the  
18 awareness and the reliance on the PI in how we make  
19 decisions, by patients, by doctors, and by  
20 pharmacists. This document has become an  
21 overwhelming presence in our day-to-day clinical  
22 decision making. As well, there are medical-legal

1 consequences, formulary encourage issues that may  
2 restrict access to medications, based on  
3 information that's excluded from the PI.

4 I'd like to give you a little bit of an idea  
5 of how we face patients on a daily basis. I don't  
6 know what causes Parkinson's and I tell my patients  
7 that as well. But patients want to know how bad is  
8 their Parkinson's when I see them, typically in the  
9 first six or twelve months of diagnosis. We know,  
10 from several early PD studies, that the average  
11 total UPDRS, which we use routinely at clinical  
12 visits, is approximately 20 to 25 points. And  
13 usually, this is made up of two-thirds motor and  
14 about a third of ADLs, which we think the ADL  
15 subscore has more to do with the clinical  
16 progression over time.

17 My patients want to know, how much worse  
18 will I get? We can extrapolate, from a number of  
19 placebo arms that tell us that in the 18 months  
20 after clinical diagnosis, patients may, if  
21 untreated, expect to worsen by 10 to 15 UPDRS  
22 points over that period.

1           Patients would like to know, is there  
2 anything they can do now? We'd love to have more  
3 research, but now is the essence of what we make in  
4 our clinical decision making at the clinic visit.  
5 We know, from recent trials, that at 18 months  
6 after clinical diagnosis, patients who begin  
7 Azilect, 1 milligram, for symptom improvement, what  
8 might be considered on label right now, may expect  
9 to be 2 and a half to 3 points worse, whereas  
10 patients who don't get treated, or in this  
11 instance, take placebo, might expect to be 8 to 12  
12 points worse.

13           My patients want to know, then, should they  
14 begin taking the medicine now or should they wait  
15 until their symptoms increase? It really is the  
16 key question, the focus on the patient, not so much  
17 on all of these statistical analyses and  
18 discussions.

19           With the current label, if patients delay  
20 beginning Azilect until symptoms increase over nine  
21 months, patients can expect to be about 4 and a  
22 half points worse at 18 months after diagnosis of

1        Parkinson's.

2                With the label that's more inclusive of the  
3        newer trials, giving that information, the clinical  
4        decision to begin Azilect earlier, instead of  
5        waiting for symptoms to progress and increase,  
6        patients may expect to be a little under 3 points  
7        worse at 18 months after diagnosis. My patients  
8        want me to help advise them on what they should do  
9        with this information.

10               Whether this difference is truly clinically  
11        meaningful is really a decision that's inherent in  
12        each unique doctor-patient discussion. Physicians  
13        and patients, together, must consider all the  
14        information in the prescribing information label.  
15        All that information is what prescribing doctors  
16        ought to know and what patients ought to be  
17        apprised of.

18               We must consider the efficacy, the  
19        tolerability, and the potential drug interactions  
20        of the medications. Excluding very important  
21        information in the product label can only curtail  
22        this discussion. It can burden the clinical

1 decision making with off-label restrictions, and it  
2 truly reduces patients' autonomy to decide on a  
3 treatment with their physician and their access in  
4 getting that therapy.

5 We would love to have more answers. We just  
6 don't have them right now, yet we have to make that  
7 decision. Tomorrow morning, regardless of what the  
8 committee will decide in the months to come, these  
9 decisions have to be made with each patient.

10 I would love to be able to know whether  
11 earlier treatment is better than delayed treatment.  
12 I think it is. And I tell my patients that we have  
13 to make that decision based on their unique medical  
14 histories, how they respond to medicines, and each  
15 patient we decide on a progressive plan.

16 We have to make these decisions based on the  
17 information that we do have, not what we want to  
18 have. And for these reasons, I strongly urge the  
19 committee to consider revising the label and aiding  
20 us in doing our job. Thank you.

21 DR. FOUNTAIN: Thank you.

22 Would speaker number 6 approach the podium?

1 DR. LANGSTON: Yes. I'm Bill Langston. I'm  
2 the scientific director and CEO of the Parkinson's  
3 Institute. Our mission is to find the cause and  
4 cure for Parkinson's disease, to give  
5 compassionate, comprehensive care to our patients,  
6 and to find better treatments. We are a non-  
7 profit.

8 I have actually just taken the entire talk I  
9 had planned to give and I'm throwing it away, based  
10 on this morning's testimony and the things that  
11 I've heard. I'll just stop when I get out of time,  
12 so if anybody wants to hear more, you can find me  
13 later.

14 I've been in this business for 25 years. We  
15 did the first attempt to slow Parkinson's disease  
16 25 years ago, in the late '80s. In fact, it may  
17 have been the first study to actually try to slow  
18 any neurodegenerative disease. That was published  
19 in Science. That was followed by DATATOP.

20 As you probably all know, these studies were  
21 very interesting. They appeared to be positive.  
22 They were also very controversial. There's still

1 two divided camps I see in our community, those who  
2 believe and those who don't believe. The washout  
3 period in those studies was never really accepted,  
4 and, in retrospect, most of us feel like that was  
5 so confounded and so difficult, we wouldn't try  
6 that again.

7           However, Paul Leber, as you know, came along  
8 with the delayed-start design, which turned it on  
9 its head and had a wash-in. And we've heard all  
10 about that this morning. I thought that was a  
11 pretty neat design and got away from some of these  
12 issues of washout.

13           However -- and I've talked to many  
14 physicians, I mean, hundreds, literally,  
15 neurologists, too. Very few have been able to come  
16 up with a good scientific explanation of a drug  
17 that would make all three of those endpoints if it  
18 wasn't altering not only the disease progression,  
19 but possibly the fundamental mechanisms of the  
20 disease, although trials never prove mechanism.

21           However, listening this morning and seeing  
22 the way that study has been parsed out, not only

1 the positive parts of it but the negative parts, it  
2 made me realize that, I think, almost any trial  
3 design we come up with is going to be very easy to  
4 disassemble.

5 For instance, taking the 24 weeks to  
6 36-weeks' slope, which happens to be similar to the  
7 placebo group before wash-in, yes, that's there.  
8 Does that disprove the whole design? I don't think  
9 so, but to sit there and take those kinds of  
10 aspects of that trial to try to say this isn't a  
11 successful trial just makes me think, if we come up  
12 with new designs, the same thing is going to  
13 happen. And I'm speaking as a researcher from the  
14 field, not a pharmaceutical company.

15 If you look at the last slide that was shown  
16 before the break, number 4, before lunch, I mean,  
17 it really seems very clear that there's a bigger  
18 picture here, and there is a signal. And that is  
19 this drug delays disability. It certainly seems to  
20 delay clinical progression. And I would add to  
21 that, that this is an extraordinarily safe drug.  
22 In fact, I think it's the safest drug that we have

1 in the field of Parkinson's.

2 I know there are a number of clinicians on  
3 the committee. They may or may not disagree with  
4 me, but I see patients every day, after almost 30  
5 years. So we have before us a very safe drug that  
6 I think has at least a signal here. And I really  
7 did enjoy and appreciate and enjoy the detail of  
8 the scientific debates that we heard, but I really  
9 hope that the committee can keep an eye on the  
10 bigger picture. Is there a signal or not? It's a  
11 very safe drug.

12 Now, why would it be important to give this  
13 approval for at least delaying disability or  
14 clinical progression? We still don't know the  
15 mechanism for sure. And I think the reason for  
16 that is -- and I think Dr. Olanow said it earlier,  
17 is that many of these patients never get to us. If  
18 they do, it's often late. And I think that kind of  
19 labeling would really get it out into the general  
20 community of practitioners, primary care  
21 physicians. I think patients at least should be  
22 able to hear the case for this safe drug, which may

1 have an effect on disease progression, and I think  
2 you can make an argument it's a good drug to start  
3 very early.

4 Without that indication or labeling, I think  
5 it's going to remain within the domain of those who  
6 do research in this area, who counsel our patients.  
7 But beyond that, many patients are not even having  
8 the opportunity to hear the case. And at least I  
9 would plead for that.

10 I would echo Joyce's comments -- I think I  
11 have 19 seconds left -- we need a path forward. I  
12 mean, if this isn't it, what is it? Because I've  
13 given my whole career to try to find ways to slow  
14 this disease down. We need guidance if we're going  
15 to stay in this field, and I hope it's not 25 years  
16 before I get back here. I won't be here anyway, so  
17 thank you.

18 DR. FOUNTAIN: Thank you.

19 Would speaker number 7 step up to the  
20 podium?

21 MR. BAUMANN: Good afternoon. Do I have to  
22 push a button to make it move?

1 DR. FOUNTAIN: Please state your name and  
2 you can begin your statement.

3 MR. BAUMANN: John Baumann. My name is John  
4 Baumann. I'm former general counsel of a NASDAQ-  
5 listed company, and I've had Parkinson's for close  
6 to 10 years, and I want to give the patient's  
7 perspective to the hearing today.

8 I have to say there are some brilliant  
9 people on this panel, and speaking on behalf of the  
10 sponsor, and I'm impressed with the discussion. I  
11 left the practice of general counsel three years  
12 ago, based on the fact that I wanted to do  
13 something a little more purposeful with my life,  
14 because I recognized the fact that I have a limited  
15 time of quality of life.

16 The positive thing is I've been taking  
17 Azilect from the get-go. I had a doctor who was  
18 from Uruguay, and she was more global-thinking, and  
19 had more of a perspective on this, and gave me the  
20 opportunity to take it. And I think I'm doing  
21 pretty well for someone that's had Parkinson's for  
22 pretty much a decade.

1           I did no study on this, but one of the  
2 things that I think has come up with my  
3 Parkinson's, as kind of a byproduct, is I feel like  
4 I'm more perceptive. I can watch people and see  
5 how they're doing. And my impression of the  
6 committee is that you actually do care. You  
7 actually do care about this issue, and you're  
8 trying to do the right thing. And I appreciate  
9 that, and I think that's important to say.

10           What I also get the impression of is that  
11 many of you have made up your mind already. And  
12 hopefully, I'm wrong on that, and I hope that you  
13 keep an open mind as to what was just said.

14           What I heard from James over here was very  
15 telling, and I confirm everything that he said. I  
16 think that it's important that we move forward. I  
17 think that the phrase that comes to mind is better  
18 safe than sorry. Well, this takes on a new  
19 definition because we know it's safe. That battle  
20 has been fought. The water is under the bridge.  
21 We know it's safe. What we're trying to do is get  
22 it to as many people as possible. And it is

1       amazing how many Parkinson's patients that I meet  
2       that don't know about Azilect, and their doctors  
3       haven't talked to them about Azilect.

4               That's the whole basis of why I'm here  
5       today. I think that if you do this early  
6       intervention labeling, or whatever it's called, it  
7       will prompt a discussion between doctors. And I  
8       heard the discussion of a general practitioner who  
9       sometimes takes on the responsibility of handling  
10      Parkinson's patients. It will prompt a discussion.  
11      And they don't have to give it to the patient, or  
12      they don't have to jointly decide to give it to the  
13      patient, but at least they have the discussion and  
14      it isn't limited to the people who happen to be in  
15      the know and deciding.

16             I thank God, and I feel blessed every day  
17      that Dr. Irene Litvan put me on Azilect from the  
18      get-go. I think I'm doing a lot better since then.  
19      Now, I've only done a study of one, because I don't  
20      have the whole control group or anything like that.  
21      But I can tell you -- and if you look at me, I'm a  
22      little bit off right now. And this is off for me.

1 And Jacqueline will be able to speak to the group  
2 about what it means to be a patient.

3 Who I'm speaking on behalf of is not me,  
4 because I'm already taking it. Who I'm speaking on  
5 behalf of are the future Parkinson's patients, many  
6 of whom could be in this room. And you are aware  
7 of Azilect right now, so you're a step ahead of a  
8 lot of people. But when you look at that from a  
9 global or United States perspective, an awareness  
10 needs to be brought to this situation.

11 We can't rely upon the doctors and we can't  
12 rely upon the wonderful groups that spoke earlier.  
13 We need to give the opportunity to the patients  
14 themselves to be able to see it and the doctors be  
15 able to know about it early on. And the way to do  
16 that, I see, is the early intervention.

17 I guess that's all I have to say. Thank you  
18 for your time.

19 DR. FOUNTAIN: Thank you. We appreciate  
20 those comments.

21 We have a last-minute request. Will speaker  
22 number 8 please step up to the podium?

1 DR. BAHROO: My name is Laxman Bahroo. I am  
2 the assistant professor of neurology at Georgetown  
3 University. Thank you very much for squeezing me  
4 in. I actually don't have any slides, and as far  
5 as disclosures, I am a consultant for Teva  
6 Neuroscience.

7 Actually, what I'll be doing is I'm actually  
8 going to echo everyone's statements here, those who  
9 preceded me, basically, about the need for disease  
10 modification and the need for medication that can  
11 help patients with Parkinson's, not only in the  
12 short term, but also in the long term.

13 On a personal note, I believe all of you  
14 have my essay about my mother, who has Parkinson's  
15 disease, who I diagnosed about four and a half  
16 years ago. But I'm not here to talk about that.  
17 I'm actually here to talk about the trial and the  
18 results that it provides.

19 When a trial comes out -- and all of you are  
20 familiar with this -- we have a choice. We have a  
21 choice to accept the results, and believe it, and  
22 initiate it into our practice, or we have the

1 choice to say the results are bunk, and we don't  
2 believe in it, and we disagree with it for various  
3 reasons. Everybody has that choice. That's a  
4 choice that all clinicians take.

5 I will tell you this. We have had a  
6 delayed-start trial that shows benefit. We've  
7 talked about the models. We've talked about  
8 disagreeing with the models, and saying this may be  
9 an effect of the model, and the results are sort of  
10 skewed because of the model, the way it is  
11 designed.

12 I will tell you, we have two trials more,  
13 the PROUD PD trial, as well as the coenzyme Q10  
14 trial, both of which are designed in a similar  
15 vein, which have not shown any significant benefit.  
16 However, we have the long-term TEMPO data and we  
17 have the ADAGIO data, both of which show benefit in  
18 a similar trial design. By default, I have no  
19 choice but to agree with the results of the trial.  
20 I believe in the results of the trial. When the  
21 long-term TEMPO data came out, I believed in it.  
22 And the ADAGIO, to me, was a confirmatory issue,

1 which confirmed what I saw in the long-term TEMPO.

2 In that sense, I have a choice to believe or  
3 not believe. We all have that choice. I choose to  
4 believe in that. And I'll tell you the other  
5 reason I choose to believe in that, and I'll echo  
6 Dr. Langston's statement as well.

7 This morning, I diagnosed a 46-year-old  
8 female with Parkinson's disease. That was the  
9 confident, confirmatory diagnosis on her. Her  
10 prior neurologist told her, basically, she had  
11 Parkinson's and to try a medication to see if it  
12 worked. He told her two things. He said, this is  
13 a progressive disease, and there was nothing  
14 available to modify the course.

15 When she came to me, she came to me with a  
16 checklist of things. On the list was, should I  
17 take coenzyme Q10? Should I take any medications?  
18 Why should I start treating myself early, and what  
19 benefit would it give me if the disease is  
20 progressive?

21 While acknowledging that the disease is  
22 progressive, I told her that early treatment makes

1 a difference, and I cited -- without going through  
2 all the details that she may not necessarily  
3 understand, I went through the details of the long-  
4 term TEMPO trial and the ADAGIO trial, showing that  
5 early treatment does give her a benefit, and early  
6 treatment will improve her quality of life. And  
7 that is what the goal was.

8 The goal was not only to treat her  
9 Parkinson's today, in these few six months, eight  
10 months, or a year that she'll live in this area for  
11 before she migrates somewhere else, it'll be to  
12 treat her Parkinson's not only when she's 46, 47,  
13 but to treat her when she's 65, 70, 75. I told her  
14 any chance at disease modification is a chance you  
15 should get. Thank you very much.

16 **Committee Discussion**

17 DR. FOUNTAIN: Thank you. The open public  
18 hearing portion of this meeting has now concluded.  
19 We will no longer take comments from the audience.  
20 The committee will now turn its attention to  
21 address the task at hand, the careful consideration  
22 of the data before the committee, as well as the

1 public comments.

2 We will now have the charge to the committee  
3 by Dr. Katz.

4 DR. KATZ: First of all, were there  
5 questions left over from -- I just want to make  
6 sure we get everybody's questions in.

7 DR. FOUNTAIN: We can finish up with  
8 questions first, if you like.

9 DR. KATZ: I can just tell you what we want.  
10 I actually don't have the question list in front of  
11 me. Oh, I do now. I think the questions -- I hope  
12 the questions are self-explanatory.

13 The first question, when we get to the  
14 discussion period after the questions have been  
15 answered, isn't the voting question. It's really  
16 to get your thoughts on the design, the propriety  
17 of the design, do we think that the design is  
18 capable of doing what we think it's capable of  
19 doing; in other words, detecting a disease-  
20 modifying effect. And then the other questions  
21 talk about the specific issues I think that we  
22 raised, that we had concerns about.

1           I have been asked to talk a little bit about  
2 the standard for approval. We often go through  
3 this at advisory committee meetings, and some,  
4 maybe many of you, are familiar with the rules, but  
5 maybe I can just give a brief explanation of what  
6 we think is required in order to approve a drug.  
7 And I'm talking entirely here about effectiveness,  
8 demonstrating effectiveness for a particular  
9 proposed indication.

10           The law requires something called  
11 "substantial evidence of effectiveness." And  
12 originally, it was defined as, and still is defined  
13 as, evidence from adequate and well-controlled  
14 clinical investigations. And for many years, that  
15 was taken to mean independent corroboration or  
16 replication of effects. So in other words, one  
17 study wasn't enough.

18           A number of years ago, the law was amended  
19 to include, explicitly, the standard that a single  
20 study plus something called confirmatory evidence  
21 would be sufficient to establish substantial  
22 evidence of effectiveness. The law didn't say when

1 that standard would apply.

2 We have typically applied that  
3 standard -- first of all, typically, we don't apply  
4 that standard. In the ordinary case, we apply the  
5 two-study standard. But in those cases in which  
6 the single study plus confirmatory evidence  
7 standard is applied, it's typically applied in the  
8 case of serious or life-threatening illnesses, in  
9 which category Parkinson's disease falls, in our  
10 view. And in order for that standard to apply, the  
11 drug has to have an effect on some important  
12 clinical finding or even mortality.

13 The question then becomes what amount of  
14 evidence, if you will, in a one-study approval  
15 would be found acceptable? And as a general  
16 matter, we tell people that if a single study is  
17 what we would call robust, and it has appropriate  
18 outcome measures, and it's the appropriate  
19 condition that would qualify for one study plus  
20 confirmatory evidence approval, that that might be  
21 sufficient. And I think that's what we pretty much  
22 told Teva in this case.

1           We looked briefly, as you heard, at the  
2 second phase results of TEMPO and said, well, this  
3 looks encouraging. Go ahead and do a second study.  
4 Design that so it can be adequately interpreted,  
5 adequately analyzed. And we said if the findings  
6 in that study are robust, that might be a  
7 sufficient package that would constitute  
8 substantial evidence of effectiveness.

9           But, of course, it's hard to know in advance  
10 what robust means. And, generally speaking, we  
11 say, well, that means a very low p value. It means  
12 that all sorts of subgroups go in the same  
13 direction. Everything is consistent with the  
14 primary outcome; in effect, as a seat-of-the-pants  
15 sort of test, we say a study that is so robustly  
16 positive, so unassailable in its results that it  
17 really can't be repeated, that people would feel  
18 that the outcome is so important and the result so  
19 definitive, even in that single study, that it  
20 can't really ethically be done again.

21           So that's, as a general sense, what we mean  
22 by substantial evidence, as applied to this single

1 study plus confirmatory evidence. Now,  
2 confirmatory evidence could come from another study  
3 that wasn't quite positive or was positive but not  
4 as positive. It could come from some other sorts  
5 of data, biomarker data. It could come even from  
6 the primary study itself, if multiple centers were  
7 all independently statistically significantly  
8 positive, in other words, if there really was sort  
9 of a sense of internal replication.

10 So I think it's important for you to  
11 understand what we think substantial evidence  
12 means, in both cases, whether in a standard  
13 two-study approval or in the more non-traditional  
14 single study plus confirmatory evidence approval.

15 The other thing I would just add is, as  
16 everyone has been saying, disease progression or an  
17 effect on disease progression is something that is  
18 tremendously important, both obviously from a  
19 clinical point of view and from the point of view  
20 of the benefit that would afford or accord to  
21 patients, but from a regulatory point of view, we  
22 think as well.

1           In other words, if you tell people in  
2 labeling that a drug has an effect on disease  
3 progression, you really want to be sure that it has  
4 an effect on disease progression. If we did that  
5 or if a drug was found to have an effect on disease  
6 progression, it would change dramatically not only  
7 clinical practice, I assume, but controlled trials  
8 in the future. You could argue everybody would  
9 have to be on such a treatment, because to deny  
10 patients a drug that actually changes the course of  
11 the disease might be highly problematic.

12           So it would be great to have a treatment  
13 that has an effect on disease progression. We  
14 think we need to be quite sure that a drug has such  
15 an effect before we would claim for such an effect  
16 in labeling.

17           The final point I would make is that the  
18 sponsor has specifically worded their proposed  
19 indication to say, clinical disease progression, in  
20 other words, clinical progression. From our point  
21 of view, there's little to no difference between a  
22 claim for clinical progression and a claim for

1 disease modification. We take those things to be  
2 the same thing. I think, once you say to people,  
3 in labeling, "progression," no matter what word you  
4 append before it, there's a strong implication that  
5 it means that the drug has an effect on the  
6 progression of the underlying disease.

7 I take the company's point that to get at  
8 this question, all we can measure is clinical  
9 outcome, as was done here. But, in our view,  
10 concluding that a drug has an effect on something  
11 called clinical progression is, for all intents and  
12 purposes, the same as saying it modifies the  
13 underlying progression of the disease. At least,  
14 that's our understanding.

15 So as an introduction, I think I'll stop  
16 there.

17 DR. FOUNTAIN: So obviously, immediately  
18 after lunch is when I should have asked for further  
19 questions. Thank you for clarifying that,  
20 Dr. Katz.

21 So now, as I had promised before lunch, we  
22 can go around and ask follow-up questions either of

1 the FDA or of the sponsor. We have a list of  
2 people, to see if you're still interested. So I  
3 think we're starting with Dr. Rosenberg.

4 DR. ROSENBERG: I can wait for the general  
5 discussion.

6 DR. FOUNTAIN: How about Dr. Zivin?

7 DR. ZIVIN: I'd like to ask the FDA. The  
8 question is, in this trial, in the ADAGIO trial,  
9 they found that the 2-milligram dose was  
10 ineffective and the 1-milligram dose was effective.

11 Your claim is, that is a questionable  
12 finding because the doses of drugs that are  
13 ineffective are usually log units different than  
14 the dose of the drug that actually is effective.  
15 And, therefore, the finding at the top of the curve  
16 is likely to require a much broader difference  
17 between doses than what was seen in this trial.

18 In my experience, there have been  
19 drugs -- and I can name them for you, although  
20 there's no point in doing it here -- that do  
21 decrease ineffectiveness with a doubling of the  
22 dose, rather than many log units' difference. And

1 I'd like to know if you still stand by your  
2 statement that it requires that much difference in  
3 order to find a dose that's not corroborative.

4 DR. KATZ: Look, I don't think we know what  
5 sort of difference you'd expect, what sort of  
6 difference in dose you'd expect to result in a  
7 difference in effectiveness. In our experience, I  
8 think it's a little unusual for doses that are very  
9 close to each other to have significantly different  
10 effects, particularly when the higher dose is the  
11 one that seems not to be working or at least not to  
12 be having the disease-modifying effect that we  
13 expected.

14 So I think that is fairly unusual. It  
15 certainly was an unexpected result; even though the  
16 statistical plan allowed for the possibility that  
17 that could occur, from a biological point of view,  
18 it seemed quite unusual.

19 So that was one of the things that concerned  
20 us about the results. The other things that  
21 concern us are that the 1-milligram dose, although  
22 on face looks like it met all the protocol-

1 specified requirements for all three hypotheses,  
2 actually, based on the analyses we did, is not  
3 quite that clear, that that is very obviously a  
4 positive dose, based on the potential baseline  
5 differences that we saw due to comparing non-  
6 randomized groups in the second phase, compared to  
7 looking at change from baseline for the ACTE  
8 analysis, compared to the primary analysis, which  
9 actually didn't meet the protocol-specified  
10 requirement for effectiveness for the 1 milligram,  
11 and then the post hoc nature of the analysis that  
12 the company did, which barely made it at .025, but  
13 in fact the interactions that caused the company to  
14 sort of jettison the primary analysis still existed  
15 in the analysis that they actually did.

16 So that suggests that we don't really the  
17 best way to correct for those baseline differences,  
18 but just ignoring the primary protocol-specified  
19 analysis might not be the way to go.

20 So we actually think that there are  
21 inconsistencies in the 1-milligram finding as well.  
22 But, again, we have to admit that the protocol

1 permits either dose to have been effective. So we  
2 do think that the 2-milligram, not being effective  
3 from a biological point of view, does raise  
4 questions about the 1 milligram, but there are also  
5 independent reasons why we think the 1-milligram  
6 finding is questionable at best.

7 DR. FOUNTAIN: Thank you.

8 Dr. D'Agostino?

9 DR. D'AGOSTINO: Just picking up on this, I  
10 mean, it seems to me -- correct me if I'm  
11 wrong -- that the root of the problem that you're  
12 facing is that there was this interaction test.  
13 Well, a couple of pieces. There was the  
14 interaction test, and it led you to do something  
15 that wasn't pre-specified in the protocol.

16 But my comment is, and I'd like you to  
17 comment on it, a response, if they didn't do the  
18 interaction test and you did it, wouldn't you be  
19 upset and found that -- so why are they being  
20 faulted? I realize it's not in the protocol, but  
21 in terms of what should they have done if it's  
22 there?

1           Let me go onto another issue, is that the  
2 imbalance that's generated -- I mean, I'm not an  
3 expert in Parkinson's disease and so forth, but  
4 you're talking about, in some of the analysis,  
5 missing 20 percent of the subjects with the long  
6 follow-up and a lot of sensitivity analyses. And  
7 we'll talk about it, but I'm struck that the FDA is  
8 not more impressed by the fact that they did the  
9 interaction test, and tried to react to it, and  
10 then did a sensitivity analysis, trying to take  
11 into account the dropout, that the FDA is not more  
12 impressed by it, as opposed to sort of picking at  
13 it with the details. And I'd love some comment  
14 from you or from anybody else in the FDA.

15           DR. FOUNTAIN: Dr. Katz?

16           DR. KATZ: Let me just respond to the first  
17 thing about the interactions. I don't know. And,  
18 again, we have a lot of statisticians here, and  
19 they're infinitely more qualified, you being one of  
20 them, to answer that question.

21           But the point is that, as I understand it or  
22 as we understand it, they did the protocol-

1 specified primary analysis. There were  
2 interactions, so they moved to a different  
3 analysis, the sort of individual dose analysis.  
4 But based on our look, that individual dose  
5 analysis suffered from the same interactions. So  
6 it's not clear that that's the fix to the problem,  
7 yet that was presented as the fix to the problem.  
8 So from the interaction point of view, I think  
9 that's sort of the lesion that we are concerned  
10 about.

11 As far as the sensitivity analyses, maybe  
12 somebody else wants to address them.

13 DR. FOUNTAIN: Dr. Massie?

14 DR. MASSIE: Yes. I think most of the  
15 sensitivity analyses were directed to the ACTE  
16 population, and that's the population where we saw  
17 a baseline imbalance. So they can correct me if  
18 I'm wrong.

19 DR. FOUNTAIN: Do you want to respond to  
20 that?

21 DR. D'AGOSTINO: Could the sponsor respond  
22 to the two questions? I think they're very

1 important, what Russ is saying.

2 DR. FOUNTAIN: Could I ask you to restate  
3 the question succinctly?

4 DR. D'AGOSTINO: Well, do the interactions  
5 still hang in there? I'm understanding that we  
6 went from the protocol-specified analysis to the  
7 separate doses because there was an interaction,  
8 and that that was, somehow or other, being  
9 addressed by going to the separate doses; was it  
10 not?

11 Then the other, in terms of the sensitivity  
12 analyses, are they addressing -- which, again, is  
13 very important points that Tristan's raising; are  
14 they addressing those issues with their sensitivity  
15 analyses?

16 DR. FOUNTAIN: Okay. So if the sponsor will  
17 answer that.

18 DR. FITZER-ATTAS: Thank you. Yes.

19 So I'd like to start with the second  
20 question, if that's okay, with the sensitivity  
21 analyses, addressing the difference in the baseline  
22 characteristics in the ACTE cohort, which is, of

1 course, inherent in the design. And I would like  
2 to ask Dr. McDermott to respond to that question.

3 DR. MCDERMOTT: Sure. I'd like to have  
4 AM-16 slide up, please. We performed many  
5 sensitivity analyses dealing with missing data in  
6 different ways.

7 There were two basic strategies that we  
8 used, or actually, three. The first is to perform  
9 analyses using the ITT cohort; second, using the  
10 ACTE cohort; and third, using, actually, both  
11 cohorts. We did an analysis that was sort of a  
12 worst-case imputation type of thing.

13 So could I have the slide up, please? The  
14 analyses we performed on the ACTE dataset, we  
15 recognize that this dataset is made up of a subset  
16 of the randomized population, hence is subject to  
17 potential biases or potential imbalance in  
18 covariates.

19 So what we did mainly to try to deal with  
20 that problem, is -- I should say the sponsor - is  
21 to use propensity score adjustment. So this is a  
22 commonly used technique, and particularly in

1 observational studies, to try to correct the  
2 imbalances in such a way that you mimic  
3 randomization. A propensity score is, essentially,  
4 formed through a logistic regression model that  
5 uses a lot of covariate information to predict  
6 treatment assignment for the people who are  
7 actually in the study.

8           So it tries to capture all the confounding  
9 that may occur, according to the things that you've  
10 observed in the data. So it's a way to try to  
11 adjust for many of the things that you could  
12 possibly adjust for in an analysis, and it does it  
13 in a way such that you try to capture the effects  
14 of a lot of different variables at baseline that  
15 could cause imbalances and to one score, so it's  
16 sort of a dimension reduction, which helps.

17           We did the analysis in two different ways,  
18 stratifying by the propensity score, using it as a  
19 continuous variable, and got very similar results.  
20 And I think the p values were something like .01 on  
21 both of them. And the magnitudes of the treatment  
22 effects were very similar to what they found in the

1 primary analysis. So we thought that that was a  
2 reasonable way to try to approach that problem for  
3 the ACTE dataset.

4           If you could, go to the next slide, please,  
5 AM-17. We also did some analyses using the  
6 intention-to-treat cohort, and this deals with it  
7 in a little bit of a different way. Because it's  
8 intention to treat -- or I should say modified  
9 intention to treat for some of this because the  
10 people who didn't have observations at week 12 were  
11 omitted from this analysis, but that's relatively  
12 small, a dozen people.

13           So for all intents and purposes, intention  
14 to treat, this is to preserve the benefits of  
15 randomization, since you're not tossing anybody,  
16 essentially, out of the analysis. But you do have  
17 people in this analysis who never make it to  
18 period 2, so you're relying on a model, the  
19 assumption of missing at random that people refer  
20 to, to get a sense of what would have happened to  
21 those people had they stayed in the study.

22           Nevertheless, with this kind of an analysis,

1 again, we got very similar results. And I think  
2 that those were two reasonable ways to try to  
3 address the missing data problem, and we got very  
4 similar results with them.

5 We also did this worst-case analysis, as  
6 I've mentioned here. All missing values of a  
7 particular visit were replaced by the mean value in  
8 the delayed-start group. So that would bias, if  
9 anything, against trying to find an effect at  
10 week 72. And as you might expect, for  
11 Hypothesis 2, the magnitude of that effect was  
12 reduced a bit. It was from 1.4 or 1.7 down to  
13 about 1.1, but still in the same direction, not  
14 affected too much, but still not statistically  
15 significant at that point.

16 I think that part of the reason all these  
17 analyses are giving very similar results is that  
18 there was pretty good retention in this study. It  
19 was an 18-month study in early Parkinson's disease,  
20 and people are going to need dopaminergic therapy  
21 eventually.

22 So given all of that, I thought that the

1 study, the high quality of the study, and the  
2 retention issue, really helped to make the overall  
3 analyses relatively insensitive to different ways  
4 of dealing with missing data, which, in my opinion  
5 were fairly reasonable.

6 DR. FITZER-ATTAS: Thank you, Dr. McDermott.

7 So the first question was regarding the  
8 interaction within the 1-milligram dose component  
9 of the study, if I clearly stated that. So  
10 Dr. Feigin, thank you.

11 DR. FEIGIN: Thank you very much. There is  
12 a qualitative difference between a dose-level  
13 interaction and the treatment interaction.  
14 Including the dose-level interactions does not  
15 change the way you elicit the treatment effects.  
16 The original model wanted to work out the treatment  
17 effects, averaged over the possible interactions.

18 Nevertheless, if you put in the treatment by  
19 baseline UPDRS interaction in a separate data  
20 analysis -- and that's really what the question the  
21 FDA I think is referring to -- it can be considered  
22 a sensitivity analysis; do you still get the same

1 qualitative result or quantitative result?

2           If I could I have slide SC-12? You'll see  
3 that if you introduce in the separate dataset  
4 analysis, and you take that one step further, and  
5 you introduce the interaction for baseline UPDRS  
6 and for center, then you get an effect of  
7 minus 1.51 in the same ballpark. The p value is  
8 larger. That's true. And if you look at adjusting  
9 for interaction with the baseline UPDRS -- and  
10 that's probably the most important interaction to  
11 enter because there are so many centers, that  
12 introducing a center-by-treatment interaction isn't  
13 terribly informative. The treatment effect at  
14 72 weeks is minus 1.63, a p value of .0305. We're  
15 talking about a consistent set of results, all in  
16 the same ballpark, showing that this effect is  
17 consistent. Thank you.

18           DR. FITZER-ATTAS: Thank you.

19           DR. FOUNTAIN: Thank you.

20           Next is a question from Dr. Ahlskog.

21           DR. AHLKOG: Well, this goes way back to  
22 this morning. Dr. Fitzer-Attas, I direct this to

1       you, and I want to make certain that I  
2       appropriately understand the rationale and the  
3       plausibility that was used to focus on the top  
4       quartile in the ADAGIO study.

5               As I understand, and you so clearly said,  
6       that it had to do with concern about a floor  
7       effect. And so I wanted just a little bit more  
8       elaboration about what the thoughts were about a  
9       floor effect.

10              Was the concern that the overall group,  
11       because of the UPDRS of 20, was going to progress  
12       so slowly that you couldn't detect a difference?  
13       Was that the concept of floor effect concern?

14              DR. FITZER-ATTAS: I will address the  
15       questions. If I may, the hypothesis was driven by  
16       Dr. Olanow for that analysis, so I would like to  
17       ask him to respond to that.

18              DR. AHLKOG: Dr. Olanow?

19              DR. OLANOW: Thank you very much. First of  
20       all, there should be no doubt, this was post hoc  
21       assessment. But I also want you to understand it  
22       was not based on dredging the data. It was based

1 on a hypothesis. We were sitting around. We were  
2 trying to think of how it might be that we missed  
3 on the 2-milligram dose. And the idea came to me  
4 when I looked at the TEMPO and ADAGIO data, that we  
5 were dealing with a very mild group of patients.

6 I don't think there's any question but that  
7 there is a floor effect in Parkinson's disease, and  
8 I wondered if the 2-milligram dose had a greater  
9 symptomatic effect that might have driven the two  
10 groups down to the same floor, and therefore  
11 prevented being able to see a difference between  
12 them.

13 I therefore thought, if that's the problem,  
14 perhaps, if we looked at patients with higher  
15 baseline UPDRS scores, where they had more room to  
16 see a difference between the two groups, if it was  
17 there, then we might be able to see it.

18 So, arbitrarily, I suggested that we do the  
19 top 25 percent. There was nothing magic about it.  
20 It just seemed that was a reasonable number. We  
21 ran the analysis looking at the upper quartile,  
22 and, in fact, the upper quartile, even with such a

1 small subset, still met all three of the primary  
2 endpoints.

3 Now, subsequent to that time, we've done  
4 other analyses, which in my mind support the  
5 possibility that this might be the explanation for  
6 the 2-milligram dose.

7 Firstly, we showed that -- there are a  
8 couple ways one could have gotten around it, by the  
9 way. One was is to take patients with higher  
10 baselines. The other is to follow them longer  
11 until they deteriorate enough, but that's not  
12 practical in a setting where we're already taking  
13 grief for the amount of dropouts we already had in  
14 this study, and you know you're starting to drop  
15 out very quickly at that stage.

16 So to try and support the idea that this was  
17 a factor, first, we showed that the placebo group  
18 deterioration for the entire population was much  
19 less in the ADAGIO study than had ever been  
20 appreciated before. Bear in mind, this is the  
21 earliest group, to my knowledge, that's ever been  
22 studied. So we were seeing a deterioration that

1 was at about half the rate you normally see in  
2 studies like DATATOP and other, L-dopa, studies of  
3 that sort. So we were not getting a separation.  
4 That was one thing.

5 The second thing we noticed was that when we  
6 looked at the change between final visit and  
7 baseline, at the end of the first period -- so  
8 you're looking at placebo versus active  
9 treatment -- for both drugs, the difference was  
10 about 3 points. But if we now looked at the upper  
11 quartile, where you now have a higher score with  
12 the same drugs, you now see a difference of, in the  
13 case of the 1-milligram dose, about 6 points, and  
14 in the case of the 2-milligram, I think it was 7.1  
15 or 7.2. So you're seeing a much greater effect  
16 where you have more room to be able to see the  
17 effect of the drug.

18 So if you can imagine, let's say even in the  
19 1-milligram dose, you have an early- and delayed-  
20 start, there's a little bit of difference. Imagine  
21 putting them on levodopa. You'd wipe that out.  
22 You wouldn't be able to see that effect. So the

1       problem is, how do you design a study where your  
2       patients deteriorate enough, and yet they're severe  
3       enough that you can still see a difference between  
4       early and delayed start?

5               I think we were fortunate that in the  
6       1-milligram group, we were able to see that. I  
7       think, in the 2-milligram group, we didn't,  
8       possibly because of the factors I mentioned,  
9       including the great symptomatic effect of the  
10      2-milligram dose.

11             I should add one other point, that I think  
12      the analysis of the lower quartiles doesn't mean  
13      anything if you're talking about a floor effect,  
14      because if you look, they're all kind of grouped  
15      together after that. And if, in fact, I'm correct  
16      and it's being pushed down to the floor, then you  
17      wouldn't expect to be able to see much of a  
18      difference. It would be random; it would be noise  
19      in those groups. But the one group that would  
20      really matter would be the higher quartile, and  
21      that's the one where we saw the effect.

22             DR. AHLKOG: Thank you. I want to put it

1       into the context of the TEMPO study. And I saw  
2       data today I hadn't seen before. And, actually,  
3       the TEMPO group, even though the UPDRS mean score  
4       was 25, as compared to 20 in the ADAGIO  
5       study -- and you could argue is that really a  
6       meaningful difference in terms of severity? But  
7       you showed data today that illustrates that, in the  
8       TEMPO group, the duration of PD at entry into the  
9       study was 12.1 years.

10               DR. FITZER-ATTAS: 12.1 months.

11               DR. AHLKOG: Well, 12 years. We'll round  
12       it out to 12 years.

13               COMMITTEE MEMBER: The slide said years.

14               DR. FITZER-ATTAS: Oh, excuse us.

15               DR. AHLKOG: Oh, 12 months. Okay. Then I  
16       stand corrected. I read that literally, and I  
17       missed that. That's actually what I wanted to get  
18       at was, now, obviously, if it's 12 years, I want to  
19       know where you find those patients.

20               [Laughter.]

21               DR. FITZER-ATTAS: Apologies.

22               DR. AHLKOG: Yes. And it's quite

1 different. Thank you very much.

2 DR. FOUNTAIN: Thank you. We have just a  
3 few more questions we'll have from Dr. Rodnitzky,  
4 Ms. Christensen, and then Dr. Ellenberg.

5 So Dr. Rodnitzky?

6 DR. RODNITZKY: My question is also a little  
7 bit of a throwback to this morning's discussion. I  
8 think it's a question for Dr. Massie.

9 So Dr. Massie showed that there's a major  
10 gender effect, both in the ADAGIO and the TEMPO  
11 studies, although, albeit, different in the two  
12 studies that benefit favoring women in the  
13 1-milligram ADAGIO study and a benefit favoring men  
14 in the TEMPO study, if I'm correct.

15 So given that difference, if you then look  
16 at the quartile analysis that Dr. Olanow was just  
17 speaking to, with the benefit in the top quartile,  
18 and, yet, the other three quartiles did not seem to  
19 fall into line, notwithstanding Dr. Olanow's  
20 discussion just a moment ago -- but the other three  
21 quartiles below that don't necessarily follow the  
22 line. It raises the question, is it really the

1 severity in that fourth quartile that accounts for  
2 the benefit that's seen in the 2-milligram ITT  
3 group? Could there be other factors?

4 My question is, has the gender been analyzed  
5 in those four quartiles? Could there be, for  
6 instance, a disproportionate group of one gender or  
7 another -- I can't say which one, because either  
8 could be the case -- in that fourth quartile that  
9 could account for the benefits seen in the upper  
10 quartile of the 2-milligram group?

11 DR. FOUNTAIN: Dr. Massie?

12 DR. MASSIE: We didn't do a thorough  
13 analysis of all the quartiles by gender, but I do  
14 believe there were more females in the upper  
15 quartile in the early group. There was a slight  
16 imbalance. It wasn't statistically significant,  
17 but there were definitely more females in the upper  
18 quartile in the early group.

19 DR. RODNITZKY: Do you think there's any  
20 chance that could have accounted for the benefits  
21 seen in that group?

22 DR. MASSIE: You can't rule that out, I

1 would say.

2 DR. FOUNTAIN: Thank you.

3 Ms. Christensen?

4 MS. CHRISTENSEN: Now, for something  
5 completely different, I am just looking at the New  
6 England Journal article that we got in our packets,  
7 and it lists falls as being 5.9 and 6.2,  
8 respectively, on the delayed start and 4.8 and 5.5,  
9 respectively, on the early start.

10 I'm wondering -- well, I guess this is more  
11 of a comment. I know, personally, friends taking  
12 Azilect who have fallen and have said that they  
13 didn't fall before they took it. Is it the disease  
14 progression? Is it the medication? But it worries  
15 me if we're going to start giving it to a lot more  
16 people, even though it shows in here as a  
17 relatively small percentage, I'm reminded of the  
18 dopamine agonists situation, where at first, it  
19 was, we'd never heard of any impulse control  
20 issues, to, well, maybe it's 10 percent, and now,  
21 it's on the label. And I've personally experienced  
22 issues with that.

1           So I'm just wondering if the company wants  
2 to -- or the sponsor wants to address that issue.  
3 And they didn't -- that falls information was not  
4 presented this morning, and I just wanted to  
5 highlight that as something that I feel is not a  
6 safe condition.

7           DR. FOUNTAIN: Thank you.

8           So the question is to the sponsor, do you  
9 have fall analysis data with regard to safety data  
10 for Azilect, particularly in regard to these  
11 studies, since it could have a larger implication  
12 if more people receive it?

13           DR. POEWE: If we maybe can show SA-38, the  
14 falls in ADAGIO were about similar in number in the  
15 placebo and in the 1-milligram arm. I think it was  
16 on the order of 3 percent. And it was, I think,  
17 4.8 in the 2-milligram arm. But that wouldn't be a  
18 signal of concern. There wasn't any significant  
19 difference in the active group and in the -- yes,  
20 here, we have it. If we could have the slide up,  
21 we can all see it. This is falls on the second  
22 line from below.

1           So a very low percentage, and although the  
2 number in the 2-milligram is slightly bigger with  
3 4.8, it's still very close to the placebo falls.

4           MS. CHRISTENSEN: I just want to point out  
5 that the numbers that I quoted are from the New  
6 England Journal article, and I can see them right  
7 here. So I don't know what the difference is, but  
8 it is a percentage point or more.

9           DR. FOUNTAIN: Any comment about that?

10          DR. FITZER-ATTAS: I think we will take a  
11 look at it and come back to it, because I can't  
12 comment offhand on what the differences are. But I  
13 would also say that we do have, of course, a larger  
14 body of safety data than just the ADAGIO study, as  
15 well as TEMPO and two pivotal studies in adjunct  
16 therapy, in which falls have not been an issue of  
17 concern for Azilect.

18          DR. FOUNTAIN: Okay. So maybe we can ask  
19 you to look into that, if there's a difference, and  
20 report back to us.

21          DR. FITZER-ATTAS: Yes. Sure.

22          DR. FOUNTAIN: Thank you.

1           The last comment will be from Dr. Ellenberg,  
2 unless it's something for the general discussion.

3           DR. ELLENBERG: I have two quick questions  
4 that I think can be answered quickly. One has to  
5 do with the sensitivity analyses. These are done,  
6 both the imputation and the propensity scores,  
7 based on data that we measured, that are supposed  
8 to be prognostic and help us understand what might  
9 have happened to the people who were lost.

10           What I don't know is, how prognostic are the  
11 variables that we have in Parkinson's? Are these  
12 likely to explain the vast amount, most of the  
13 variability? Because to the extent that they may  
14 not be all that prognostic, you may worry about how  
15 much in the data that you haven't measured. It's  
16 the issue of missing at random versus not missing  
17 at random analysis. So information about the  
18 prognostic strength of the factors is important.

19           The other question I have is --

20           DR. FOUNTAIN: If they're not directly  
21 related, maybe we could have an answer to that  
22 first.

1 DR. ELLENBERG: Okay.

2 DR. FOUNTAIN: It sounds a bit complicated.

3 So to reframe the question, are there any  
4 other factors considered that could have impacted  
5 the data besides those we've discussed?

6 DR. ELLENBERG: Well, we know that there  
7 will be factors that we don't even know about yet.  
8 That's always the issue with these kinds of  
9 analyses; how much can you really predict with what  
10 you know about and can measure? And in some  
11 diseases, you really know a lot, and in some, you  
12 don't know all that much. So that's my question.

13 DR. FOUNTAIN: Your question is, what's the  
14 degree of other factors not accounted for that we  
15 haven't discussed?

16 DR. ELLENBERG: What's the strength of the  
17 prognostic factors of the ones that they did  
18 measure and can account for?

19 DR. MCDERMOTT: So I wasn't a part of  
20 performing these analyses, so I can't speak  
21 directly to your question. I can tell you what was  
22 in the models. And I have a little bit of

1 experience from other databases and some of the  
2 literature as to what's been found to be prognostic  
3 in the past, if that will help.

4 DR. ELLENBERG: I know what's in the model.

5 DR. MCDERMOTT: Okay.

6 DR. ELLENBERG: And I believe that they're  
7 prognostic. My question is, are they really  
8 prognostic or are they modestly prognostic?

9 DR. MCDERMOTT: Are they -- I'm sorry.  
10 What? Are they what prognostic?

11 DR. ELLENBERG: Highly prognostic, or are  
12 they moderately, or modestly prognostic?

13 DR. MCDERMOTT: Yes. I would say that as a  
14 baseline value for detecting outcome, probably, the  
15 baseline UPDRS scores are going to be the most  
16 prognostic of what happens afterwards. People have  
17 found middling results regarding things like  
18 gender, and age at onset of Parkinson's disease,  
19 and things like this, but nothing really as  
20 striking as where you started in terms of the UPDRS  
21 score.

22 DR. ELLENBERG: Thank you.

1 DR. FOUNTAIN: Thank you.

2 Do you have another brief question?

3 DR. ELLENBERG: Another question is, has  
4 there ever been any kind of study to look at the  
5 extent of changes in UPDRS score that would be  
6 recognized to a patient, kind of a validation kind  
7 of thing that I know is done in other areas?

8 That is, if a patient improves by 3 points  
9 and you ask the patient, do you feel better, are  
10 you different from before, do they recognize that  
11 they feel different if it's changed by 3 points, up  
12 or down, or 2 points, or 1 point? Do people know  
13 what the extent of change is that a patient  
14 recognizes that they are either better or worse?

15 DR. FOUNTAIN: So we can direct that to the  
16 sponsor, if you have an answer to it.

17 DR. FITZER-ATTAS: Thank you. Yes.

18 Dr. Olanow, would you please respond? And I  
19 think we also have a response to the question about  
20 falls as well.

21 DR. OLANOW: So people have done studies.  
22 They've typically done them in more advanced

1 disease. So in more advanced disease,  
2 approximately 8 points was necessary in order to  
3 detect a change. In milder patients, there was a  
4 recent study showing that about 3 points was  
5 something they could recognize and detect. But  
6 even in what we call mild disease, that was still  
7 much later than what we're talking about here,  
8 where we're talking about very early disease.

9 I think an important point to appreciate  
10 here is, in my mind, this is more like an  
11 experiment, where the main goal is not to find out  
12 how much better this makes a patient, but to  
13 determine if you can separate out symptomatic and  
14 slowing of progression effects. That's the main  
15 reason for doing this study. And in that regard, I  
16 think the 38 percent reduction in rate of decline  
17 is the more important number.

18 If I could, I'd also just like to bring you  
19 up to date on the falls. I now understand what the  
20 issue is. The numbers you were quoting was for the  
21 placebo phase, where you were comparing rasagiline  
22 treatment to placebo. The number you're looking at

1 in the New England Journal is in the second period,  
2 where you're looking at delayed start versus early  
3 start. And in the delayed versus early-start, the  
4 numbers are almost identical.

5 It's also worth knowing that this is just  
6 preliminary -- not preliminary, but it's literature  
7 studies. But one of the interesting things that's  
8 been seen with rasagiline is that freezing, which  
9 is one of the major causes of falls, has been  
10 reported independently to be reduced in rasagiline-  
11 treated patients.

12 DR. FOUNTAIN: Thank you.

13 Dr. Twyman?

14 DR. AHLKOG: Can I comment about that  
15 before you go on?

16 DR. FOUNTAIN: Yes. There's a comment about  
17 that. Go ahead.

18 DR. AHLKOG: I just have a quick comment.  
19 To make a distinction between -- this relates to  
20 Dr. Ellenberg's question -- clinically meaningful  
21 and clinically detectable, they're two  
22 fundamentally different things. And it's important

1 in this particular set of studies because the  
2 second phase is open label, so you can become  
3 unblinded. Thank you.

4 DR. RODNITZKY: If I could make a comment  
5 about --

6 DR. FOUNTAIN: Yes. Dr. Rodnitzky?

7 DR. RODNITZKY: -- Dr. Ellenberg's comment  
8 and Dr. Olanow's response. Actually, that question  
9 was raised -- there's a publication by Bob Hauser,  
10 one of the co-authors of the ADAGIO study. He  
11 looked at that issue for the TEMPO cohort. For  
12 that exact cohort, he found that the minimal amount  
13 of UPDRS points that could be detected as  
14 improvement was 3.5, and those were fairly early  
15 patients.

16 DR. FOUNTAIN: Thank you.

17 Dr. Twyman?

18 DR. TWYMAN: Just following some of the  
19 discussion earlier, many of the questions are more  
20 directed towards the statisticians, and the  
21 question surrounds the robustness of the data.

22 Normally, the type 1 error controls for a

1 single primary variable is set at a threshold  
2 p value of .05. And in a situation of multiple  
3 dose-testing, you can use the Hochberg in order to  
4 analyze the influence of multiple doses and testing  
5 for multiple doses. But when you go across doses  
6 and multiple primary variables, how is that type 1  
7 error control maintained? And is the approach  
8 that's outlined, at least in the analysis plan for  
9 this program, an appropriate level of type 1 error  
10 control or an excessively conservative amount of  
11 type 1 error control, meaning that .05 is being  
12 applied across three variables, rather than just  
13 one variable?

14 Maybe the statisticians can help me  
15 understand that.

16 DR. FOUNTAIN: Can we save the discussion on  
17 the panel for our open discussion, which will be  
18 very shortly, in regard to the questions? But  
19 would you like to direct it to sponsor about a  
20 rationale of .05?

21 DR. TWYMAN: Your prerogative, Chairman.

22 DR. FOUNTAIN: Why don't we direct it to the

1 sponsor, for why .05 is across three variables in  
2 multiple-study analysis?

3 DR. FITZER-ATTAS: Yes. Dr. McDermott,  
4 would you please respond to that question? Thank  
5 you.

6 DR. MCDERMOTT: Yes. A quick comment on  
7 that is, this is known. I think what you're  
8 referring to is the reverse multiplicity problem,  
9 because in normal circumstances, when you have  
10 multiple testing, people think about it as, well,  
11 we need to correct the multiple comparisons because  
12 the interest is in finding a significant result in  
13 at least one of those tests.

14 Here, it's a completely different ball game.  
15 You need to find a significant result in all of  
16 them. So the type 1 error, actually, the threshold  
17 is -- really, the deck is stacked against you in  
18 terms of finding a positive result in that sense  
19 because you actually have -- what it causes is less  
20 power to detect a significant result for all three,  
21 if you just think about individually powering for  
22 each endpoint separately. And so that causes the

1 opposite problem from what you usually think about  
2 as a multiple comparison problem.

3 DR. FOUNTAIN: Is there a comment directly  
4 in reference to that? We can have lots of  
5 discussion separately.

6 DR. FLEMING: Yes. So there are three  
7 conditions that have to be met. But it's important  
8 to keep in mind, this is an agent for which there's  
9 already considerable evidence of symptomatic  
10 benefit. The question is, does it have, in  
11 addition to that, a disease-modifying benefit?

12 That symptomatic benefit is going to drive a  
13 positive result in your first hypothesis. So even  
14 if you have no disease-modifying benefit, you're  
15 not at jeopardy of missing that first hypothesis.  
16 It's the second and third hypotheses. And there  
17 are two analyses that have to be done, but they're  
18 very correlated.

19 If you have an agent that truly provides a  
20 disease-modifying effect, then that's going to  
21 drive the positivity of that second hypothesis, as  
22 would, potentially, any residual added symptomatic

1 benefit that may exist at a greater level from the  
2 early start. And, of course, as we've already  
3 said, the NI margin that they used here was so  
4 extraordinarily extreme that having no effect  
5 whatsoever on disease modification, you're still  
6 going to win, although you could have a more  
7 rigorous margin, as you should, and that would add  
8 a second target that you'd have to hit, in addition  
9 to Hypothesis 2.

10 But Hypothesis 2 and Hypothesis 3 are  
11 certainly very correlated, so the degree of added  
12 penalty or added risk that you have in the false  
13 positive is not as much as you might think. And on  
14 the flip side of that is the need for robustness in  
15 the results. And we'll talk about this later, the  
16 great concern, if we allow the data to generate the  
17 hypothesis.

18 DR. FOUNTAIN: Yes, Dr. D'Agostino.

19 DR. D'AGOSTINO: What they did is they took  
20 the alpha .05 and split it with the 1, and then  
21 with the 2. And then they did this hierarchical  
22 analysis. They win on the stage 1, they win on the

1 difference at stage 2, and then they win on the  
2 non-inferiority. And as long as they keep winning,  
3 they're in good shape. Once they lose, that's  
4 where they stop.

5           What our problem really is here is that by  
6 doing their interaction test and then splitting out  
7 1 alone, they win on this splitting, but they  
8 didn't win on the original analysis, because in the  
9 original analysis,  $\alpha$  was a .05, and it had to be a  
10 0.025.

11           So they really didn't sacrifice a lot of the  
12 alpha. It's this splitting of the two groups that  
13 really creates the problem, I think, in the  
14 statistical analysis, and then, second, what Tom  
15 said about the non-inferiority.

16                           **Questions to the Committee**

17           DR. FOUNTAIN: So this set of questions  
18 really, I think probably transitions us well to the  
19 next session, which is the panel discussion. It  
20 doesn't preclude us from asking other direct  
21 questions, but then we can speak among ourselves.

22           So we'll now proceed with the questions to

1 the committee and panel discussions. I would like  
2 to remind public observers of this meeting that  
3 while this meeting is open for public observation,  
4 public attendees may not participate except at the  
5 specific request of the panel.

6 For the voting questions, you'll be using an  
7 electronic voting system for this meeting. Each of  
8 you has three voting buttons on the base of your  
9 microphones, yes, no, and abstain. Once we begin a  
10 vote, the buttons will start flashing and will  
11 continue to flash, even after you've entered your  
12 vote. Please press the button that corresponds to  
13 your vote. If you're unsure of your vote or you  
14 wish to change your vote, you may press the  
15 corresponding button until the vote is closed. The  
16 vote will then be displayed on the screen and I'll  
17 read the vote from the screen into the record.

18 Next, we'll go around the room and each  
19 individual who voted will state their name and vote  
20 into the record, which I'll remind you. And you  
21 can also state the reason why you voted, if you  
22 wish to. We'll continue in the same manner until

1 all questions have been answered or discussed. So  
2 first we'll discuss them, and vote, and discuss a  
3 bit more.

4 So the first question is, please  
5 discuss -- this is more of a discussion than a  
6 question, which is why I bring it up first. Please  
7 discuss whether randomized start design,  
8 appropriately designed and conducted, is capable of  
9 detecting a disease-modifying effect for treatment  
10 of patients with Parkinson's disease, and if not,  
11 are there alternative designs that can demonstrate  
12 such an effect?

13 DR. KATZ: Again, I said this before, but,  
14 really, we mean this to be a generic discussion.  
15 We don't mean to discuss the results of these  
16 particular trials in this discussion. We really  
17 just want to know whether or not -- and not only  
18 for this application but future applications, is  
19 this the right way, or a right way -- if it was  
20 done adequately, analyzed adequately, that sort of  
21 thing, is this the way to go when we're talking  
22 about trying to detect disease modification? It's

1 a generic discussion.

2 DR. FOUNTAIN: Ms. Christensen?

3 MS. CHRISTENSEN: I would have to say that,  
4 under the current system, no, because there's not  
5 patient involvement in the development of the  
6 design, and there's not family input, care partner  
7 input. For instance, on the UPDRS scale, when  
8 you're asking the patient about depression and  
9 such, you would probably get very different answers  
10 from my husband than you would get from me.

11 I'm not sure exactly how one would go about  
12 designing a study because I don't understand  
13 slopes, and p values, and all that in any official  
14 sense, but I really just want to get the point  
15 across that having patient involvement at this  
16 level is wonderful. I am thrilled to be here. I'm  
17 very glad the agency has these opportunities. But  
18 I think they need to be expanded, because we really  
19 are the experts. And as people in the Parkinson's  
20 community like to say, if you've met one patient  
21 with Parkinson's, you've met one patient with  
22 Parkinson's.

1           Our symptoms are all varying. I mean, mine  
2           have fluctuated wildly throughout the day. I think  
3           it's the variation in what symptoms, when, and how  
4           soon one gets diagnosed, and access to care, and so  
5           many variables, I think it will be very difficult,  
6           but I think the main component that needs to be  
7           added is patient input.

8           DR. FOUNTAIN: So to summarize your comment,  
9           you'd like to see more patient input into primary  
10          outcome measures, like health-related, quality of  
11          life, or something like that, that comes directly  
12          from the patient's experience, rather than  
13          something observable?

14          MS. CHRISTENSEN: Yes. But also, in  
15          designing a clinical trial, sometimes the things  
16          that are asked of us are ridiculous, like can you  
17          come to NIH every month for a week? And they're  
18          asking this of people who are still working and  
19          live across the country. I mean, some of you may  
20          do that, but you don't have Parkinson's.

21          DR. FOUNTAIN: So also, the corollary to  
22          that would be, then, that we should be mindful of

1 the design so that people with the appropriate  
2 degree of disease severity who are working, for  
3 instance, could participate.

4 MS. CHRISTENSEN: Right.

5 DR. FOUNTAIN: Okay. Next is Dr. Zhao.

6 DR. ZHAO: Yes. I have just a couple  
7 questions. One is really, how do you really define  
8 the disease-modifying effect? So we've seen, I  
9 think, the sponsor uses this particular score in  
10 their presentations. By looking back on their  
11 presentation, the slide number 51, in a paper  
12 published in Movement Disorders, they use rather  
13 the percent of change.

14 So I don't know if it was in one score  
15 versus the absolute score or relative score, but  
16 it's really -- even between this particular  
17 content, there are differences that could make some  
18 impact on the analysis results. And also, there  
19 are some discrepancies that seem to be between what  
20 was reported here, but this is more of a technical  
21 issue. I don't think -- how to really define this  
22 modifying effect, I don't really know.

1           The second thing is, if you also look at the  
2 same figure, you can really see, depending on which  
3 time point you are following the patient through,  
4 you may see very different results -- it's the  
5 same publication, cohort. If you settle on a  
6 particular phenotype or particular thing to define  
7 modifying effect, what would be the rate, a good  
8 measure, indicative of the long-term prognosis of  
9 these patients?

10           So I found like for this particular study,  
11 I'm still struggling with these standard points,  
12 72 weeks, how indicative, if this patient will  
13 still be able to see the total benefit of having  
14 early-start treatment.

15           DR. FOUNTAIN: So the comment is, should it  
16 be measuring absolute values, rate of change, and  
17 at what point it should be measured? Would that  
18 be --

19           DR. ZHAO: No, this particular -- what I'm  
20 saying, I think they need to still settle on a  
21 particular score, why this score is a good one, not  
22 the other one.

1 DR. FOUNTAIN: At one particular scoring  
2 method?

3 DR. ZHAO: No. I'm just saying that the  
4 UPDRS score or the percentage change, well, they  
5 give, like, two different ways to look at --

6 DR. FOUNTAIN: So the percent change or  
7 absolute score?

8 DR. ZHAO: Yes. I don't know which one is  
9 the better one, because if you look at standard  
10 deviation of this patient from the entry point, the  
11 mean of 18 or 20, but the standard deviation is  
12 about 8, so there's a wide spread of scores that  
13 come -- to the same change, to very different  
14 percentage change.

15 DR. FOUNTAIN: Dr. Ellenberg?

16 DR. ELLENBERG: Again, as not somebody who  
17 has expertise in Parkinson's disease and looking at  
18 these kinds of issues for the first time, I'm  
19 pretty skeptical about this design. I do think  
20 that, if you had a drug that clearly made a huge  
21 drop in this -- if you had something that was very  
22 extreme on all the things that you measured, I

1 think this design -- you know, you'd see it in this  
2 design, and everybody would feel very comfortable  
3 with it.

4 I think, when you're trying to evaluate what  
5 might be a modest effect, and we have all of these  
6 issues -- what about the interactions, and what  
7 about the 2-milligram dose, and what about this,  
8 and what about that, and all these other things,  
9 it's very difficult to know where you are. Your  
10 basis for determining a disease-modifying effect is  
11 exactly the same measure that you used to determine  
12 a symptomatic effect. And that's not what we have  
13 in other diseases, where you can identify a  
14 disease-modifying effect because you can see  
15 something physiologically happening. And I think  
16 that makes it very complicated.

17 I think this kind of study, if there weren't  
18 all the complications and there was still this  
19 modest effect, would still be difficult to explain  
20 to the community and patients. And I'm always a  
21 fan of trying to see a simpler way to do things,  
22 something that's a little clearer.

1           So I think this is a very challenging  
2 design. I think if you had a fabulous drug, almost  
3 any design you would pick is going to convince  
4 people. And I think the kind of drug that may give  
5 you a modest but incremental improvement may be  
6 very difficult to show with a design like this.

7           DR. FOUNTAIN: So I'm going to take my  
8 prerogative to make a comment, because it follows  
9 on that one. And that is sort of what you say, if  
10 you have a positive result, I guess it's a good  
11 design, even for a small effect. So I would say  
12 that it would appear to be a reasonable design  
13 because you've found an effect at 1 milligram, but,  
14 of course, not a good design because you didn't  
15 find it at 2. So two prongs of the design are the  
16 drug.

17           So I think that within the limitations of  
18 how to do a study, this seems like a reasonable  
19 design, but the two factors are almost unavoidable  
20 are that it has to be done on a very long duration,  
21 so dropouts will be inevitable.

22           The second problem is that it seems to me

1 that progression isn't or maybe can't be linear in  
2 Parkinson's disease, because as you get worse, you  
3 get worse faster. So if you're looking at rate of  
4 change or change from baseline, it's not going to  
5 be a line.

6 Now, I suppose, over the 18-month period,  
7 it's going to be more or less a line, because at  
8 any point in that, what might be sigmoidal shape,  
9 is going to be adequate, but you're going to have  
10 to decide which point in that to start. And maybe  
11 that's the effect of the people who are more  
12 severely affected, and maybe that is what Dr.  
13 Olanow is saying.

14 So it seems to me that this design, with an  
15 enriched population, meaning more affected, seems  
16 like it might show another result, or maybe the  
17 question I could turn around back to you is if they  
18 reproduced exactly with the 1 milligram with  
19 2 milligrams at a higher UPDRS, it seems to me,  
20 that would be satisfactory for a robust, if it's  
21 robust in the ways we talked about, an adequate  
22 p value done with protocol-specified sequential

1 hypothesis testing that met that, that that would  
2 meet the bar that I think is moderately high.

3 Dr. Rosenberg is next, I think.

4 DR. ROSENBERG: Thanks.

5 I think this is the best design we have for  
6 a disease where we do not have a well-validated  
7 biomarker of disease severity. In Alzheimer's, we  
8 might have one, so we might use it the  
9 might -- Rusty's raising his eyebrows  
10 appropriately -- but for Parkinson's, we're not  
11 near there. So we have to design -- if we're going  
12 to look for disease modification or slowing down of  
13 clinical progression, whichever buzz word you want  
14 to use, it's got to be clinical outcome.

15 I think this is as good of a design as I've  
16 seen, and I'd love to see a better one if there is  
17 one. In some ways, randomized withdrawal is  
18 stronger, but I don't think we're going to be able  
19 to do that.

20 I see a problem here, because these not only  
21 do the -- these hypotheses 1, 2, and 3 are actually  
22 generic to the study design. They're not specific

1 to this drug or this disease. And the problem with  
2 Hypothesis 1 and 3, which are analyses of slopes,  
3 is that the models are all -- I'm not a  
4 statistician; I'm just a civilian here, so I'd love  
5 to be corrected. They're based on linear models,  
6 and not only do these data not fit a linear model,  
7 they fit a quadratic model, so are most  
8 neurodegenerative disease outcomes.

9 I mean, in Alzheimer's, I'm deep in  
10 epidemiology, and every outcome is better modeled  
11 with a quadratic term. But lack of linearity has  
12 nothing to do with whether a drug works. You're  
13 looking for divergence of curves. And I'm sure  
14 somebody knows how to show whether curves diverge,  
15 as opposed to lines diverging. I think that's a  
16 really important point. That's what you were  
17 getting at, Nathan, about the linearity.

18 The other thing is, some of the issues that  
19 have come up with this trial are routine issues on  
20 trials. Most trials will find these issues, an  
21 interaction with an important outcome variable, or  
22 we start with baseline levels of your outcome

1 variable, an imbalance between the groups. These  
2 are routinely handled in other contexts by control  
3 variables. In this case, you could control for the  
4 three-way interaction with UPDRS and dose. You  
5 could control for sex. If you didn't change your  
6 results, it would reassure you as to what the  
7 results were. And I'm a little surprised in the  
8 primary analysis that there isn't any room for  
9 these inevitable confounds.

10 DR. FOUNTAIN: Is this a response to that  
11 comment or a separate comment?

12 DR. D'AGOSTINO: In terms of the linearity,  
13 I think the people that develop this -- and it goes  
14 back to Leber and so forth trying to do it -- what  
15 we've oftentimes done with statistical analyses,  
16 when we're looking at something over time and we  
17 have repeated measures, we just fit a linear curve,  
18 and we say, is there a trend in the curve?

19 Now, that's turned out to be a crucifying  
20 aspect for the sponsor here and following that,  
21 because it isn't linear. Linear is a seat of the  
22 pants that works in many situations. But here,

1 we're actually looking for the split in the slope.  
2 We're looking for the separation in phase 1 and  
3 we're looking for this parallel in phase 2. And in  
4 phase 2, we want to make sure that the curves don't  
5 collapse on each other. And this approximation  
6 with linearity, it works in a lot of sense, in  
7 terms of saying, can you fit the curve or can you  
8 fit the data to a linear curve and get a sense of  
9 what's going on? But here it comes much more  
10 important, and we're seeing the ramifications of  
11 running with this simple linear model.

12 As far as the dropout, I'm almost convinced  
13 that when you went to the second phase, that you  
14 almost were in an observational study, as opposed  
15 to a clinical trial, with the potential dropout and  
16 the differential dropout. And we really have to be  
17 careful when we buy into a study like this, on how  
18 we're going to look at the data in that second wing  
19 or the second phase.

20 DR. FOUNTAIN: Dr. Ahlskog, comment on that?

21 DR. AHLKOG: Well, I'm going to comment  
22 about that, and then I'm happy to comment, too,

1 about the study design. But you know what's  
2 plagued us, collectively in the field, going back  
3 to DATATOP, is, we're not always certain about the  
4 pharmacodynamics. So when you have curves that  
5 don't form a straight line, then the question is,  
6 are you seeing, still, the lingering symptomatic  
7 effect, and then, was it simply, we didn't go long  
8 enough? Should we have changed the whole timing of  
9 the study?

10 So if you're going to use this design, you  
11 really have to know more about the  
12 pharmacodynamics. The half-life of all of these  
13 irreversible MAO-B inhibitors, according to nuclear  
14 medicine studies, is 40 days. But there's this  
15 thing called the long duration response. And there  
16 was a nice paper by Anderson and J. Nutt in the  
17 most recent issue of Parkinsonism and Related  
18 Disorders that discusses the long duration  
19 response. And they are very authoritative in terms  
20 of the respect for Dr. Nutt, who writes extensively  
21 about this. And he's not certain if that goes on  
22 for months or a year. And so we're dealing with

1 unknowns, and maybe some time, money, and  
2 investment ought to be made into looking at the  
3 pharmacodynamics of the drugs.

4 So that brings me to the study design, which  
5 was the original question.

6 DR. FOUNTAIN: Before you elaborate, I think  
7 maybe Dr. Katz wants to respond.

8 DR. KATZ: Yes. I just want to pick up on  
9 that exact point. We had agreed, as the sponsor  
10 described, that, for example, in the first phase,  
11 we would calculate data -- the slope from data from  
12 week 12 on. And the presumption was that any early  
13 effect -- that, again, I don't want to call it  
14 symptomatic, because if we knew that was  
15 symptomatic, we would not have to get into such  
16 complicated design. But the early acute effect, we  
17 said, well, that will be gone by 12. And, in fact,  
18 I think someone said that it's actually fairly  
19 conservative because it's usually gone by four or  
20 six weeks, something like that.

21 We didn't present it here, but if you look  
22 at the actual individual patient curves about when

1 this sort of inflection point occurred -- in other  
2 words, when did that early effect start to sort of  
3 wane -- it's highly variable. And in many  
4 patients, that inflection point, if there ever was  
5 one -- and sometimes, there wasn't -- occurred well  
6 past 12 weeks.

7 So this design, again, to the extent that,  
8 for example, phase 1 depends on linear slope, the  
9 choice of this inflection point, we made a choice.  
10 But it turns out that the data didn't necessarily  
11 support that.

12 DR. AHLKOG: Well, I don't want to be a  
13 Monday morning quarterback about that. And I think  
14 it was a rational selection, and it's hard to be  
15 critical. It is Monday, and I am a football fan,  
16 but, nonetheless, I think the study design was very  
17 nice. Unfortunately, stuff doesn't always work out  
18 in science. That's the truth of things.

19 Is this a good time to give my two bits  
20 about --

21 DR. FOUNTAIN: Can I come back to you?

22 DR. AHLKOG: You may.

1 DR. FOUNTAIN: Okay. Dr. Frank has been  
2 waiting very patiently.

3 DR. FRANK: So when I saw this question in  
4 our packet, I thought, great. Dr. Katz wants us to  
5 discuss and dissect decades of debate about  
6 clinical trial design. I actually think that the  
7 design has been published a lot and talked about a  
8 lot. And I'm okay with the design. I think it's  
9 applying the tools in clinical trials.

10 So, for example, we're talking about a floor  
11 effect for the UPDRS. Well, there's the newer,  
12 updated movement disorder society UPDRS, which has  
13 a little wider span on the lower end of things.  
14 And so I think that may be a better tool. And  
15 until we do have a good biomarker, as Dr. Rosenberg  
16 brought up, I think that we need to just apply more  
17 objective information as it comes along, DaTscan,  
18 for example, if there's a better way to objectify  
19 findings in DaTscan. So I think those are tools  
20 that can be applied to clinical trial design.

21 Just two other points about this; you had  
22 mentioned about patient and caregiver input, and

1 that actually is incorporated into the new UPDRS as  
2 well, so not in terms of clinical trial design, but  
3 in terms of collecting data.

4 Then one other question for Dr. Katz, just  
5 because I think it's important for us to consider.  
6 You said that you consider clinical progression the  
7 same thing, essentially, as disease modification.  
8 I think, for some diseases, I have an issue with  
9 that, particularly Parkinson's disease, where  
10 people may have disease that progresses for years  
11 or even decades before they show up with symptoms.  
12 So we're not picking up the disease until they  
13 develop symptoms, and then we can follow their  
14 symptoms based on that, and as a surrogate marker  
15 for the underlying disease.

16 DR. KATZ: Well, if I can respond, I  
17 completely agree. But the very last thing you  
18 said, I think is the point I was trying to make,  
19 which is that we're using -- and I think we are  
20 using the clinical manifestations, the clinical  
21 measurement, as a surrogate for the underlying  
22 progression of the actual disease process.

1           So that's what I mean when I say that we  
2 think clinical progression is the same thing as  
3 disease modification. It doesn't -- the timing as  
4 to when you're assessing it, whether it's 10 years  
5 before the disease or after the disease actually  
6 had its onset, I don't think that's particularly  
7 material to the question of whether or not what  
8 we're assessing is modification of the disease.  
9 That doesn't mean we prevented it. It certainly  
10 doesn't mean we are curing it, although that would  
11 be nice. But I'm just absolutely saying that the  
12 clinical measure is sort of, if you will, a  
13 surrogate for the underlying disease process. And  
14 I think that's what we're trying to get at here.

15           DR. FOUNTAIN: Dr. Black?

16           DR. BLACK: Thanks. If I could, I wanted to  
17 first address the question about what constitutes a  
18 clinically meaningful response, because, in a  
19 sense, in this study design, it doesn't matter as  
20 much. The reason I say that is because here, the  
21 question is about whether one can detect in a short  
22 period of time an effect that you are hoping to

1 apply over a long period of time. And if the drug  
2 made a difference in a period of nine months of,  
3 say, 2 points, and if one assumes that progression  
4 were linear, then over the course of 10 years,  
5 let's say, that's a whole lot of huge difference to  
6 people.

7           So having a treatment that makes a  
8 clinically relevant effect is very important, and  
9 this differs substantially from acute-phase study  
10 design, where you have to know where you're  
11 expecting to see the meaningful effects during the  
12 course of the trial. In this kind of study design,  
13 you aren't. So I don't know that it's the same  
14 question that you have with most clinical trial  
15 designs.

16           But if I could, I'm skeptical. I mean, I  
17 don't know of a better solution when you're using  
18 the clinical outcome, that the clinical severity is  
19 an indicator, approximately, for cell death or  
20 something. And I'm very skeptical because of some  
21 of the simulation data that were published right  
22 around 2009 I think, as a reference.

1           But if I understand correctly, a change in a  
2 decrease in the rate of progression of, say,  
3 30 percent, that would mean that -- again, assuming  
4 that life is all perfect -- to get to this state  
5 where, right now, it takes you 10 years to get with  
6 PD, that would change you to something like 14  
7 years. It would take 14 years to get to that point  
8 at that slower rate.

9           Four years of extra function at a certain  
10 level, that would be a huge gift if it worked. And  
11 yet, the power to detect that, even with 600 people  
12 per arm of a study -- and this is assuming a  
13 progression rate of about 8 or 9 points a year  
14 rather than 4; in that model was only something  
15 like 40 percent to show an effect that was  
16 real -- that's a high hurdle to pass. Either we'll  
17 have to have measures that are less variable, or  
18 more approximate to what we're trying to measure, I  
19 suspect, to find most clinically useful disease-  
20 modifying drugs.

21           DR. FOUNTAIN: So in other words, would you  
22 say the drug would have to be more potent to

1 demonstrate an effect in that number of  
2 people -- is what you're saying -- with this  
3 design, or are you suggesting that you need a  
4 design, which just takes much longer to find a  
5 difference?

6 DR. BLACK: I mean, taking the realities  
7 that people are going to use something like the  
8 UPDRS, and the clinical variability that exists in  
9 PD, and the other assumptions that were put into  
10 the modeling for that, you have to assume that  
11 there's a huge effect, an effect that would  
12 translate to being clinically enormous during the  
13 lifetime of your typical patient with PD, in order  
14 to find it at all. And I think people would be  
15 interested in smaller effects, and those designs,  
16 those studies, probably aren't going to be  
17 practicable with this method. I mean, a 20 percent  
18 drop in a rate of disease would mean that, like,  
19 you'd get an extra two or two and a half years of  
20 time until a certain functional state, compared to  
21 10 years with current treatments, you know.

22 Two years? Everybody would want two years

1 of extra life or extra function. That's clearly a  
2 substantial difference. And yet, you have almost  
3 no power to detect that, even with enormous sample  
4 sizes. So I think that either the -- I don't know  
5 how to improve on the design, so I think you'd have  
6 to have a more approximate measurement of the  
7 disease or substantially less variable disease  
8 measure in order to hope to find most drugs that  
9 would, in fact, exert a real meaningful effect.

10 DR. FOUNTAIN: So we're talking in general  
11 terms, rather than on this specific study?

12 DR. BLACK: Yes.

13 DR. FOUNTAIN: But if we said that the  
14 1-milligram response was the -- you know, if we  
15 take it at face value that the 1-milligram response  
16 was perfect, as exactly as presented and that was  
17 reproduced, do I understand your back-of-the-  
18 envelope calculation would extend -- would give you  
19 substantial improvement you'd realize and would not  
20 have as much deterioration in 12 years as opposed  
21 to 10?

22 DR. BLACK: Yes. What was it, a 30 percent

1 decrease or something like that, in the rate?

2 COMMITTEE MEMBER: Thirty-eight percent

3 DR. BLACK: Yes. I mean, it's something  
4 like an extra four or five years, compared to  
5 10 years, over the course of 10 years.

6 DR. FOUNTAIN: That back envelope makes  
7 sense to me, and I think that's important. So  
8 you're saying that if that all played out, that  
9 would be worthwhile, if you found a difference in  
10 this design. But you may not be able to, because  
11 you're asking so much of the drug.

12 DR. BLACK: Right. And just to address the  
13 question that's up on the screen, I think you will  
14 miss most meaningfully useful drugs with this kind  
15 of study design.

16 DR. FOUNTAIN: Okay.

17 Dr. Fleming?

18 DR. FLEMING: Just before getting into the  
19 specific comments, however, I really worry about  
20 extrapolation. I mean, all of this discussion is  
21 based on extrapolation, and we've spent a lot of  
22 time talking about lack of linearity of curves.

1 And that extrapolation is a huge assumption that  
2 might be true, but very plausibly isn't true.

3 So my own sense about this question, it's  
4 obviously a highly challenging one that a lot of  
5 very thoughtful people have given great attention  
6 to for a long time. I wish this were an OARA  
7 setting, where we could discern the differences  
8 between NSAIDs and DMARDs by saying, okay, we have  
9 different measures. We have our pain measures and  
10 we have loss of joint function measures that we use  
11 to assess the disease-modifying aspect. If there  
12 were a way, that would be wonderful, because I hate  
13 doing it this way. But I'm sure there isn't.  
14 We've, I'm sure, thought about it greatly.

15 So I think Paul Leber's design with  
16 randomized withdrawal was very clever, and I think  
17 the variation for this randomized start, that we  
18 would all view it as a not-quite-as-good option  
19 here, does surely make sense when you argue, as we  
20 do, that you've got to have high levels of  
21 retention in order to maintain an integrity of  
22 randomization and interpret the results.

1           So my sense is, the randomized start design  
2 does have merit. There are four quick things that  
3 I would say are really important in thinking about  
4 its actual utility. One is, to state the obvious.  
5 We need to understand the course of the disease and  
6 the course of the symptomatic effect well enough to  
7 be confident that each phase is long enough to  
8 fully capture the symptomatic effect. And it's  
9 been mentioned, pharmacologic assessments and  
10 anything else that we can use to help us along  
11 those lines, is key, because if the symptomatic  
12 effect is still emerging for a period of time that  
13 exceeds 36 weeks, or however long each phase is, it  
14 really compromises the interpretability.

15           Second area of comments, is the design  
16 failing the drugs or the drugs failing the design?  
17 And I don't know. But I don't want to assume that  
18 the design is failing the drugs. We have, in this  
19 setting, agents that by estimate for their effect  
20 on disease modification, over a differential of 36  
21 weeks of exposure. When we look out at 72 weeks,  
22 an estimate of what's in the wrong direction, minus

1 .3 and a plus 1.6 in the right direction, which  
2 averages out to be about 0.7 or something along  
3 those lines. We're looking at the data. A highly  
4 effective agent looks to have been capable of  
5 producing two-, threefold, that magnitude of  
6 difference.

7 So, in essence, obviously, for this type of  
8 design, that isn't the most capable in showing  
9 smaller differences, if you have a very effective  
10 agent for disease modification relative to the  
11 symptomatic benefit, then that type of  
12 design -- this implementation of this design I  
13 think is going to be adequately sensitive.

14 Obviously, what we would have seen, what we  
15 would have needed to see in ADAGIO, is big effects  
16 at week 48 that grow up to week 72, that actually  
17 continue to grow, which is, in theory, what should  
18 happen if we have an optimal efficacy.

19 Third specific issue is, if we're going to  
20 use these slopes and a non-inferiority margin  
21 approach -- and I understand the rationale behind  
22 it -- that margin needs to be chosen in an

1 evidence-based fashion to rule out what would be an  
2 unacceptable loss of efficacy. Non-inferiority  
3 margins don't allow us to conclude the slopes are  
4 parallel. All they allow us to do is conclude that  
5 they're not non-parallel by worse than your margin.  
6 And so, at a minimum, if in ADAGIO, you have  
7 whatever the effect is at 48 weeks, that margin  
8 needs to be small enough so that it rules out a  
9 complete loss of that, between 48 and 72.

10           So if you had a 1.2 delta at 48 weeks, that  
11 margin can't be any more than .05. And in many  
12 circles, when we choose non-inferiority margins, we  
13 don't try to rule out complete loss. We try to  
14 rule out even half the loss, which would give you a  
15 margin of 0.025. But, by the way, if I  
16 extrapolate, then that means I've lost it all by  
17 week 96. Now, I'm not going to extrapolate for the  
18 reasons that I was uncomfortable a minute ago  
19 extrapolating. But the margins have to be much  
20 more rigorous. But those margins could be met by  
21 an agent that is substantively slowing disease  
22 modification over a period of the 72 weeks.

1           The last point is, as we'll talk about later  
2           on and as you've already mentioned, we need robust  
3           and compelling results from pristine trials that  
4           are internally consistent. Some of those  
5           adjectives, we can't legislate. Some of them are  
6           just inherent to what the agent's performance is.  
7           But some of them, we can. A classic example of  
8           that is addressing missingness.

9           There's only one way, in my view, to address  
10          missingness, only one way. Okay? It's to prevent  
11          it, because treating, like in many diseases, is so  
12          much harder than preventing. With missing data,  
13          treating it is so much harder than preventing.

14          A lot of very thoughtful analyses have been  
15          discussed here about imputations. By the way, LOCF  
16          worst case and a plea case are not thoughtful  
17          analyses. But the imputation methods that have  
18          been discussed are thoughtful. Nevertheless,  
19          coming back to what Dr. Ellenberg said earlier,  
20          what makes any two of us different from each other  
21          that's based on known recorded covariates is the  
22          tip of the iceberg. The vast majority of what

1 does, in fact, explain differences will never be  
2 addressed, no matter how sophisticated your  
3 statistician and no matter how effective you are in  
4 collecting data.

5           It doesn't mean I don't want you to do it.  
6 I want you to do it. But preventing missing  
7 data -- and, in fact, I'm an ITT guy. If we're  
8 going to randomize and maintain the integrity of  
9 randomization, I think we should be following  
10 everybody, and then certainly including at least an  
11 ITT analysis, retaining those people who were  
12 rescued early and retaining those people who become  
13 non-adherent over the entire course, hopefully  
14 achieving not perfect adherence, but what I call  
15 best real-world achievable adherence. So if we can  
16 achieve that and follow everybody, then that will  
17 not prevent the problems that we're talking about,  
18 but it will reduce them.

19           But, fundamentally, my sense here is, this  
20 is not a perfect way to evaluate an intervention.  
21 But until we come up with a better out-  
22 endpoint -- and I'm not saying I have any clues

1 about that -- I think this is a potentially viable  
2 approach. And I'm not sure that the design is  
3 failing the drug here. I think the magnitude of  
4 the effect -- if I take literally the estimates,  
5 the fact that there's no effect at 2 milligrams has  
6 really complicated the interpretation. If we had a  
7 very effective agent, there is plenty of  
8 opportunity for bigger separations that would, in  
9 fact, have been able to be more reliably detectable  
10 with less controversy.

11 All this discussion about tests for  
12 interactions, that's not the fundamental problem  
13 here, folks. It's relevant, but it's not the  
14 fundamental problem. The fundamental problem is  
15 how clear is the signal.

16 DR. FOUNTAIN: Dr. Wang, do you have a  
17 comment on this?

18 DR. WANG: Actually, following Dr. Katz and  
19 Dr. Fleming, I think this issue was brought up  
20 multiple times. That is, in order to assess this  
21 design, I think it's really critical to realize how  
22 important it is to pick the right time, in this

1 case 12 weeks, to start looking at the linearity,  
2 or the disease modification.

3 Therefore, I want to show one backup slide  
4 from the FDA. That's slide 57. The top row is for  
5 the ADAGIO trial. The bottom row is for TEMPO.  
6 The Y axis is the UPDRS change from baseline. And  
7 these are the median summary, not the mean. And  
8 the X axis is basically the time.

9 Each panel represents, basically, the  
10 summarized data for two subgroups, and the blue and  
11 circle ones are for the individuals who had a  
12 positive slope during the first phase. I'm only  
13 showing the early-start full-time course and the  
14 late start, only the placebo-controlled phase, and  
15 those numbers are the number of subjects at each  
16 time point.

17 What I want to show you is the proportion of  
18 patients with a much longer symptomatic effect. As  
19 you can see, even within placebo group, the first  
20 time point is 12 weeks. Almost 30 percent of the  
21 placebo patients are still dropping in terms of the  
22 UPDRS score, up to the last point of the first

1 phase. In the two treated groups, the percentage  
2 is 40 percent. Forty percent of people have this  
3 prolonged symptomatic effect. If you consider, at  
4 any moment, it comes up, that's the end of the  
5 symptomatic effect.

6 It takes much longer for some individuals.  
7 Of course, this, again, is a summary of 40 percent  
8 of the individuals. If you think about the  
9 individuals, some have even longer and some even  
10 shorter. But, overall, after 12 weeks, this is the  
11 profile you see in terms of you did achieve full  
12 symptomatic effect at 12 weeks or not. And I think  
13 this is a very important feature for the randomized  
14 withdrawal design.

15 If you have such a high percent of patients  
16 that have such a long symptomatic effect, then any  
17 comparison -- for example, now you can understand  
18 why during the first phase, you see this curvature,  
19 because you have such a proportion of patients that  
20 are going down and are still going through the  
21 symptomatic effect. And even at the end of  
22 72 weeks -- if you can show the slide 62, that

1 actually is the delayed group. Again, this is 43  
2 percent for 1 milligram, 41 percent for the 2  
3 milligrams. And that's for the TEMPO. That's a  
4 sample size much smaller.

5 The bottom line is, even at the end of  
6 72 weeks, you have almost half of the patients  
7 still going through this. You can call it a  
8 symptomatic effect phase. And therefore, I even  
9 don't know the end of the 72-week difference is  
10 truly disease-modifying effect or is a mixture of  
11 some ongoing, unfinished symptomatic effect.

12 So when we consider this design -- I don't  
13 know whether this drug failed this design or the  
14 design failed the drug -- this proportion of  
15 patients is critical. Unless you say I'm only  
16 going to include this proportion of patients by  
17 whatever criteria, if you include those patients in  
18 the trial, it makes results very hard to interpret  
19 and also probably will fail eventually, for the  
20 disease-modifying claim.

21 DR. FOUNTAIN: Thank you.

22 I think next is Dr. Clancy. Do you still

1 have a comment?

2 DR. CLANCY: So I think, getting back to our  
3 original question, is this an appropriate design, I  
4 just would like to weigh in to say I think it is  
5 reasonable. I think, in the history of these types  
6 of trials, it's good.

7 The part that concerned me, always, is that  
8 even if both of these drugs had shown to be  
9 effective, all we'd really be able to say is that,  
10 for a very short period of time, it modified the  
11 progression of the disease. I would be very  
12 uncomfortable making long leaps of faith about much  
13 beyond there.

14 On the other hand, the longer the study, the  
15 more the dropouts. So in this particular case, I  
16 just wondered why there wouldn't be an option to  
17 give symptomatic treatment to keep the patients in  
18 the study, and, therefore, satisfying the criteria  
19 of having all the patients, the intent-to-treat  
20 patients, in there, because we just discussed that  
21 these symptomatic treatments do nothing to alter  
22 the fundamental progress of the disorder, so that

1 we could maintain the comfort of the patients, the  
2 functionability of the patient, keep them retained  
3 in that, but be able to look over a much broader  
4 time, to times we're more concerned about. We're  
5 not concerned about the good function in the first  
6 year. We're concerned about the slope at the end,  
7 where the patients become dysfunctional.

8 So that would be my comments about the study  
9 design.

10 DR. FOUNTAIN: So if I could just follow up  
11 on that, I come to this from a little different  
12 disease perspective. That's exactly what I was  
13 thinking, so that in other diseases, you treat to  
14 maximum benefit, and then either add placebo or  
15 drug to see if you get benefit. And, of course,  
16 that's what you do in a symptomatic treatment for  
17 this.

18 But our problem is, you need to over a very  
19 long duration, and so why not do just that, so  
20 everyone gets treated symptomatically to maximum  
21 benefit? And then half get placebo, half get  
22 rasagiline. I suppose the problem would be, you'll

1 never know if rasagiline is a better symptomatic  
2 treatment than something else, and so your lines  
3 could still diverge.

4 So what you would do in that, if we're on  
5 the same page here, is you eliminate the whole  
6 first half of the study, the part that's so  
7 problematic, and just look for the lines diverging  
8 over a long time at the end, of those who got drug  
9 versus not. But then the problem is you never know  
10 if the symptomatic treatment of rasagiline is so  
11 much better than existing therapy that they diverge  
12 forever.

13 So it seems to me, and my contribution to  
14 your comment is, I suppose after you treat them  
15 long enough, do you think they have diverged, or  
16 you've observed they've diverged, then you withdraw  
17 rasagiline, give them maximum available L-DOPA,  
18 whatever therapy, symptomatic therapy, and see if  
19 they then converge again or if they stay apart. If  
20 they stay apart, you'd say, okay, you've had an  
21 effect.

22 So you've done the same thing without the

1 placebo arm and all of its confounding problems.

2 That might be a naive question on my part.

3 Dr. Ahlskog?

4 DR. AHLKOG: I'm just going to respond to  
5 that, and I have a larger response, too. You know  
6 I've been waving my hand over here. And this is a  
7 very interesting discussion, and it's very apropos,  
8 I think. This is a huge issue for us in the  
9 clinic. How do you help the community folks with  
10 Parkinson's disease? And that's why we're all  
11 here.

12 Just borrowing from Dr. Clancy's comments, I  
13 think you've started on the right track. We are  
14 focused on dopaminergic deficits. And depending  
15 upon how you view the world of Parkinson's  
16 disease -- but I would view it, that's sort of a  
17 very narrow, intermediate phase in Parkinson's  
18 disease. And somebody mentioned earlier it starts  
19 years before. So I can cite you good data that  
20 argues that such things as dysautonomia,  
21 constipation, and REM sleep behavior disorder,  
22 anxiety, are significantly increased when you go

1 back from prior to the onset of the motor symptoms  
2 of Parkinson's disease, 10 years, 20 years, and  
3 before.

4           So you could argue, I think pretty  
5 compellingly, that Parkinson's disease starts  
6 relatively early, at least a couple of decades  
7 before the motor symptoms of Parkinson's disease,  
8 A.

9           B, if you're my patient in the clinic, and  
10 you can assure me you only have dopaminergic  
11 symptoms, I'm going to keep you playing golf. You  
12 may have to use a cart. I'm going to keep you  
13 walking. And you may even be working for years.  
14 And I've got a patient who was in the original  
15 levodopa trial in Rochester, Minnesota in 1969, and  
16 for four decades, he's been managed on carbidopa  
17 and levodopa alone, levodopa originally and then  
18 carbidopa. But this gentleman got it at a very  
19 young age and never developed the progression that  
20 somebody alluded to earlier, which is to say,  
21 dysautonomia, levodopa unresponsive motor symptoms,  
22 and cognitive impairment, dementia. And that's

1 really what -- in the clinic, that's what I want to  
2 stop. I want to halt the progression to dementia.  
3 I want to halt the progression to these levodopa  
4 refractory gait problems, freezing, and imbalance,  
5 urinary incontinence, orthostatic hypotension.  
6 Yet, collectively, we're focused on something  
7 that's easy to measure. We're measuring  
8 dopaminergic kinds of things. The UPDRS, it's all  
9 dopaminergic. And we're giving dopaminergic drugs,  
10 which have a symptomatic effect.

11 So this is why we're having this convoluted  
12 discussion today, and we're going to keep going in  
13 circles until we kind of take a little bit of a  
14 broader perspective. And maybe we need to look at  
15 long-term outcomes.

16 DR. FOUNTAIN: Thank you.

17 Dr. Twyman?

18 DR. TWYMAN: Yes. I think Dr. Fleming  
19 answered my question around how do you determine  
20 the non-inferiority margin. But I also want to  
21 comment on the intent-to-treat portion of this,  
22 because the withdrawal in these long-term studies

1 are actually quite problematic, and I don't think  
2 we'll ever get around that. And, namely, it's  
3 because these are human subjects, and human  
4 subjects are human. They have a choice, and they  
5 can withdraw from the study at any time that they  
6 want. And I think if they want to withdraw, you  
7 have to allow that to occur.

8           Then the other part of this is that, in an  
9 agent that does not have clear-cut symptomatic  
10 effects, a time-to-event type of approach is  
11 perfectly amenable, I would propose. So time to  
12 some threshold of severity, time to some escape  
13 criterion or something like that might be  
14 potentially appropriate for an early-type  
15 population.

16           Now, a symptomatic agent would be quite  
17 problematic in that design, whereas, I think in  
18 this delayed-start approach, the symptomatic  
19 effects, although observed, I also raise a caveat  
20 that the ideal disease modifier could potentially  
21 be one that actually not only slows the disease,  
22 but actually allows room for improvement.

1           So being able to tease the effect out is  
2 going to be very, very difficult. And I really  
3 implore the committee to think hard about this,  
4 because the science is now evolving to the point  
5 that there might be agents that could be tested in  
6 this format.

7           We really do need help, from an industry  
8 standpoint, as to how to really tackle these,  
9 because I think, if the study designs are too  
10 formidable, or the challenges are too formidable,  
11 moving ahead with agents in disease modification is  
12 going to be very problematic for us.

13           DR. FOUNTAIN: Thank you. And I suppose you  
14 could even say, as sort of a corollary to that,  
15 there could be agents or are likely to be agents  
16 that would be disease modifying that wouldn't be  
17 symptomatic at all, in which case, it would be a  
18 much easier question.

19           DR. TWYMAN: Right.

20           DR. FOUNTAIN: Next, Dr. Khatri?

21           DR. KHATRI: Just a few brief points and a  
22 question. So I think the randomized start design

1 and concept is realistic and appropriate. It makes  
2 sense. But how we analyze it is where I'm a little  
3 bit stuck.

4 Hypothesis number 2 is compelling to me. If  
5 it's pre-specified in a protocol-plan manner and it  
6 were positive, that makes sense, and I think that  
7 would be potentially evidence for a disease-  
8 modifying effect.

9 I do think that with something like  
10 Hypothesis number 2, where you're looking at the  
11 difference between the delayed-start, and the  
12 early-start group, and how they look at the end of  
13 these time frames, it would be helpful to have  
14 other secondary endpoints in addition to the UPDRS,  
15 so you knew just how robust these findings are,  
16 whether that be quality of life, other things that  
17 may not be as well validated, but are clearly  
18 meaningful to patients.

19 What I'm not clear on, as a clinician with  
20 some statistical background but clearly primarily a  
21 clinician, is with Hypothesis number 3. We've been  
22 talking about the slopes. We've talked about how,

1 on a patient level the datapoints are non-linear.  
2 Is that an unrealistic bar to set? Are there too  
3 many assumptions being made there for something  
4 like Hypothesis number 3 to be required in this  
5 design? And that might also apply to Hypothesis  
6 number 1.

7 DR. FOUNTAIN: Any comment?

8 DR. KATZ: Well, again, as far as whether  
9 it's realistic or unrealistic, I think we've heard  
10 some comments that said, for a drug that had a very  
11 powerful, clear manifest effect on modification,  
12 you could set the margin sufficiently small so that  
13 you could convince yourself it meant something.

14 But, again, the point of it was to prevent  
15 the situation where you saw a difference in  
16 Hypothesis 2 at the end of the study, but that the  
17 lines were clearly converging, so that if you'd  
18 continued the study for another two weeks, they  
19 would have met. And, therefore, your conclusion  
20 based on the minus two-week outcome, that the drug  
21 was disease modifying, would be spurious. It would  
22 be misleading.

1           So that was the point of it. It's  
2           difficult, operationally, perhaps, to look at it  
3           and analyze it, and particularly when a drug isn't  
4           particularly powerful. But that was the goal.  
5           Everybody who was involved thought that that was a  
6           reasonable goal, to try to prevent the outcome  
7           where you saw a difference, conclude it was disease  
8           modifying, but had you continued it another few  
9           weeks, you'd come to a very different conclusion.  
10          So that was the point.

11           DR. KHATRI: So maybe just a follow-up  
12          question of the statisticians as well. Is there a  
13          way to not have to assume linearity, and still get  
14          that point where you can believe that the lines  
15          aren't crossing, and they're actually making sense?  
16          Is there a way to build that into the analysis?

17           DR. FOUNTAIN: Dr. Ellenberg?

18           DR. ELLENBERG: I think you're back to  
19          extrapolation, and I think that's the problem. You  
20          can construct any kind of model you want. If we  
21          thought it was quadratic, we could develop tests  
22          with quadratic curves. If you thought it was cubic

1 or something else exponential, you could -- but the  
2 problem is you have to be able to assume it's going  
3 to continue.

4 I hear that a 30 percent decrease in the  
5 rate of change could be really terrific over 10  
6 years, but if you tell me what you see after a year  
7 and a half may not even be noticeable to patients,  
8 and we have to make the leap to say this is going  
9 to continue for another 10 years, and then it would  
10 make a big difference, I'm confused about how we  
11 can make such a leap.

12 DR. FOUNTAIN: Dr. D'Agostino?

13 DR. D'AGOSTINO: It's back to the notion of,  
14 are you looking at the subjects long enough? And  
15 you can fit all kinds of curves. We can fit  
16 quadratic curves. We can fit spline fits, and so  
17 forth, and then say there's somehow or other equal  
18 in these time points out. Then you never have a  
19 test that says they're exactly equal, but they're  
20 not collapsing on each other.

21 But the idea of the linearity is that you're  
22 following them, hopefully, long enough where you

1 would see a rapid -- or you would see an effect  
2 collapsing if there wasn't this right progression.  
3 And then some other linear curve would be a nice  
4 approximation, and we see that it's not a nice  
5 approximation, and we could go to quadratic and so  
6 forth. We could work out a hypothesis test and so  
7 forth, an analysis. But then, at the end, you'd be  
8 scratching your head, is this phase 2 long enough,  
9 and what's going to happen three months out?

10 DR. FOUNTAIN: We'll also have an  
11 opportunity to discuss some of these and more  
12 questions.

13 Dr. Katz, would you like to respond?

14 DR. KATZ: The same Paul Leber who invented  
15 the design used to call John Maynard Keynes all the  
16 time, in the end, we're all dead. So at some  
17 point, the effect goes away.

18 I think, as Dr. D'Agostino said, the choice  
19 of the duration, particularly the second phase, I  
20 think what goes into it all, went into it, was the  
21 fact that we thought that it would be sufficient  
22 time for any immediate so-called symptomatic effect

1 to sort of wash out or maximize, and long enough to  
2 observe whether or not the curves were approaching  
3 each other, operationally defined by some non-  
4 inferiority margin, parallelism.

5 So I think, from our point of view, sure,  
6 it's true. We can't say anything about -- even if  
7 the lines are strictly parallel by any test you  
8 could possibly apply, we couldn't possibly say what  
9 happens the month after the study is over. But we  
10 thought, for the reasons I described, it was long  
11 enough to get a good handle on whether or not the  
12 drug was disease modifying.

13 Every study we do in every -- now, maybe  
14 it's different here, but every study we do for any  
15 treatment, symptomatic or otherwise, is of a finite  
16 duration. And we say, well, okay, this anti-  
17 epileptic drug worked for three months. We assume  
18 that means it's going to work for some period of  
19 time after that, too.

20 DR. D'AGOSTINO: Yes. I think there were  
21 two parts to the way we were responding, is that  
22 you've got the observation time. Is it long enough

1 for you to be able to see that the effect has worn  
2 off? And then within that, are you saying that  
3 they look parallel; do they look equal? How do we  
4 anticipate what the appropriate curve could be,  
5 mind-boggling and so forth? But you can work that  
6 out. And so that's part one. And that's what I  
7 think the design can address.

8 The other part that we were also alluding to  
9 is, who knows what happens afterwards, and you just  
10 can't address that with the analysis.

11 DR. FOUNTAIN: A few more comments, then do  
12 you actually want us to vote on this question in a  
13 specific way?

14 DR. KATZ: No. We just want to really get a  
15 sense of the committee as to whether or not this is  
16 a reasonable way to proceed. And, certainly, if  
17 anybody hasn't weighed in on it who wants to, we  
18 certainly want to hear from them.

19 DR. AHLKOG: I haven't weighed in on that  
20 particular subject, and I'd like to.

21 DR. FOUNTAIN: We've got quite a list here,  
22 so we'll go around and get everyone in.

1           Dr. Zivin? Especially those who haven't had  
2 a chance to comment.

3           DR. ZIVIN: I want to answer strictly the  
4 question that has been asked here, and particularly  
5 by Dr. Katz. This design, as far as I am  
6 concerned, is adequate to detect a disease-  
7 modifying effect, and that there are alternate  
8 techniques that are capable of doing that as well.

9           The trouble is that we have to stop. I take  
10 care of Parkinson's patients, but I don't take care  
11 of a lot of them. It's not my special interest.  
12 But what we need to do is have treatments that are  
13 sufficiently effective so that there aren't these  
14 questions and quibbles about little efforts to find  
15 changes that are minute and try and blow them up  
16 into something that's really important.

17           What I think we need is drugs that are  
18 significantly more potent than the ones that we  
19 currently have, and that way, almost any of these  
20 designs will work well. And we have to stop  
21 kidding ourselves and our patients to think that  
22 that's what we've actually done up to this point.

1 DR. FOUNTAIN: Ms. Christensen?

2 MS. CHRISTENSEN: Yes. I just wanted to  
3 respond to a couple of points. When we talk about  
4 disease modification, I think we need to be a  
5 little bit careful because if you had seen me six  
6 years ago, before I had deep brain stimulation and  
7 was a human slinky from dyskinesia, my UPDRS scores  
8 would have been very high.

9 Right now, I'm doing pretty good, but the  
10 deep brain stimulation surgeons, in my opinion, the  
11 good ones, make it clear to their patients that  
12 it's not halting disease progression. So I think  
13 that's where it gets dicey in terms of clarity and  
14 also the length of time, because for a lot of us,  
15 the longer you've had Parkinson's, the more  
16 impatient you get. You want something. We want  
17 relief now. But at the same time, I think if  
18 you're going to prove something works, it needs a  
19 little more time to prove that it is actually  
20 something that will truly address the disease  
21 significantly.

22 So I haven't answered any questions. I've

1 just tried to, unfortunately, highlight conundrums  
2 and add more questions.

3 DR. FOUNTAIN: That's part of what we're  
4 here for, so that's good.

5 Now, Dr. Ahlskog?

6 DR. AHLKOG: Well, we've spent a lot of  
7 time talking about the statistics. And just as an  
8 aside, I wonder what Dr. Leber would say if he were  
9 here and we cited his article. And he might say,  
10 "Darn it, I was talking about Alzheimer's disease,  
11 not Parkinson's disease."

12 You can see the problem. We're using a  
13 symptomatic drug, and we're modifying the symptoms,  
14 and then we're trying to measure something at the  
15 same time. So you might argue, maybe this is not  
16 the ideal design, just based on that.

17 Then having spent a lot of time in the  
18 clinic, I first started doing clinical trials in  
19 1983 with pergolide. Dr. Olanow and I co-authored  
20 a paper a number of years ago on pergolide, and  
21 there wasn't enough money in the kitty for us to  
22 hire a nurse. At least, my senior colleague chose

1 not to hire one. So we were doing basically what  
2 was the UPDRS in the clinic. So I got a lot of  
3 insight.

4 As Ms. Hunt Christensen noted, there's a lot  
5 of variability in that. And I hope everybody here  
6 had a chance to look at the UPDRS questions, of  
7 which there are 44. They're conducted in the  
8 clinic time, after time, after time. There's a lot  
9 of time pressure in clinics, so you have to get  
10 these done in a timely fashion.

11 Parkinson's folks, notoriously, aren't quite  
12 as quick as they were before. And so we're going  
13 through things kind of laboriously. And there's  
14 kind of a tendency, "What did I say the last time?  
15 Let's see. Mild trouble eating. Or what did I say  
16 the last time?" Then they ask their wife, and you  
17 say, "No, we can't tell you what you said the last  
18 time," but they remember and they record that.

19 So there's a potential for whatever you  
20 recorded in the placebo phase to carry through,  
21 because there are just the time pressures, and the  
22 habit, and the inclination just to move onto the

1 next thing. So that's one of the things that's  
2 quite troublesome in all of this.

3 The second thing is, if you look at the  
4 differences, 1.68, that's two digits to the right  
5 of the decimal point. And in my basic college  
6 chemistry class, I would have been told something  
7 about significant figure problems here, you know,  
8 because we're dealing with something that's  
9 measured in scores of 0, 1, 2, 3, or 4. And I can  
10 tell you, the difference between 1 and 2 on some of  
11 those 44 items is very nuanced and very subjective.  
12 And these are things that can vary from day to day,  
13 good night's sleep, upbeat, or if you're convinced  
14 that you're on the real drug and you're positive  
15 about it, that might have a pretty prominent  
16 placebo effect.

17 So you might ask, does a placebo effect ever  
18 occur in Parkinson's disease? Well, this was  
19 looked at, actually, three years ago in the Journal  
20 of Movement Disorders. Dr. Christopher Getch was  
21 the first author. He did a meta-analysis of all  
22 the placebo arms in randomized, controlled trials

1 of Parkinson's disease. He set a very conservative  
2 measure, a 50-percent improvement in the UPDRS  
3 motor battery, 50 percent or a score change of two  
4 items on the UPDRS motor battery. And just with  
5 those very conservative outcome measures,  
6 16 percent of people in these control arms, in  
7 these placebo arms, improved and met those  
8 qualifications.

9           Then I'm going to repeat, again, the second  
10 half of the study is open label. So that's why the  
11 point was made earlier. Is this clinically  
12 meaningful or is it clinically sufficient when you  
13 get on the drug, to tell that you're on the real  
14 drug? And people do improve. That's the first  
15 half of the TEMPO trial. That's the LARGO trial.  
16 That's the PRESTO trial. All these trials; it's a  
17 good drug for treating symptoms. Is it fabulous?  
18 No. But it treats the symptoms.

19           So you go into first phase and something  
20 happens, and then in the second phase, where you  
21 know that you're getting the real drug, and you  
22 compare retrospectively to the first phase, and you

1 go onto week 52 or 72, and then somebody has to  
2 make a decision about that. And there's potential  
3 for observer bias, and there's a potential for a  
4 placebo effect from the patients.

5 Is there ever observer bias? Absolutely.  
6 There's pretty profound observer bias. Dr. Olanow  
7 just published a paper on this, in these seven  
8 trials on surgery for Parkinson's disease, and  
9 commented in there that, actually, in those trials,  
10 which I realize are a horse of a different color,  
11 observer bias overshadowed the placebo effect.

12 So my thought about this whole approach to  
13 measuring whether drugs slow the progression of  
14 Parkinson's disease is that I'm not confident we're  
15 ever going to go beyond having these discussions we  
16 are having today, unless, as Dr. Zivin pointed out,  
17 we find the drug where the curve flattens and it  
18 never changes. Boy, then we're on to something.  
19 But so far, all the drugs that we have stumbled  
20 upon -- and a lot of these are just your best guess  
21 about what's going to be helpful -- they're not  
22 there by a long shot. Thank you.

1 DR. FOUNTAIN: So just for clarification, do  
2 you mean to say that weeks 36 through 72 were open  
3 label?

4 DR. AHLKOG: Is that correct? Were they  
5 open label?

6 DR. FOUNTAIN: Was it still blinded in weeks  
7 36 through 72?

8 DR. OLANOW: It depends how you define open  
9 label. They were blinded to their original  
10 treatment assignment, so that they did not know if  
11 they had received early-start or placebo, but all  
12 patients received active treatment in the second  
13 phase. That's the way it was.

14 So I don't know how you want to call that.  
15 They all knew they were on active treatment in the  
16 second drug --

17 DR. FOUNTAIN: They were blind as to whether  
18 they were treated --

19 DR. OLANOW: -- but they were blind as to  
20 what their early treatment was.

21 DR. FOUNTAIN: Okay.

22 DR. KATZ: But they were also blind to dose,

1 were they not, in the second phase?

2 DR. OLANOW: They were also blind to dose.

3 Correct.

4 DR. FOUNTAIN: A couple of more comments  
5 before moving onto some of the specific questions.

6 Yes?

7 DR. D'AGOSTINO: The individuals who  
8 generated the design were aware of the concern in  
9 the second phase. That's why they don't stop with  
10 the data immediately when you switch to the  
11 positive-positive. They throw out a period of  
12 time. And the question is, how long must that  
13 period of time be so that this halo effect of  
14 knowing you're on the positive drug, that's wearing  
15 out?

16 DR. AHLKOG: Right. And my point, though,  
17 was that when you go through the two phases and one  
18 is defined, you know you're on the active drug,  
19 then you can define what you were in the first  
20 half. And that might conceivably have influenced  
21 what you do at the end. And it might also  
22 influence the observer's assessment at the end.

1           All of us who have participated in drug  
2 trials -- I don't do that anymore, but I used to do  
3 a lot of that -- I really wanted these drugs to  
4 work. That's why you do it. I wasn't getting rich  
5 doing this. I was getting my usual salary. But  
6 you want to help people. You want the drugs to  
7 work. And so there's sort of this subconscious  
8 need to have things go well.

9           DR. FOUNTAIN: Dr. Rodnitzky?

10          DR. RODNITZKY: This is in response to my  
11 colleague, Dr. Ahlskog's, point that, when you go  
12 into the active phase, you know what you  
13 were -- what your assignment was in the previous  
14 phase because you see an effect. I'm not so sure  
15 in this study that was the case, because even the  
16 active -- even the early-start patients had a  
17 placebo response at the beginning of the active  
18 phase, so indicating that they didn't know what  
19 they were on; they had a placebo effect. So I'm  
20 not so sure the blind was broken when the  
21 changeover occurred.

22          Can I also go onto comment in a general

1 sense? So in comments in response to Dr. Zivin's  
2 analysis, I agree with him. I think this is a  
3 design that could work under the proper  
4 circumstances. But I think Dr. Zivin went on to  
5 say that when you have an effect that's as small as  
6 this appears to be, there will continue to be  
7 quibbling over whether it's real or not.

8 I would submit that, in this particular  
9 case, if we had before us a positive effect for the  
10 1-milligram doses, the 2-milligram doses, as well  
11 as the 2-milligram dosage in TEMPO, in other words  
12 all three, although small effect, were positive,  
13 probably the quibbling would be at a minimum, or  
14 much less quibbling. So I think it is possible,  
15 even with a small effect, to have a positive result  
16 that most people could live with.

17 Regarding Dr. Fleming's point that you have  
18 a small effect and how you know that's going to  
19 continue, true, we can't extrapolate forever. But  
20 on the other hand, you can't be that nihilistic to  
21 say that it's not going to happen, so you have to  
22 take a glass-half-full approach if you have a

1 positive effect and hope, at least, that you can  
2 extrapolate, and it will hold to be true for years  
3 to come.

4 DR. FOUNTAIN: Thank you..

5 One last comment, then maybe we'll move on  
6 through some more, specific to the questions.

7 Dr. Rosenberg?

8 DR. ROSENBERG: Just to follow up, it  
9 doesn't sound to me like we've had great huge  
10 qualms about the overall design, Dr. Katz. But  
11 there is a problem with this design, which is that  
12 you randomized once and you have two phases. So  
13 you have non-random. You've got a lot of missing,  
14 a lot of dropouts into phase 2. But the way you  
15 analyze is in the two phases.

16 So there has to be some statistical way to  
17 account for this, because you're not going  
18 to -- because you have symptomatic treatments for  
19 Parkinson's, you're going to be losing patients.  
20 This is not merely a matter of following them  
21 better or retaining them better. You're going to  
22 have people going on drug. I don't know how you

1 account for that, but I think it's crucial.

2 DR. FOUNTAIN: I'm going to read Question 2.  
3 I think we've addressed many of these things, but  
4 I'm going to read them so that everyone can  
5 consider them if they have further comments for  
6 Dr. Katz and the FDA.

7 Agency reviewers have identified numerous  
8 issues related to the analysis and result of ADAGIO  
9 and TEMPO, A, non-linearity of slopes, presumably  
10 related to varying effects of treatments -- seems  
11 to me we've discussed that at some  
12 length -- re-analysis of slopes without early data  
13 suggests parallel slopes in phase 1 for drug and  
14 placebo; potentially significant baseline  
15 differences in UPDRS scores between early-start and  
16 delayed-start patients, particularly in Hypothesis  
17 2 and 3 databases, or datasets; and potential  
18 biases in the analysis to compare these non-  
19 randomized groups, which we just had a comment from  
20 Dr. Rosenberg about; differential response in men  
21 and women; and baseline differences in early and  
22 delayed women's starters in ADAGIO; and then

1 sponsor-conducted analyses that differed from those  
2 specified in the protocol, which I think we  
3 discussed earlier.

4 So we'd like to make sure that you discuss  
5 the impact of these issues, as well as any other  
6 issues, scores, have on interpretations of the  
7 studies submitted.

8 Would you like to comment, Dr. Katz?

9 DR. KATZ: Not about that, other than that's  
10 a very potentially long thing. The agenda called  
11 for a break at 3:00. I'm just wondering whether or  
12 not you want to do that briefly.

13 DR. FOUNTAIN: Well, if we don't have any  
14 comments about this, then we'll take a break now.  
15 Maybe that's an incentive. I'm not sure.

16 DR. KATZ: Yes. Well, I don't know how  
17 folks feel.

18 DR. FOUNTAIN: Okay. So why don't we take  
19 just a brief 10-minute break? We'd like to be done  
20 by 5:00. There are people that need to make it to  
21 flights and so forth, so we will be done by 5:00,  
22 one way or another. We want to make sure that

1 everyone's here, available to vote, since that's  
2 the purpose of being here, among other things.

3 So, please, let's take just a 10-minute  
4 break right now. It's a quarter after, so we'll be  
5 back at 25 past. Thank you.

6 (Whereupon a recess was taken.)

7 DR. FOUNTAIN: If everyone would like to  
8 take their seats, we'll reconvene the meeting.

9 All right. We were just finishing up  
10 discussion of a question, and I think I cut it a  
11 bit short. I think we have one more comment to  
12 make as follow-up to the last question before  
13 moving on to the next question. And that comes  
14 from Dr. Rosenberg.

15 DR. ROSENBERG: I'm sorry. This actually  
16 may be part of the next question. I just want to  
17 talk about my bottom line here and my concern. And  
18 I'd like to hear from the committee about this. I  
19 actually think A through E, it doesn't blow me away  
20 that these concerns alter my fundamental feeling  
21 about the result of ADAGIO, which I think is pretty  
22 positive for the effect of the 1-milligram dose.

1           What I'm concerned is question number 5,  
2           substantial evidence, we talked about having two  
3           studies, or one robust study and one confirmatory  
4           study. My problem is, I see two studies. They  
5           both have reasonable evidence, but at different  
6           doses, and they do not replicate each other. TEMPO  
7           has some decent evidence for a 2-milligram disease-  
8           modifying effect, and ADAGIO, a 1 milligram.

9           I'd like to hear from the committee. I  
10          really can't get around this problem. I could  
11          happily accept that one dose works and one dose  
12          doesn't. I don't think we know enough about  
13          disease modifying to assume that's illogical or  
14          impossible biologically. But I can't get around  
15          this.

16          DR. FOUNTAIN: Any other comments in regard  
17          to that specific issue, which is a perfectly  
18          reasonable paradox to provide you a conundrum for.

19          Dr. Katz?

20          DR. KATZ: I think that is probably  
21          Question 5, the ultimate question, if you will. I  
22          think, before we get there, it would be useful for

1 us to hear what people think about some of the  
2 specific issues we talked about, our reservations  
3 about the 1 milligram, and our reservations about  
4 the quartile analysis with the 2-milligram. But,  
5 again, if we could have some discussion, again, it  
6 would be useful for us to hear sort of how people  
7 are thinking through this. And, obviously, we'll  
8 get to that question.

9 DR. FOUNTAIN: So let's do that by  
10 considering Question 3, discussing it, and then  
11 voting on it, and then sort of bring it to  
12 resolution, answer one part of the question.

13 So Question 3 is, does ADAGIO provide  
14 compelling evidence that the 1-milligram dose of  
15 rasagiline met the protocol-specified criteria for  
16 success? So, first, we'll have some discussion,  
17 and then we'll vote at the time of voting. Then  
18 you can make a comment that you can agree, or  
19 disagree, or say whatever you like.

20 Dr. Fleming?

21 DR. FLEMING: So we're going to answer  
22 Question 2 first, right? I mean, that sets the

1 stage for Question 3.

2 DR. FOUNTAIN: Well, I guess -- I assume  
3 that we already -- we can either discuss -- because  
4 we're discussing it, we can discuss whatever we  
5 like. Ultimately, it will lead to answering  
6 Question 3. So if there are comments about  
7 Question 2 and the subparts of Question 2, we can  
8 talk about that first.

9 Is that what you would like to do? Okay.  
10 Sure. Go for it.

11 DR. FLEMING: So, in fact, to me, Question 2  
12 is maybe the most important. I view, literally,  
13 our role here, it's the FDA advisory committee, not  
14 the FDA decision-making committee. So I've long  
15 felt it would be great to get rid of the voting and  
16 spend the time talking about the strengths and  
17 weaknesses. And I see that's very much what  
18 Question 2 is.

19 So very quickly here, there are half a dozen  
20 points. I'm going to try to be very concise. The  
21 2-milligram results are quite clear. When you have  
22 Hypothesis 2 and there's no difference, there's

1 nothing there for disease modification.

2 So my interpretation of Question 2 is really  
3 focusing that, in particular, on the interpretation  
4 of the 1-milligram dose results. And there are  
5 multiple issues, no single one of which is the  
6 dominant one, but they're all important together.  
7 And a number of these were identified by the agency  
8 and are listed on A to E. Some of these are not.

9 But, in essence, if we have a disease-  
10 modifying drug, you would hope and think that you  
11 could have, if not positive, at least neutral  
12 slopes. But the slopes go in somewhat the wrong  
13 direction in the first phase, from week 24 to 36,  
14 with some reliability in that estimate. So that  
15 certainly contributes to some concern about the  
16 reliability of the 1-milligram result.

17 There's been lots of discussion about  
18 missingness, and 16 to 20 percent missingness is  
19 certainly, in general, what we would consider  
20 problematic when it's as informative as it is. And  
21 it becomes more problematic when it differs by arm.  
22 And there's some evidence here that we're creating

1 an imbalance in the Hypothesis 2 and 3 populations,  
2 due to the fact that we have imbalances in the  
3 informative missingness. Interestingly, it's  
4 particularly apparent in the females.

5 I don't know what to make of gender subgroup  
6 effects. I actually don't think that the effect is  
7 probably only in the females. But the imbalances  
8 have shown up in the females, hence, rendering me a  
9 little more concerned about the female analysis,  
10 which is driving the positive signal in the  
11 1 milligram. So, again, not a showstopper, but  
12 contributing to the concern about the  
13 interpretation of the results.

14 We talk about the overall analysis, the two  
15 fundamental results. One is, the pre-specified  
16 primary analysis for the 1 milligram didn't make  
17 the statistical significance level. Not only  
18 wasn't it robust and highly significant, it didn't  
19 actually make the statistical significance level.  
20 A post hoc analysis comes close. The 2-milligram  
21 result didn't make -- in fact, showed no effect.  
22 But a post hoc analysis explains why maybe there's

1 a floor effect, although the FDA's evidence against  
2 that is pretty strong.

3 My concern is -- I was on a panel a year ago  
4 of an industry FDA statistics workshop, and I was  
5 asked, when you're presented supportive analyses,  
6 can you really put emphasis on those? And my  
7 answer is -- and I think it's true here, there's  
8 some interesting, thoughtful, supportive analyses  
9 that would say, maybe the results are stronger than  
10 the pre-specified analyses would indicate. But I  
11 said, somebody needs to answer for me the mystery.

12 Countless times, I've worked with sponsors  
13 who have said, you know the primary analyses?  
14 Trending didn't quite make it, but look at these  
15 supportive analyses. It really strengthens the  
16 case.

17 Never once has someone said to me, you know  
18 the primary analysis is really great, but look at  
19 all these other things, because it really  
20 diminishes my sense of reliability. That's a  
21 mystery. I don't know why that's happened that  
22 way. But it does make me worry about the

1 interpretation of results when we have to rely on  
2 the supportive analyses to add further strength.

3 The overall result or effect sizes here are  
4 certainly relevant. The estimated effect size that  
5 we come up by the 0-to-72-week difference is  
6 slightly in the wrong direction with the  
7 2-milligram dose; the 1-milligram dose in the right  
8 direction, modest effect size, less than the  
9 minimal clinically detectable effect. And Dr. Eric  
10 Ahlskog's comment was right. I was about to say  
11 the same thing that he said.

12 Minimally detectable is not the same as a  
13 minimal clinically meaningful difference. And so  
14 it's a small effect, whether it's sufficient -- and  
15 I agree with Dr. Black and Dr. Rodnitzky. We have  
16 to hope that maybe the differences we see are  
17 sustained, but we're having to hope that because  
18 the magnitude of these effect sizes are pretty  
19 small. And that adds to some concern.

20 There's some inconsistency when you look at  
21 ADAGIO and TEMPO. The TEMPO study was really only  
22 formally designed for symptoms. I'm not

1 criticizing it. It did what it was intended to do  
2 well. It gave us some supportive evidence,  
3 particularly for the 2-milligram dose, and provided  
4 a hypothesis, suggested a hypothesis, which, in  
5 fact, when you look at ADAGIO, is the arm that  
6 didn't show the difference. So it's hard to argue  
7 that there's a supportive role for that.

8 I'll be brief on the next point, and that  
9 is, the NI margin, we can celebrate. We made the  
10 NI margin, but the NI margin is non-scientific.  
11 And I won't go through the logic again. But I  
12 think we could justify, for the 1-milligram dose,  
13 an NI margin on the order of 03 to 04. But even  
14 with that margin, the results are fairly marginal.

15 So there are multiple issues here, many of  
16 which you've recognized, that add together when  
17 you're starting with the result that even at the  
18 beginning, before you brought these issues up, were  
19 somewhat marginal.

20 So we heard in the open public hearing some  
21 things that I think are true. There's a signal in  
22 the data at the 1 milligram. I think that's true.

1 We need a path forward. I think that's true. But  
2 those two are not at all the same as what you said,  
3 in terms of what our mission is here, what our  
4 responsibility is; is there substantial evidence of  
5 effectiveness from adequate and well-controlled  
6 trials? And there's plenty of precedent, both in  
7 FDA and EMEA, clarifying what that means,  
8 adjectives that you've talked about. Are the  
9 results, when it's a single trial, robust and  
10 compelling, internally consistent, pristine?

11 So we worry about things like how strong is  
12 the p value. In fact, EMEA and FDA have both said,  
13 pristine and compelling doesn't just mean two-sided  
14 05 p values anymore. We're marginally there even  
15 before we start working on all of these results  
16 that you have brought out about inconsistencies.  
17 And that's ignoring the fact that the 2-milligram  
18 dose arm shows nothing. And then you've got the  
19 issue around missingness. You've got imbalances by  
20 gender. All of these are features that need to be  
21 taken into account when we're about not answering  
22 the question, is there an unmet need. Absolutely.

1           We need a way forward. Absolutely. Those  
2 aren't the questions here. The question is, does  
3 this agent, based on these data, answer that unmet  
4 need with evidence that's substantial evidence of  
5 efficacy?

6           DR. FOUNTAIN: So we'll get to vote  
7 specifically on that later.

8           Do you have a comment to that, Dr. Katz?

9           [Dr. Katz shakes head no.]

10          DR. FOUNTAIN: Okay. Dr. Ellenberg?

11          DR. ELLENBERG: So that was Tom Fleming  
12 concise.

13          [Laughter.]

14          DR. ELLENBERG: My concise is, all of these  
15 problems I think chip away, to some extent, at the  
16 credibility. The big chip is that the 2-milligram  
17 is different from the 1 milligram. If you didn't  
18 have all these other chips -- in the paper, they  
19 said you can't rule out that the 1-milligram result  
20 was a fluke. Well, maybe the 2-milligram was a  
21 fluke. But all of these other chips I think reduce  
22 the credibility. The word in Question 3 is

1 "compelling," and I have a hard time seeing that we  
2 have compelling evidence here.

3 DR. FOUNTAIN: I would like to say, though,  
4 we probably at some point need to visit each of  
5 these specific points in Question 2.

6 DR. D'AGOSTINO: Yes. Now, I'll add my two  
7 cents. I think part A and B are just straw men in  
8 terms of so what. If we're looking at the  
9 1 milligram, the data in the first phase is just  
10 very compelling, and you can start arguing about  
11 linearity and not. I think in the part 1A with the  
12 second phase, that however you look at it, you do  
13 get this sort of parallel line. I think when you  
14 get to Question -- or part C and E in particular,  
15 you start running into trouble that sort of makes  
16 the compellingness very uncomfortable.

17 I think the sponsor did, actually, a  
18 tremendous job on part C in terms of their  
19 analyses, but there's always the question that's  
20 begging; is it enough? Do these techniques really  
21 make the adjustment in terms of dealing with non-  
22 randomized groups?

1           As far as D, I don't know how to respond to  
2 D. Male, females, I just don't know how to respond  
3 to that. There may be some differential bias going  
4 on there, but I just don't know.

5           So I think, for me, C and E are the ones  
6 that are really plaguing me and leaving me with a  
7 lot of discomfort, and especially the E part. But  
8 I think what they did was quite reasonable, and how  
9 compelling is where I have to draw the inference.

10           DR. FOUNTAIN: That's an excellent summary  
11 of each point that I think reflects, more or less,  
12 the consensus opinion.

13           So are there any more comments about  
14 that -- Question 2? I'm sorry.

15           Dr. Todd?

16           DR. TODD: I think that A and B actually are  
17 pretty important or relevant because it really gets  
18 to the fundamental question of when does the  
19 symptomatic phase end and the putative, protective  
20 effect begin? We're talking about a slope from  
21 week 12 to 36, and there's only three measurements  
22 there. I think, in some sense, they might have

1 gotten lucky that 12 to 36 turned out to have a  
2 different slope, when after the line diverges, and  
3 the second half of the line does not diverge at  
4 all, and one dose is almost perfectly parallel, and  
5 the other dose begins to look like it's converging.  
6 So I'm not really convinced that slopes truly  
7 diverge in phase 1.

8 DR. FOUNTAIN: I would just make the comment  
9 that it seems to me, following up on what Dr. Todd  
10 said, that if you had more datapoints in phase 1,  
11 of course, you'd have greater resolution to know  
12 when the upswing occurs, so you could define the  
13 slope better, because defining a slope with two  
14 points is risky at best, I should think. And the  
15 same, of course, would apply to later, although  
16 more than more points later, I guess I'd rather  
17 like more time later if you assume that the lines  
18 are going to diverge.

19 So to summarize for Question 2, non-  
20 linearity of slopes, we just talked about that,  
21 whether it's linear or not. Maybe it matters or  
22 maybe it doesn't, but there seem to be other

1 issues. The re-analysis slopes without early data,  
2 suggesting parallel slopes in phase 1 for drug and  
3 placebo are similar. And we might even overlay to  
4 say, if it's not linear, the group seems to say,  
5 that's okay, we can find another way to analyze it,  
6 ultimately, as long as we know what it is.

7 Then potentially significant baseline  
8 differences in UPDRS seem important, although, I  
9 guess we haven't really discussed what implication  
10 that might have for future studies. Does that  
11 imply that UPDRS should be more narrowly defined at  
12 a higher level for future studies, if we're  
13 assuming that it works? At least, in this case,  
14 neuroprotection, or preventing disease progression,  
15 differentially affected those with higher UPDRS  
16 scores. Should you enrich the population by higher  
17 UPDRS scores?

18 Dr. Rosenberg?

19 DR. ROSENBERG: Well, the limits, you can  
20 probably measure it better on sicker patients, but  
21 it's more important to be doing neuroprotection as  
22 early as possible. So I would be inclined to try

1 to do it as early as possible, and just guts it  
2 out, and enroll more patients or follow them longer  
3 if you need to.

4 DR. FOUNTAIN: Ms. Christensen?

5 MS. CHRISTENSEN: Yes. I would just ask  
6 that the modified UPDRS be used instead of the one  
7 that doesn't offer family and patient input.

8 DR. FOUNTAIN: Thank you.

9 In regard to D, differential response in men  
10 and women, we don't seem to be able to make any  
11 sense of that in any consistent way, since it's  
12 different in different groups.

13 Dr. Ellenberg?

14 DR. ELLENBERG: I've seen a lot of studies  
15 that showed what appeared to be very substantial  
16 subset effects like this, where all the effects in  
17 women -- and maybe even goes the other way -- is  
18 harmful in men, or some other subgroup. And it's  
19 not unusual if a second study is done based on  
20 that, to find that there's no difference  
21 whatsoever, or to find other studies. People look  
22 at other studies to see similar drugs in similar

1 populations, and they don't find it. I've seen  
2 this -- of course, I haven't worked in this area,  
3 but I've seen it in cancer studies. I've seen it  
4 in AIDS studies. It's not so unusual.

5           So while, certainly, the response score is  
6 one where you might have a lot of basis to believe  
7 that it might have some impact, the gender issue is  
8 puzzling. And I certainly wouldn't hang my hat on  
9 that without having a substantial replication of  
10 that kind of finding. I think it's more -- it's  
11 not so unlikely as you might think to simply be a  
12 chance finding.

13           DR. FOUNTAIN: That makes sense. So in  
14 terms of -- Dr. Katz?

15           DR. KATZ: Yes. Just to sort of respond to  
16 that, we see that, too. I think when you cut the  
17 data, dichotomize the data in many, many, many  
18 ways, sometimes you find these things and that  
19 they're not replicated here.

20           What caught our attention was that it was in  
21 the women who had significant baseline differences.  
22 And I think that raised the question of what are we

1 dealing with here?

2 DR. ELLENBERG: Right. So is it gender, or  
3 is it -- which is the important variable?

4 DR. KATZ: Yes.

5 DR. ELLENBERG: Or is all of that just  
6 a -- it still could also be a fluke.

7 DR. KATZ: Yes. And wherever else we  
8 looked, in 2 milligrams, where there's no  
9 difference, there were no baseline differences  
10 between men and women. So I think it was that  
11 fact, not so much what appeared to be all the  
12 effect coming from women. It was that all the  
13 effect appeared to be coming from women and they  
14 had significant baseline differences, whereas the  
15 men didn't anywhere.

16 DR. FLEMING: And, in fact, I tried to make  
17 a similar point. I agree with Dr. Ellenberg that  
18 there's a great risk, that when you slice and dice,  
19 you'll see things at random. It was the aspect  
20 that the women were the ones that when you had the  
21 Hypothesis 2/3 subgroup, that was so imbalanced at  
22 baseline, and that's what's driving the signal.

1 And I couldn't walk away from as irrelevant.

2 But I agree with everybody who says, be  
3 cautious about that. But that's exactly the same  
4 principle, though, when you should say, but be  
5 cautious about a post hoc analysis that says, we'll  
6 explain why the 2-milligram group didn't work  
7 because we'll look at quadrants.

8 We have skillful statisticians. We can make  
9 a case. If our goal is to establish a treatment as  
10 effective and we're allowed to explore the data, I  
11 guarantee you we'll succeed. But our goal should  
12 be to determine whether a treatment is effective.  
13 And that argument -- that's fundamentally different  
14 because under that argument, you're going to look  
15 for things that weaken as well as strengthen the  
16 case.

17 So while we shouldn't make too much of  
18 gender because it's post hoc, we should be cautious  
19 about explaining away the primary analysis of no  
20 2-milligram difference or the fact that the primary  
21 analysis, at 1 milligram, wasn't significant, but  
22 if you find interactions, you can do another

1 analysis to help the p value. Same principle.

2 DR. FOUNTAIN: That does make sense.

3 Following up on that, then, is the sponsor  
4 conducted analyses that differ from those specified  
5 in the protocol. Our general consensus seems to be  
6 that it's important it was specified. But what the  
7 real risk is, that it is analyzed in many different  
8 ways, looking for something positive. Even if that  
9 wasn't what was done, that is the risk that happens  
10 in post hoc analysis. And unless someone else has  
11 an opinion, it seems to be the consensus opinion.

12 Now, to an actual voting question. Question  
13 number 3, does ADAGIO provide compelling evidence  
14 that the 1-milligram dose of rasagiline met the  
15 protocol-specified criteria for success? Comments  
16 about this? And I guess looking at the specific  
17 wording here, "compelling evidence of the protocol-  
18 specified criteria for success" is the important  
19 part here, as we talked about the generality.

20 Dr. Clancy, first?

21 DR. CLANCY: So, actually, if this study had  
22 been done at a single dose, that they wanted to do

1 the 1-milligram first, and then next year do the  
2 2-milligram, or whatever, in looking at the data, I  
3 would be very interested in voting yes for this.  
4 But, in a sense, we almost can't vote for this in  
5 isolation, because we know other things.

6 So if this was a situation where the  
7 1-milligram almost reached significance, just a few  
8 little points off, and the 2 milligrams was a dead  
9 ringer on, then I might be willing to think that  
10 the 1 milligram truly is just underpowered,  
11 something like that. But in real practice, what  
12 this is going to mean is the doctor's going to say,  
13 here's a 1-milligram dose of this medication. It's  
14 neuroprotective, but please don't take the second  
15 because you lose your neuroprotection. And that's  
16 not common sense.

17 So I would actually -- in isolation, I might  
18 vote yes for this, but knowing the whole story, I  
19 find a hard time to do that.

20 DR. FOUNTAIN: Dr. D'Agostino?

21 DR. D'AGOSTINO: My comment is very similar.  
22 It's hard to divorce this from the full study, and

1 this protocol specified, as one of my colleagues  
2 have said over here, is once you've stated in the  
3 protocol and you don't stay with it, then it's very  
4 hard to understand what the results are.

5 I asked earlier in the day if, when they  
6 decided to split the two up because of the  
7 interaction, did they have a discussion with the  
8 FDA, and evidently, they did not. So this  
9 compelling evidence and protocol specified is  
10 really a very, well, powerfully worded statement  
11 that makes it very hard to, I think, separate the  
12 individual components that we saw.

13 DR. FOUNTAIN: We can consider it any way we  
14 like, in isolation or in other contexts, by what  
15 you feel is appropriate.

16 Dr. Black?

17 DR. BLACK: Yes. I have a question to  
18 clarify. I wanted to clarify something about this  
19 particular question. Dr. Massie mentioned that the  
20 test of Hypothesis 1 in the 1-milligram data was  
21 only supposed to proceed if there was evidence for  
22 linearity, if I understood correctly.

1           Is that something that was in the written  
2 analysis plan, the final one that was supposed to  
3 be done with the data?

4           DR. FOUNTAIN: Dr. Massie, if you're able to  
5 comment, that's okay; otherwise, we'll ask the  
6 sponsor.

7           DR. MASSIE: I think they can answer.

8           DR. DARKEN: Because the trial was not  
9 designed to look at linearity, to even look at  
10 Hypothesis 1, there was only those three visits,  
11 and when this came along later, there was a pre-  
12 specified test for linearity, for Hypothesis 3,  
13 where there were a lot of visits, but there was not  
14 a pre-specified test to look at linearity for  
15 Hypothesis 1 because what are we going to do? We  
16 didn't really have a choice.

17           DR. FOUNTAIN: Dr. Frank?

18           DR. FRANK: If this question was, does  
19 ADAGIO provide compelling evidence that the 1- and  
20 2-milligram doses are safe, I think we all would  
21 agree that the answer is yes. Does it provide  
22 compelling evidence that the 1- and 2-milligram

1 doses are effective in treating symptoms? I think  
2 we would all also say yes, but not so much for the  
3 question at hand.

4 So I think that there's a lot of hesitation,  
5 and I think it's an important question, as it  
6 really does change the way research will be done in  
7 the future for Parkinson's disease, because it will  
8 be very ethically difficult to do a placebo-  
9 controlled trial if we say that, yes, it does.

10 DR. FOUNTAIN: I think another way to look  
11 at this would be to look at it in isolation. So if  
12 you just look at the graph of data analysis, just  
13 the data for compelling evidence for the  
14 1-milligram dose, and if you accept the modified  
15 protocol, I could imagine saying, yes, because  
16 we've said, if you just look at it in isolation and  
17 not worry about the other things, if you accept the  
18 fundamental premise that either you accept the  
19 original hypothesis or that there wasn't an  
20 adequate ability to address the later hypothesis,  
21 because you only had three visits, for instance,  
22 for Hypothesis 1, then I could see how you'd look

1 at the graph that reflects the data from the  
2 1-milligram dose and say, this is a positive study.

3 So, in isolation, I could see how that could  
4 be the case, in isolation. So that can be  
5 equivocated in a lot of different ways, but I'd say  
6 we have to come back to considering that.

7 Dr. D'Agostino?

8 DR. D'AGOSTINO: But how are we supposed to  
9 look at this? I mean, I'm taking this as there's a  
10 submission that has two doses in it and that's the  
11 package. And the analysis was directed at that, to  
12 try to separate out this one component, which I  
13 have no problem with following your logic, except  
14 that when they've tried to give an answer to it, 2  
15 keeps coming back, and it's driven by the fact that  
16 they did split the data up because of the  
17 interaction test, and they got their nice results.  
18 But it's not what's happened to the full set of  
19 data.

20 DR. FOUNTAIN: I agree.

21 Dr. Khatri?

22 DR. KHATRI: I just want to clarify what you

1 were saying, Dr. Fountain. What I understand here  
2 is that the pre-specified analysis was not  
3 significant for 1 milligram. The p value was  
4 .0506, and it needed to be less than .0250. And  
5 also what I understood was that if we went with the  
6 original hypothesis, when they had just the two  
7 hypotheses, it still wouldn't have been positive  
8 with 1 milligram at that .025 threshold.

9 Do I have that right, from the FDA  
10 presentation?

11 DR. FOUNTAIN: Dr. Massie or Dr. Katz, can  
12 you answer that; or the sponsor?

13 DR. FITZER-ATTAS: Can we put the slide on  
14 from the core, which shows the three analyses for  
15 endpoint 2, just to clarify that?

16 In any case, the original analysis for which  
17 the study was designed had a point estimate of 1.4  
18 and a p value that I believe was .01 something, if  
19 I'm not correct. So that was, according to, again,  
20 what the study was powered for and what we  
21 originally agreed upon with the FDA.

22 DR. KATZ: Are you asking about

1 Hypothesis 2, the original Hypothesis 2?

2 DR. FITZER-ATTAS: Yes.

3 DR. KHATRI: I was asking about the fact  
4 that the design had not been -- or the hypothesis  
5 had not been revised from two to three hypotheses,  
6 and the original power had been there. My  
7 impression was, at 1 milligram, this would still  
8 not have been statistically significant. But  
9 perhaps I have this wrong.

10 DR. KATZ: Well, I think you have the answer  
11 that's --

12 DR. FITZER-ATTAS: The third column there is  
13 the original statistical analysis plan, and that  
14 was less than the .025 criteria.

15 DR. KATZ: I would just point out that I  
16 don't think we did a detailed analysis of that  
17 particular endpoint, since the endpoint, we  
18 believed and ultimately had agreement I believe  
19 from the company, was it would be the week 72, what  
20 we've been discussing as the second endpoint.

21 So we didn't really review that .012, the  
22 analysis that led to the p value of .012.

1 DR. FOUNTAIN: Dr. Fleming?

2 DR. FLEMING: So I think it's FDA slide 13  
3 that answers the question. I don't know if you  
4 have that at your fingertips. The original SAP is  
5 not an operative issue here; it's what's the SAP  
6 that's in place at the time you unblind the data.  
7 That's the issue. So that third line is a smoke  
8 screen, the third column.

9 These are the data, as I understand them,  
10 which is what you were saying. The data, according  
11 to the primary analysis, even at 1 milligram,  
12 needed to have an 025 p value, and it was 0506.  
13 Now, p values should not be viewed as black and  
14 white, if you make it you win, if you lose, you  
15 don't, because there is, certainly, as somebody  
16 said before, a signal here.

17 There is a signal here. It's the totality  
18 of the data, though, as well. And, generally, if  
19 it's a single study that's a standalone trial, that  
20 effectively it is, it's robust and compelling. And  
21 many of us would argue that the 0250 p value isn't  
22 the right target for a single standalone trial. It

1 would be something lower than that.

2 But, fundamentally, the pre-specified  
3 analysis, as the SAP indicated, that was intact at  
4 the time the trial was unblinded, which is the  
5 operative SAP, said it had to be 0.25, and it was  
6 0.0506. So not only did the 2 milligram completely  
7 miss, the 1 milligram was a signal, was a trend,  
8 but didn't formally hit even what I call strength  
9 of evidence at one trial significance.

10 DR. FOUNTAIN: So the consensus opinion  
11 seems to be that it's certainly not robust, and  
12 this question is, is it compelling. And your  
13 argument is no because that p value's not really  
14 there, even though it might be a signal, it might  
15 be --

16 DR. FLEMING: I would hope we would look at  
17 much more than the p value.

18 DR. FOUNTAIN: Right.

19 DR. FLEMING: But the primary analysis or  
20 the primary endpoint is at least the one p value  
21 that I can interpret, everything else -- yet, in  
22 those sampling contexts, everything else should be

1 viewed with great caution.

2 DR. FOUNTAIN: Ms. Christensen?

3 MS. CHRISTENSEN: I just want to clarify  
4 something. Is it correct that this labeling that  
5 the sponsor is asking for has not been done before  
6 and would be setting a precedent?

7 DR. FOUNTAIN: I believe that's correct.

8 MS. CHRISTENSEN: Yes.

9 DR. KATZ: It's certainly true in our area.  
10 I can't speak for other areas that the agency deals  
11 with, but in neurology, this would be the first.

12 MS. CHRISTENSEN: Yes. That was my  
13 understanding, and I guess unfortunately for the  
14 sponsor, in my mind, them being first, I feel that  
15 the data have to be much more robust than they are.

16 DR. FOUNTAIN: All right. Any more  
17 questions or comments before voting?

18 [No response.]

19 DR. FOUNTAIN: If there's no further  
20 discussion on this question, we'll now begin the  
21 voting process. Once your microphone begins  
22 flashing, then please press the button on your

1 microphone that corresponds to your vote. It'll  
2 continue flashing until we stop it, even after you  
3 vote.

4 [Vote taken.]

5 DR. FOUNTAIN: Can we see the votes on the  
6 screen? Everyone has voted. The vote is now  
7 complete. Zero yeses, 17 nos, zero abstain, and  
8 zero no-voting.

9 Now that the vote is complete, we'll go  
10 around the table and have everyone who voted state  
11 their name, vote, and reason that they voted the  
12 way they did, if they wish to, into the record.

13 Can we start?

14 DR. D'AGOSTINO: Any order?

15 DR. FOUNTAIN: Well, why don't we go around  
16 the room. Our vote can't change because it's  
17 displayed on the screen here, and we know everyone  
18 was in there.

19 Why don't we start with Dr. Zivin? If  
20 you'll state your name and your vote, and if you  
21 wish, why you voted. If you'll turn on your  
22 microphone.

1 DR. ZIVIN: Justin Zivin, and I voted no  
2 because of the fact that the results were simply  
3 not compelling. That was the summary of the  
4 arguments that I heard everybody make, and the vote  
5 was unanimous, and I think that that was  
6 justifiable.

7 DR. KHATRI: Pooja Khatri. I voted no. I  
8 think the data are promising, but they're just not  
9 compelling. And I think it's just too much of a  
10 risk for -- it's crucial that there be compelling  
11 data for us to really move forward, and it's just  
12 not compelling.

13 DR. FLEMING: Fleming. I voted no for  
14 reasons that were articulated in my comments for  
15 Question 2, but also my colleagues' comments in  
16 discussing Questions 2 and 3.

17 DR. D'AGOSTINO: D'Agostino. I voted no. I  
18 think the data is consistent with disease-modifying  
19 effect for the one, but I think that it's just not  
20 compelling for reasons given previously.

21 DR. ELLENBERG: Ellenberg. I voted no, and  
22 I don't have anything to add to previous comments.

1 DR. ZHAO: Hongyu Zhao. I voted no for the  
2 reasons that have been discussed.

3 DR. MARDER: Ellen Marder. I vote no for  
4 all reasons discussed.

5 MS. CHRISTENSEN: Jacqueline Christensen. I  
6 vote no for the reasons I presented right before we  
7 voted.

8 DR. CLANCY: Robert Clancy. I also voted no  
9 for the reasons cited. But also just to comment  
10 that if this is really going to be the flagship of  
11 neuroprotection or disease modification, I think we  
12 have to be very solid in this and set a very high  
13 standard. If we are wishy-washy with this, then  
14 the next thing that comes around, they're going to  
15 be expecting being close is good enough. And this  
16 is close, but it's not good enough.

17 DR. FRANK: Samuel Frank. I voted no.

18 DR. FOUNTAIN: Nathan Fountain. I voted no  
19 for the reasons mentioned before, particularly  
20 Dr. Clancy's suggestion to meet a high bar and  
21 because I'd like to see some corroborative  
22 evidence.

1 DR. TODD: Jason Todd. No.

2 DR. RODNITZKY: Robert Rodnitzky. I voted  
3 no because I thought the evidence was not  
4 compelling.

5 DR. BLACK: My name is Kevin Black. I was  
6 somewhat ambivalent, I think. I voted no, largely  
7 because the question as carefully worded described  
8 a very specific bar that, as it was pointed out,  
9 wasn't quite met with the data.

10 DR. AHLKOG: Eric Ahlskog. I voted no. In  
11 medical science, things have to make sense, and  
12 they have to be consistent. Thank you.

13 DR. HINSON: Vanessa Hinson. I voted no for  
14 the reasons outlined by others, and I agree with  
15 Dr. Clancy. We have to set the bar high. And the  
16 public health ramifications here and the cost  
17 associated with the drug are very high.

18 DR. ROSENBERG: I'm Paul Rosenberg. I voted  
19 no. I thought the evidence was not compelling  
20 because the primary analysis did not achieve  
21 statistical significance, and I was unconvinced by  
22 the change in datasets.

1 DR. FOUNTAIN: Everyone has read their vote  
2 into the record. Now, we'll proceed to the next  
3 question.

4 The 2-milligram dose failed to show a  
5 differential effect between the early and delayed  
6 starters at the end of the study. The sponsor has  
7 offered some explanations. For example, patients  
8 in the worst quartile at baseline UPDRS scores  
9 seemed to have a better response than other  
10 patients.

11 The question is, did the 2-milligram group  
12 fail to meet the protocol-specified criteria for  
13 success? So first we'll have discussion and then  
14 voting.

15 Does anyone have any comments?

16 DR. FOUNTAIN: I guess I can make the  
17 comment that there seems to be consensus that the  
18 2-milligram dose didn't meet the study endpoint.

19 Anyone have any comments?

20 DR. AHLKOG: A yes vote is really a no  
21 vote?

22 DR. KATZ: Yes, that's right.

1 DR. FOUNTAIN: Yes. It means you agree with  
2 the question.

3 DR. KATZ: If you think that it didn't meet  
4 the criteria, you vote yes. We'll figure it out.

5 [Laughter.]

6 DR. FOUNTAIN: Any discussion?

7 [No response.]

8 DR. FOUNTAIN: All right. If there's no  
9 further discussion on this question, we'll now  
10 begin the voting process. Please press the button  
11 on your microphone that corresponds to your vote.

12 [Vote taken.]

13 DR. FOUNTAIN: Everyone has voted, and the  
14 vote is now complete. We have 17 yeses and zero  
15 nos, zero abstain, and zero no-voting. Now that  
16 the vote is complete, we'll go around the table and  
17 have everyone who voted state their name, vote, and  
18 if they wish, the reason that they voted into the  
19 record.

20 Let's start at this side this time, with  
21 Dr. Rosenberg.

22 DR. ROSENBERG: I voted yes. I saw very

1 little evidence, really no evidence, that the  
2 2-milligram dose worked.

3 DR. HINSON: I voted yes for the reasons we  
4 discussed earlier. Vanessa Hinson.

5 DR. AHLKOG: Eric Ahlskog. I voted yes,  
6 which is really no.

7 [Laughter.]

8 DR. BLACK: Kevin Black. Yes.

9 DR. RODNITZKY: Robert Rodnitzky. Yes.

10 DR. TODD: Jason Todd. Yes.

11 DR. FOUNTAIN: Nathan Fountain. Yes.

12 DR. FRANK: Samuel Frank. Yes.

13 DR. CLANCY: Robert Clancy. Yes.

14 MS. CHRISTENSEN: Jacqueline Christensen.

15 Yes.

16 DR. MARDER: Ellen Marder. Yes.

17 DR. ZHAO: Hongyu Zhao. Yes.

18 DR. ELLENBERG: Susan Ellenberg. Yes. But  
19 I would like to say that I appreciated the attempts  
20 that the sponsor made to try and look at the  
21 possible reasons, and I think it may be helpful in  
22 future research.

1 DR. D'AGOSTINO: D'Agostino. Yes.

2 DR. FLEMING: Fleming. Yes.

3 DR. KHATRI: Pooja Khatri. Yes.

4 DR. ZIVIN: Justin Zivin. Yes.

5 DR. FOUNTAIN: All right. That moves us to  
6 the next question, to Question 5. The question is,  
7 has the sponsor provided substantial evidence of  
8 effectiveness for rasagiline as a treatment to  
9 delay clinical disease progression in patients with  
10 Parkinson's disease?

11 Dr. Black?

12 DR. BLACK: I just have a question. So  
13 there are a couple of questions I wanted to ask  
14 that I think pertain only to this question and not  
15 to the others.

16 Is this an appropriate time?

17 DR. FOUNTAIN: Yes. This is the time for  
18 discussion.

19 DR. BLACK: First of all, the article by  
20 Leber in which he described this design discussed  
21 also the FDA's not generally requiring external  
22 validity indicators, in other words, how widely the

1 results might apply.

2 I am curious whether the FDA has a position  
3 on whether this -- and I understand this is an  
4 issue for every drug, for every indication, because  
5 clinical study samples are almost always non-  
6 representative. But my question is whether you  
7 have a position on whether there's a difference in  
8 that question, in the case of an indication for  
9 changing disease progression, for instance, in  
10 people with early Parkinson's disease, or in people  
11 with UPDRS total scores over 25, or things like  
12 that.

13 DR. KATZ: Personally, I don't think there's  
14 a fundamental difference. As you say, all clinical  
15 trial samples are highly skewed and highly  
16 unrepresentative of the universe of people with  
17 that particular condition.

18 So I don't -- whether or not the conditions  
19 of study would be reflected in the labeling for a  
20 disease modifier, possibly -- they usually are for  
21 routine treatments. But I personally don't think,  
22 fundamentally, that we would apply a different sort

1 of approach about representativeness of a sample  
2 for a disease modifier, as compared to, let's say,  
3 a symptomatic treatment.

4 DR. BLACK: The other question is whether  
5 the issue of unmet need is relevant to this, to  
6 Question 5.

7 DR. FOUNTAIN: Can you clarify that?

8 DR. KATZ: It's not relevant in the sense of  
9 you still have to have substantial evidence of  
10 effectiveness. Now, an unmet medical need, which  
11 is specific statutory language that talks about  
12 fast-track drugs, you can contemplate, for example,  
13 the approval of a drug based on an invalidated  
14 surrogate marker to fulfill an unmet medical need.  
15 But you still have to substantial evidence of  
16 effectiveness for that surrogate marker.

17 So the requirement for substantial  
18 evidence -- and, again, it is the one-study  
19 standard, the two-study standard, but whichever  
20 standard you apply, substantial evidence has to be  
21 met regardless of need, or orphan status, or  
22 anything like that.

1 DR. BLACK: Right, right. I would offer a  
2 comment, which is that I agree that it's important  
3 to have a drug whose labeling indicates that it's  
4 effective for disease progression slowing, if there  
5 is such a drug. But I think it's important to  
6 recognize, in Parkinson's disease, that although  
7 there's substantial disagreement on this -- it was  
8 just discussed in Neurology I think this month, in  
9 two editorials.

10 Did you write one, Professor? Yes. I  
11 thought so.

12 Anyway, but there is convergent evidence in  
13 humans, I would say, that L-DOPA actually slows the  
14 progression of Parkinson's disease, both from the  
15 DATATOP study, the L-DOPA study modeling from John  
16 Nutt and his collaborators.

17 So the fact that that has a different side  
18 effect profile from the drug we're considering and  
19 maybe others that come up in the future is an  
20 important issue. I wouldn't argue with that, but I  
21 don't think anybody's going to pursue the expense  
22 necessary to try to seek an FDA indication for that

1 use of L-DOPA. But I think it's an issue that has  
2 to be considered when you take into account what's  
3 available for treatment.

4 DR. FOUNTAIN: So then you really don't like  
5 my idea of maximum symptomatic therapy in  
6 selegiline, which has lots of other problems, I'm  
7 sure.

8 Ms. Christensen?

9 MS. CHRISTENSEN: Yes. I just wanted to add  
10 to Dr. Black's comments that I think -- with the  
11 sponsor's submission, I just don't know if this  
12 would be worth the money that's been invested,  
13 since we don't know -- even if we agreed that it  
14 slowed disease progression, for how long? I mean,  
15 I think the study is too short. I don't know how  
16 you'd get us to participate in longer ones. I  
17 can't answer that.

18 DR. FOUNTAIN: Dr. Rosenberg?

19 DR. ROSENBERG: In Alzheimer's disease,  
20 there are several multi-year studies for similar  
21 purposes, delaying progression of mild cognitive  
22 impairment to Alzheimer's, differences. There are

1 absolutely no -- I'm sorry. There are FDA-approved  
2 symptomatic treatments which are so mildly  
3 effective that people aren't too worried about them  
4 confounding. But people have participated in such  
5 long studies.

6 DR. FOUNTAIN: Dr. Clancy?

7 DR. CLANCY: So we've heard repeatedly that  
8 there seems to be a signal out there, that this is  
9 not totally random, that in the TEMPO study and in  
10 the 1 milligram, there may well be some protective  
11 effects.

12 So at least I am comforted by the knowledge  
13 that this drug, which is approved for symptomatic  
14 amelioration of symptoms, might secretly be doing  
15 some neuroprotection in some subsets of patients,  
16 even though we can't demonstrate it consistently  
17 across all the patient strata.

18 DR. FOUNTAIN: Other comments, questions,  
19 before we vote on the final question?

20 Dr. Ellenberg?

21 DR. ELLENBERG: I remain skeptical about  
22 this, the ability of this design. It sounds

1       like -- I mean, really, it's very hard to  
2       distinguish between doing something with symptoms  
3       and seeing whether you're modifying the disease  
4       without some way to measure. It's kind of ironic  
5       that in almost every other area, we're struggling  
6       to find markers that are surrogate endpoints for  
7       clinical outcomes. And here it's kind of the  
8       opposite. And given all of the problems, it  
9       wouldn't surprise me if somebody could come up with  
10      a hypothetical situation where everybody would  
11      believe it was disease modifying, but didn't meet  
12      the criteria, exactly, of this design.

13                 Given all of the problems with this, with  
14      this design, I think it was a very good job of  
15      taking this forward and doing the best that one  
16      can. I take the point that several people have  
17      made, both on this panel and in the audience, that  
18      this may be the best that we can do now. It just  
19      doesn't mean that it's good enough.

20                 DR. FOUNTAIN: Any more comments or  
21      discussion?

22                 [No response.]

1 DR. FOUNTAIN: If there is no further  
2 discussion on this question, we'll now begin the  
3 voting process. Please press the button on your  
4 microphone that corresponds to your vote.

5 [Vote taken.]

6 DR. FOUNTAIN: Everyone has voted. The vote  
7 is now complete, zero yeses, 17 nos, zero abstains,  
8 and zero no-voting. Now that the vote is complete,  
9 we'll go around the table and have everyone who  
10 voted state their name, their vote, and if they  
11 wish to, the reason that they voted this way into  
12 the record.

13 Let's start with Dr. Zivin again.

14 DR. ZIVIN: Justin Zivin. I voted no. I  
15 believe that the drug does show signs of  
16 symptomatic effect in this, for which it is already  
17 approved. But the higher bar is whether it does  
18 anything for disease modification. And,  
19 unfortunately, it didn't meet that standard, at  
20 least under the circumstances that were shown to us  
21 today.

22 DR. KHATRI: Pooja Khatri. I voted no.

1 DR. FLEMING: Fleming. I voted no for  
2 reasons given earlier.

3 DR. D'AGOSTINO: D'Agostino. No. I think  
4 that there is a very strong signal in the data, but  
5 the full package leaves many, many questions.

6 DR. ELLENBERG: Ellenberg. No, for reasons  
7 just stated.

8 DR. ZHAO: Hongyu Zhao. No.

9 DR. MARDER: Ellen Marder. No.

10 MS. CHRISTENSEN: Jacqueline Christensen.  
11 No.

12 DR. CLANCY: Robert Clancy. No.

13 DR. FRANK: Samuel Frank. No. And I will  
14 continue to prescribe this medication because it is  
15 safe. It is an effective medication. And I think  
16 that there is an interesting signal here, but just  
17 not enough compelling evidence to show disease  
18 modification.

19 DR. FOUNTAIN: Nathan Fountain. No. And  
20 sort of analogous to that, I would feel that the  
21 evidence we've seen so far, though, if there were  
22 another well-done randomized controlled study at

1 1 milligram that demonstrated protocol-specified  
2 results, that this would be supportive of that in  
3 the usual manner of two well-controlled studies.

4 DR. TODD: Jason Todd. No.

5 DR. RODNITZKY: Robert Rodnitzky. I voted  
6 no. And to reiterate what others have said, the  
7 bar has been set very high, appropriately, and I  
8 think the sponsors are to be commended for taking a  
9 large leap at this bar. And, unfortunately, to  
10 complete the analogy, they hit the bar with their  
11 trailing toe.

12 DR. BLACK: Kevin Black. I voted no. I  
13 think for this question that lots of other factors  
14 come into play, such as the difference in the  
15 results in the 2-milligram group, even if that's  
16 not the question about the indication.

17 DR. AHLKOG: Eric Ahlskog. I take no  
18 pleasure in voting no on a very important subject,  
19 but I feel I have no alternative.

20 DR. HINSON: Vanessa Hinson. I voted no.

21 DR. ROSENBERG: Paul Rosenberg. I voted no.

22 DR. FOUNTAIN: That completes the voting.

1           Are there any other comments from the FDA,  
2           Dr. Katz, or anyone on the panel?

3           DR. KATZ: I'd like to thank the committee,  
4           and I think it is a very difficult issue, very  
5           complex. Your recommendations are very clear. I  
6           thank you for serving as acting chair. That's not  
7           an easy job.

8           I'd also like to thank the agency's review  
9           team, who did a tremendous amount of work. I  
10          didn't do any of that work, so I can say that. And  
11          I'd also like to thank the company because we had  
12          many discussions. This study was conducted very  
13          well. It was a complicated study, as you've heard.  
14          Keeping patients in this study is very difficult.  
15          It was a state-of-the-art study. But I understand  
16          that today's vote isn't one that the company is  
17          happy with, undoubtedly, but I think the company  
18          did a tremendous job in getting this study done.

19          DR. FOUNTAIN: Thank you. I thank all the  
20          panel members for coming.

21          DR. UNGER: I just want to add a couple  
22          comments to what Dr. Katz said. I mean, this is a

1       devastating disease, and you dealt with some very  
2       complicated issues.  And, actually, I'd like to  
3       commend the company for taking two doses into this  
4       study, because we always try to convince companies  
5       to study more than one dose.  And it's often very  
6       difficult to get them to take our advice.

7                Again, I'd just like to also thank the  
8       committee and the public speakers.  I think we had  
9       a very thoughtful discussion, the statisticians and  
10      the clinicians, and we're very grateful to have  
11      everybody's participation.  Thanks.

12                               **Adjournment**

13               DR. FOUNTAIN:  I'd also like to express my  
14      thanks to the panel members, who have been so good  
15      today about making my job easy.  Please remember to  
16      drop off your name badge at the registration table  
17      on your way out, so that they may be recycled.  
18      Thank you, and the meeting is adjourned.

19               (Whereupon, at 4:23 p.m., the meeting was  
20      adjourned.)

21

22