1 FOOD AND DRUG ADMINISTRATION

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6 CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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8 THURSDAY, JULY 29, 2010

9 8:00 a.m. to 4:15 p.m.

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13 Marriott Conference Centers, University of Maryland

14 University College Inn and Conference Center

15 3501 University Boulevard East

16 Adelphi, MD

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5 Department of Internal Medicine
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7 New York, New York
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11 Mount Sinai School of Medicine
12 Director, Cardiology Clinical Services
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14 Institute and the Marie-Josée and Henry R. Kravis
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8 **Industry Representative (Non-Voting)**
9 Enrico P. Veltri, M.D. (Acting Industry
10 Representative)
11 Industry Representative
12 Pharmaceutical Industry Consultant
13 Princeton, New Jersey
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15 **Temporary Voting Members**
16 Allan Coukell, BscPharm. (Acting Consumer
17 Representative)
18 Director, The Pew Prescription Project
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1 **FDA (Non-Voting)**

2 Robert Temple, M.D.

3 Director of the Office of Medical Policy

4 Director, Office of Drug Evaluation I

5 CDER

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7 Norman Stockbridge, M.D.

8 Director, Division of Cardiovascular and

9 Renal Drug Products

10 CDER

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1 I N D E X

1 I N D E X (continued)

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

2 (8:00 a.m.)

3 DR. KAUL: Good morning, welcome. I'd like
4 to call the meeting to order. My name is Sanjay Kaul.
5 I am the acting chair for the Cardio-Renal Drug
6 Advisory Committee today. I'm a cardiologist at
7 Cedars-Sinai Heart Institute in Los Angeles.
8 I'd like to introduce the committee today,
9 starting from the FDA end.
10 DR. STOCKBRIDGE: Good morning. My name is
11 Norman Stockbridge. I'm the Director of the Division
12 of Cardiovascular and Renal Products at FDA.
13 DR. VENITZ: Jurgen Venitz, clinical
14 pharmacologist, Virginia Commonwealth University.
15 DR. NEWMAN: I'm John Newman, pulmonary and
16 critical care medicine at Vanderbilt University.
17 DR. HALPERIN: Jonathan Halperin, a
18 cardiologist at the Mount Sinai Medical Center in New
19 York.
20 DR. BLACK: I'm Henry Black. I'm a
21 preventative cardiologist at New York University and a
22 systemic hypertension specialist.

1 DR. RICH: Stuart Rich, cardiologist,
2 University of Chicago.
3 DR. NEATON: Jim Neaton, biostatistician,
4 University of Minnesota.
5 MS. FERGUSON: Elaine Ferguson, Designated
6 Federal Official.
7 DR. KRANTZ: Good morning. Mori Krantz,
8 University of Colorado in Denver.
9 MR. COUKELL: Good morning. Allan Coukell,
10 I'm a pharmacist at the Pew Charitable Trusts and the
11 acting consumer representative.
12 DR. D'AGOSTINO: Ralph D'Agostino,
13 biostatistician from Boston University and the
14 Framingham Study.
15 DR. MCGUIRE: Darren McGuire, general
16 cardiology, University of Texas Southwestern in
17 Dallas.
18 DR. KAWUT: Steve Kawut, I'm a pulmonologist
19 at the University of Pennsylvania.
20 DR. ROSENTHAL: Good morning. I'm Geoff
21 Rosenthal. I'm a pediatric cardiologist at the
22 University of Maryland, and I'm a member of the

1 Pediatric Advisory Committee at the FDA.

2 DR. VELTRI: Ric Veltri, cardiologist,

3 industry representative.

4 DR. KAUL: Thank you.

5 For topics such as those being discussed at

6 today's meeting, there are often a variety of

7 opinions, some of which are quite strongly held. Our

8 goal is that today's meeting will be a fair and open

9 forum for discussion of these issues and that

10 individuals can express their views without

11 interruption. Thus, as a gentle reminder, individuals

12 will be allowed to speak into the record only if

13 recognized by the chair. We look forward to a

14 productive meeting.

15 In the spirit of the Federal Advisory

16 Committee Act and the Government in the Sunshine Act,

17 we ask that the advisory committee members take care

18 that their conversations about the topic at hand take

19 place in the open forum of the meeting.

20 We are aware that members of the media are

21 anxious to speak with the FDA about these proceedings.

22 However, FDA will refrain from discussing the details

1 of this meeting with the media until its conclusions.
2 Also, the committee is reminded to please refrain from
3 discussing the meeting topic during breaks or lunch.
4 Thank you. At this point, I'd like to call
5 upon Elaine Ferguson to deliver the conflict of
6 interest statement. Elaine?
7 MS. FERGUSON: The Food and Drug
8 Administration, FDA, is convening today's meeting of
9 the Cardiovascular and Renal Drug Advisory Committee
10 under the authority of the Federal Advisory Committee
11 Act of 1972. With the exception of the industry
12 representative, all members and temporary voting
13 members of the committee are special government
14 employees, SGEs, or regular federal employees from
15 other agencies and are subject to federal conflict of
16 interest laws and regulations.
17 The following information on the status of
18 the committee's compliance with federal ethics and
19 conflict of interest laws covered by, but not limited
20 to, those found at 18 U.S.C. Section 208 and Section
21 712 of the Federal Food, Drug, and Cosmetic Act, FD&C
22 Act, is being provided to participants in today's

1 meeting and to the public. FDA has determined that
2 members and temporary voting members are in compliance
3 with federal ethics and conflict of interest laws.
4 Under 18 U.S.C. Section 208, Congress has
5 authorized FDA to grant waivers to special government
6 employees and regular federal employees who have
7 potential financial conflicts when it is determined
8 that the agency's need for a particular individual's
9 services outweighs his or her potential financial
10 conflict of interest. Under Section 712 of the FD&C
11 Act, Congress has authorized FDA to grant waivers to
12 special government employees and regular federal
13 employees with potential financial conflicts when
14 necessary to afford the committee essential expertise.
15 Related to discussions of today's meeting,
16 members and temporary voting members have been
17 screened for potential financial conflicts of
18 interests of their own, as well as those imputed to
19 them, including those of their spouses or minor
20 children and, for purposes of 18 U.S.C. Section 208,
21 their employers. These interests may include
22 investments, consulting, expert witness testimony,

1 contracts, grants, CRADAs, teaching, speaking,
2 writing, patents and royalties, and primary
3 employment.
4 Today's agenda involves Revatio, sildenafil,
5 manufactured by Pfizer for the treatment of pediatric
6 pulmonary arterial hypertension and whether to amend
7 the clinical trial section of the written request
8 issued by FDA to Pfizer to include assessment of
9 hemodynamic, i.e., blood pressure and blood flow
10 endpoint. An area of particular interest will be what
11 the appropriate study endpoint should be in patients
12 with pediatric pulmonary arterial hypertension, PAH,
13 unable to perform exercise testing.
14 The discussion will help the agency
15 determine what studies to request for products
16 intended to treat pediatric PAH. This is a particular
17 matters meeting during which specific matters related
18 to Pfizer's Revatio, sildenafil, will be discussed.
19 To ensure transparency, we encourage all
20 standing committee members and temporary voting
21 members to disclose any public statements that they
22 have made concerning the products at issue.

1 With respect to the FDA's invited industry
2 representative, we would like to disclose that
3 Dr. Enrico Veltri is participating in this meeting as
4 a nonvoting industry representative acting on behalf
5 of regulated industry. Dr. Veltri's role at this
6 meeting is to represent industry in general and not
7 any particular company. Dr. Veltri is an independent
8 pharmaceutical industry consultant.
9 We would like to remind members and
10 temporary voting members that if the discussions
11 involve any other products or firms not already on the
12 agenda for which a FDA participant has a personal or
13 imputed financial interest, the participants need to
14 exclude themselves from such involvement and their
15 exclusion will be noted for the record. FDA
16 encourages other participants to advise the committee
17 of any financial relationships that they may have with
18 the firm at issue.
19 At this time, I'd like to recognize the FDA
20 press representative, Karen Mahoney. Thank you.
21 I would like to also inform the committee
22 that the patient representative e-mailed us on Monday

1 informing that she will not be able to attend today.
2 Thank you.
3 DR. KAUL: Thank you, Elaine.
4 At this point, I will call upon
5 Dr. Stockbridge to deliver his opening remarks and
6 provide us with some context behind this meeting and
7 highlight the core issues that the committee is
8 charged with to adjudicate today.
9 Dr. Stockbridge?
10 DR. STOCKBRIDGE: Good morning and thank you
11 to the committee for your work today. As Plato once
12 said, "And now for something completely different."
13 There are a number of things that are quite
14 different about this meeting than possibly any you've
15 ever attended, certainly any other cardio-renal
16 meeting. For one thing, there's no approval decision
17 at stake today. This is, in part, because the data
18 that relate to a particular development program have
19 not, in fact, been reviewed by FDA at this point.
20 So the question that you're going to have to
21 address with respect to those data is whether or not
22 they appear in a certain formal sense to be useful.

1 There is a proposal before you to reinterpret the data
2 that the sponsor has collected. That in itself isn't
3 particularly unusual.
4 What's unusual in this case is that the data
5 analyses and supporting material that support this
6 reinterpretation of the data come from the FDA, not
7 from the sponsor. It's not from the sponsor's
8 development program. That aspect of this has led to
9 an unusual degree of cooperation and coordination of
10 the presentations that you're going to hear in this
11 meeting.
12 There's an expectation that you'll be
13 probably fairly unfamiliar with the regulatory context
14 before you, so we're going to try to provide for you
15 today a coordinated presentation that will provide you
16 with the background that you need.
17 So the first speaker is going to be
18 Dr. Elizabeth Durmowicz from our pediatric team, who's
19 going to describe the pediatric written request
20 process for you. I will then provide a very brief
21 discussion of the sildenafil pediatric written request
22 and certain key aspects of it.

1 Dr. Robyn Barst, on behalf of the sponsor,
2 will then describe the relationship between pulmonary
3 arterial hypertension in adults and children. Then
4 FDA's Dr. Satjit Brar will describe the agency's work
5 to evaluate a surrogate endpoint that's being proposed
6 by us to bridge a drug from an approved use in adults
7 to an indication in children. And then finally, the
8 Pfizer team will describe their data from their
9 development program.
10 Despite the degree of cooperation that
11 appears in these presentations, there's a serious
12 matter before you and reasonable basis by which you
13 might disagree with what's being contemplated by the
14 agency. And the issues that you'll have to deal with
15 are, one, for the purpose that's being outlined, do
16 you think we have a validated surrogate here; and then
17 second, even if you do think that's true, do you
18 believe it's proper and reasonable for us to alter
19 Pfizer's pediatric written request to incorporate that
20 surrogate?
21 So with that as introduction, I think we're
22 ready to start.

1 DR. KAUL: Thank you, Dr. Stockbridge.

2 We have Dr. Durmowicz who is going to start

3 with the FDA presentations. And while she's walking

4 over to the podium, Dr. Temple, would you like to

5 introduce yourself?

6 DR. TEMPLE: Good morning, Bob Temple,

7 director, ODE I.

8 DR. DURMOWICZ: Good morning. I have the

9 pleasure to talk with you today a little bit about

10 pediatric drug development and the Best

11 Pharmaceuticals for Children Act, or BPCA.

12 Traditionally, drugs were not studied in the pediatric

13 population, and, hence, the number of medicinal

14 products labeled in pediatric patients is limited.

15 Because of this, legislation has been passed to both

16 require and request studies in the pediatric

17 population.

18 Today I will briefly review the pediatric

19 legislation, with a focus on the Best Pharmaceuticals

20 Act for Children, or BPCA. It's important to remember

21 that pediatric drug development happens in the context

22 of overall drug development, and, therefore, studies

1 performed in the pediatric population often rely on
2 studies previously performed in the adult population,
3 the pediatric population or both. Therefore, I will
4 review FDA's approach to extrapolation of data, which
5 is consistent with International Conference on
6 Harmonization's guidelines for clinical investigations
7 in pediatric patients, and I'll also review the
8 written request process.
9 The history in acknowledging the need for
10 pediatric information and labeling began in 1994 with
11 the pediatric labeling rule. In 1997, the Food and
12 Drug Administration Modernization Act, or FDAMA,
13 passed and included an incentive program for the study
14 of medications in children. These exclusivity
15 provisions were renewed under the Best Pharmaceuticals
16 for Children Act in 2002.
17 In 1998, the FDA published the pediatric
18 rule requiring studies in the pediatric population for
19 certain products. And in 2003, these requirements
20 were codified under the Pediatric Research Equity Act,
21 or PREA. Both BPCA and PREA were reauthorized in the
22 Food and Drug Administration Amendments Act, or FDAAA,

1 in 2007.

2 Under BPCA, a written request can be issued
3 for studies in the pediatric populations, and
4 companies can perform the studies to obtain marketing
5 exclusivity. I will first talk a little bit about the
6 pediatric written request and then discuss the process
7 for obtaining pediatric exclusivity under BPCA.

8 The written request is a legal document
9 requesting studies that are intended to obtain
10 sufficient information on the use of a medication in
11 the pediatric population. The written request
12 specifies the indication or indications to be studied;
13 the population, including the age range of the
14 patients to be studied; the types of studies; the
15 safety parameters that must be monitored; the plan for
16 analysis; and the time frame for submitting study
17 reports. A written request must be reviewed by an
18 internal pediatric review committee before being
19 issued.

20 When designing studies for a written
21 request, available information is assessed to
22 determine what kind of studies will be needed.

1 Extrapolation of efficacy is allowed if the course of
2 the disease and the response to therapy are
3 sufficiently similar in adults and pediatric patients.
4 There are reasons why it is important to
5 extrapolate when possible. Research in pediatric
6 patients carries additional responsibilities, and just
7 because larger studies can be performed does not mean
8 they should be performed. Pediatric patients are
9 considered a vulnerable population, and special
10 measures to protect the study patients are needed.
11 Research should involve the fewest number of patients
12 needed to answer the question at hand, and pediatric
13 trials should be designed with efficiency in mind.
14 Extrapolation of efficacy still requires
15 supportive data in the pediatric population. However,
16 this approach may reduce the number and complexity of
17 pediatric trials necessary for pediatric drug
18 development.
19 I realize that this algorithm may not
20 project well, and we'll walk through each of these
21 steps separately in the forthcoming slides. But this
22 is a decision tree that is used by FDA as a framework

1 to help determine if extrapolation may be used in
2 pediatric studies and if so, what type of studies
3 would be required to support the extrapolation of
4 efficacy.
5 So now, to walk through the algorithm, if
6 there is not a scientific determination that the
7 course of the disease and response to treatment are
8 the same in adults and pediatric patients, then
9 efficacy cannot be extrapolated and full dosing,
10 safety and efficacy data will be required in the
11 pediatric population.
12 If it is determined that the disease and
13 responsive treatment are similar in adult and
14 pediatric patients and there is likely to be a similar
15 concentration response, then an indication can be
16 supported by efficacy extrapolated from adults, a
17 pharmacokinetic study in pediatric patients to match
18 adult exposure, and additional pediatric safety
19 information would be required.
20 In the scenario where the disease and the
21 response to treatment are similar, but one cannot make
22 a determination that there is likely to be a similar

1 concentration response relationship and no
2 pharmacodynamic measures exist, then full studies are
3 needed to establish dosing, safety and effectiveness
4 in pediatric patients.
5 In the last scenario, where the condition
6 and the response to treatment is similar enough and
7 one cannot assume that there will be a direct
8 concentration response that is the same in adults and
9 children, but a pharmacodynamic measurement that can
10 predict efficacy in pediatric patients does exist,
11 then efficacy can be extrapolated from adults and a
12 PK/PD study to establish the concentration response in
13 pediatric patients and a safety study can support the
14 indication in the pediatric population, since
15 situations have occurred when a concentration response
16 or a PD response had to be established before
17 extrapolation of efficacy could be supported.
18 Over the last decade, FDA has made extensive
19 use of the principle of extrapolating efficacy when
20 issuing written requests for pediatric studies. A
21 number of approaches have been used, and these
22 approaches have evolved differently in different

1 therapeutic areas and they do continue to evolve.
2 This table provides examples where efficacy
3 was, in part, extrapolated from the adult clinical
4 trials and studies using endpoints other than those
5 used in adult patients supported the pediatric
6 indication.
7 For sotalol, PK studies were performed and
8 exposure response was established based on beta
9 blockade and QTC and safety was assessed. For
10 argatroban, a direct thrombin anticoagulant, event
11 rates were assessed in adults and active partial
12 thromboplastin time was used as a study endpoint in
13 studies of heparin-induced thrombocytopenia.
14 For bivalirudin, a PK study with a PD
15 endpoint activated clotting time was used. With the
16 example of loratadine, safety and effectiveness was
17 established in adults and pediatric patients 12 years
18 of age and older, and PK data and safety studies
19 supported extrapolation of efficacy to younger
20 patients. For the anti-retrovirals, these have been
21 studied in the pediatric population using PK/PD and
22 reduced viral load.

1 So now that we've reviewed some of the ways
2 that the necessary studies to support pediatric
3 labeling are determined, I'll review the process for
4 obtaining pediatric exclusivity. Once the study in
5 response to a written request are submitted to the
6 agency, the pediatric exclusivity board determines if
7 the studies performed were those that were requested
8 in the written request and if the studies were
9 conducted using good scientific principles. If so,
10 then six months of marketing exclusivity is granted,
11 and the marketing of a generic drug product is blocked
12 for six months.
13 The exclusivity is granted to the drug
14 moiety and is not indication specific. Therefore, for
15 example, if sildenafil is granted pediatric
16 exclusivity based on a written request to study
17 pediatric pulmonary arterial hypertension, the
18 exclusivity would apply to both Revatio tablets and
19 injection, as well as Viagra.
20 Of note, the financial incentive is usually
21 not dependent on obtaining a pediatric indication, but
22 rather, it comes from protection of sales in the adult

1 market. In addition, exclusivity is not determined by
2 the outcome of the trials. It only matters that the
3 sponsor has fairly responded to the terms of the
4 written request, and thus it is important that FDA ask
5 for sufficient information in the written request.
6 Information from the studies conducted under a written
7 request must be incorporated into labeling.
8 Written requests are frequently revised, and
9 the language in all written requests advises the
10 sponsor that if they want a revision, to contact the
11 agency to discuss the proposed changes. Revisions are
12 common as the development program progresses, and
13 there are currently 34 written requests posted on the
14 FDA website. And these are written requests where an
15 exclusivity determination was made since the passage
16 of FDAAA in September of 2007.
17 Of those 34 written requests, 25 have been
18 revised. As you can see, changes are often made close
19 to the due date of the studies, and the changes have
20 ranged from changes that are considered more major,
21 like changes in the development plan, to more minor
22 changes, such as the due date of the studies.

1 So why should we revise a written request
2 after it is issued or why would we? Essentially, we
3 must allow for change to accommodate for new
4 knowledge. For example, the sponsor may need
5 additional time to complete the studies. This could
6 happen if recruitment was lower or slower than
7 expected or perhaps an interim analysis of the data
8 identified the need to recruit and enroll more
9 patients. Sometimes certain pediatric populations
10 cannot be recruited, and they are removed from the
11 study.
12 In addition, medical knowledge may change,
13 and the practice of medicine may change. When the
14 written request for the proton pump inhibitors were
15 first developed, the resolution of apnea, of
16 prematurity was the primary endpoint in newborns.
17 However, studies were subsequently published that
18 acknowledged that even though reflux and apnea often
19 occur in the same patient population, that reflux was
20 not the cause of apnea and the endpoint was changed.
21 So in summary, we’ve discussed the written
22 request process under BPCA and the concept of

1 extrapolation. And I will summarize by saying that
2 BPCA is intended to encourage studies in the pediatric
3 population with the goal of providing evidence-based
4 use of medication for children. The pediatric
5 development program is part of the overall development
6 program, and thus is not required to stand alone.
7 Data should be leveraged to minimize pediatric
8 exposure to study. However, that being said, the data
9 must be sufficient to adequately support the
10 indication in the pediatric population.
11 DR. KAUL: Thank you, Dr. Durmowicz.
12 Dr. Stockbridge?
13 DR. STOCKBRIDGE: I'm just going to give you
14 a few slides to take you through the evolution in the
15 sildenafil written request thus far. As Dr. Durmowicz
16 points out, the intent here is to ensure that a
17 development program provides useful information that
18 supports something intelligible in the label.
19 It might be that it's okay to use it in
20 children. It might be that it's probably not a good
21 idea to use it in children. But either of those is
22 worth what is being offered to the sponsor in terms of

1 their written request so long as the result is
2 interpretable.
3 So one aspect of that is ensuring that a
4 successful trial is interpretable, and what you need
5 in order to decide that has to do with what you know
6 externally and how closely related you think the
7 external data are to the disease in children. Thus if
8 there's no corresponding indication in children, then
9 the agency has to think that there's a reasonable
10 likelihood for success.
11 But the development program in children has
12 to carry the full regulatory burden of establishing
13 the effectiveness there. If there is a similar
14 indication in adults, then you can borrow some
15 strength from that, depending on how confident you are
16 in that. That can range from, as Dr. Durmowicz says,
17 PK data only in children all the way up to another
18 trial.
19 The other aspect is ensuring that a failure,
20 if that's what happens, is informative. We do that by
21 establishing what we think is a minimally important
22 effect size in children that we want to make sure that

1 the trial is capable of excluding if the true effect
2 ends up being zero. And so the written requests
3 generally have some clause that establishes either a
4 sample size or a number of events, and the trials are
5 adaptable to establish that they have the appropriate
6 power by the time they are completed.
7 So the sildenafil program began in 2001, at
8 which point sildenafil did not have an indication for
9 pulmonary hypertension in adults. Thus they were
10 asked to conduct three separate placebo-controlled
11 trials in children. One of those was in primary
12 pulmonary hypertension of the newborn; one was in
13 children who had undergone corrective cardiac surgery;
14 and, the third one was a placebo-controlled trial in
15 the primary and secondary pulmonary hypertension, more
16 analogous to their adult indication that they
17 eventually got.
18 In addition, the sponsor was asked to
19 provide some long-term uncontrolled safety data from
20 the children who had been enrolled in the placebo-
21 controlled studies.
22 By 2005, the world had changed. Revatio was

1 approved to treat pulmonary hypertension in adults.
2 In addition, there was uptake in the use of nitric
3 oxide in the settings of primary pulmonary
4 hypertension of the newborn and in post-surgical
5 patients. This largely rendered infeasible, as well
6 as unnecessary, the studies that Pfizer had been asked
7 to do in those settings. And at that point, both of
8 those studies were dropped from the written request.
9 There have, in addition, been four other relatively
10 minor amendments to the written request during its
11 history.
12 I wanted to call your attention to one key
13 aspect of written requests, at least ones that come
14 from the Cardio-Renal Division, that anticipates that
15 there may be a need for very late change in a written
16 request. We are not allowed to make success in a
17 trial be the criteria for deciding that the trial
18 fulfills the terms of the written request. It can't
19 actually be dependent on the outcome of the trial.
20 So to finesse the fact that that's
21 interpretable information, we have a clause that says
22 if you've obtained unexpected benefits or indeed your

1 DMC has shut you down because of safety concerns --
2 that's an interpretable result -- we allow for the
3 sponsor to provide us not a complete study report, but
4 at least a summary of that information that will allow
5 us to revise, at the last possible moment, the
6 requirements of the written request.
7 So in summary, the written request is based
8 on the collection of useful information. It does not
9 necessarily lead to an extension of the indication for
10 use in children. And substantial and late changes to
11 the written request are an expected part of what
12 happens as one's background information on the use in
13 children evolves.
14 Questions that you'll have to face later
15 today are then whether or not we have identified a
16 surrogate endpoint that is suitable for use in
17 deciding whether or not a drug that you know is
18 effective in adults is also likely to be effective in
19 children with the same disease.
20 Then if you've bought into that, we'll ask
21 you how you'd think through establishing what effect
22 size might be important to ensure an interpretable

1 program.

2 So I'll stop there, and Dr. Durmowicz and I

3 will take questions about the written request process

4 and sildenafil's written request specifically, if you

5 have any.

6 DR. KAUL: Thank you, Dr. Stockbridge.

7 I will open it up for questions from the

8 committee.

9 Dr. Coukell?

10 DR. COUKELL: Thank you for that

11 introduction.

12 Did the original written request for the

13 placebo-controlled study in primary and secondary

14 pulmonary arterial hypertension specify the use of a

15 performance or a physical outcome measure?

16 DR. STOCKBRIDGE: It did. Their original

17 program in PAH had an exercise endpoint, and the

18 Pfizer folks will describe those results to you during

19 their presentation.

20 DR. KAUL: Any further questions?

21 [No response.]

22 DR. KAUL: Thank you.

1 Before I call upon the sponsors to give
2 their presentation, both the Food and Drug
3 Administration and the public believe in a transparent
4 process for information gathering and decision-making.
5 To ensure such transparency at the advisory committee
6 meeting, the FDA believes that it is important to
7 understand the context of an individual's
8 presentation.
9 For this reason, FDA encourages all
10 participants, including the sponsor's nonemployee
11 presenters, to advise the committee of any financial
12 relationships that they may have with the firm at
13 issue such as consulting fees, travel expenses,
14 honoraria, and interests in the sponsor, including
15 equity interests and those based upon the outcome of
16 the meeting.
17 Likewise, FDA encourages you, at the
18 beginning of your presentation, to advise the
19 committee if you do not have any such financial
20 relationships. If you choose not to address this
21 issue of financial relationships at the beginning of
22 your presentation, it will not preclude you from

1 speaking.

2 At this point, I'm going to call upon the

3 sponsors to give their presentation. I think the

4 first speaker is going to be Dr. Robyn Barst.

5 DR. BARST: Dr. Temple, Dr. Stockbridge,

6 members of the advisory committee, and ladies and

7 gentlemen in the open forum, good morning. My name is

8 Robyn Barst, and I'm from Columbia University in New

9 York City. It is my great pleasure this morning to

10 have been asked to speak with you to give an overall

11 clinical perspective on pulmonary arterial

12 hypertension in children and adults.

13 For complete transparency, my disclosures

14 are shown in this slide. I have received support for

15 research and consulting in the field of pulmonary

16 hypertension form the pharmaceutical companies as

17 listed on this slide. I also am currently serving as

18 a consultant to Pfizer for this advisory committee

19 meeting.

20 Having spent the past 30 years working in

21 the field of pulmonary hypertension, we have made

22 significant advances. From being in the field when

1 the only treatment we had to offer patients and their
2 families was comfort with patients dying within
3 several years of being diagnosed and children often
4 dying within one year of diagnosis, the advances have
5 made a significant impact. We now have eight drugs
6 approved for PAH, and these drugs have significantly
7 improved the overall quality of life and outcomes for
8 many patients.
9 However, we have no drugs approved for
10 children. A primary reason for this is lack of an
11 agreed upon, clinically relevant, accepted endpoint to
12 use in children with PAH in controlled studies.
13 After giving a brief overview of pulmonary
14 arterial hypertension in children and adults, I will
15 discuss why we believe that hemodynamics, specifically
16 pulmonary vasculature resistance index, is an
17 appropriate endpoint to consider using for controlled
18 studies in children.
19 Following my presentation, you will hear
20 from the FDA and from the sponsor, their proposal
21 discussing exploring hemodynamics, specifically PDRI,
22 for us to discuss as a potential appropriate endpoint.

1 What is pulmonary hypertension? Pulmonary
2 hypertension is a hemodynamic and pathobiologic state
3 that is found in many clinical conditions. By itself,
4 it is not a disease. By definition, it means that the
5 main pulmonary artery pressure is elevated above
6 normal, with a minimum elevation of 25 millimeters of
7 mercury when we measure the main pulmonary artery
8 pressure directly.
9 Pulmonary hypertension is classified in just
10 five groups, as shown on this slide. Group 1, which
11 is termed pulmonary arterial hypertension or PAH, as
12 it may be discussed today, is the group that we will
13 be focusing on today. We use the same clinical
14 classification in both children and adults.
15 If we move forward and we look more closely
16 at Group 1 PAH, we see different forms that are
17 considered under this umbrella of Group 1 PAH.
18 This classification has been assessed and
19 has been put forward by the PH expert consensus
20 community, because all of these forms share similar
21 clinical presentations and virtually identical
22 histopathologic features in the small pulmonary

1 vasculature of the pulmonary arterials where this
2 disease arises. The same classification and subgroups
3 under Group 1 PAH we use in children and adults based
4 on U.S. and European guidelines.
5 Where is the problem in PAH? PAH in both
6 children and adults is shown where it's schematically
7 localized on this slide in that it is pre-capillary
8 pulmonary arterial hypertension, after excluding all
9 other causes of pulmonary hypertension. In addition
10 to excluding other causes of pulmonary hypertension
11 and requiring that the main pulmonary artery pressure
12 must be at least 25 millimeters of mercury measured
13 invasively by right heart catheterization at rest, a
14 right heart catheterization is required to confirm the
15 diagnosis to make sure that there is no evidence of
16 increased left-sided filling pressure as a cause of
17 the pulmonary hypertension, as well as to demonstrate
18 that the pulmonary vasculature resistance is
19 increased.
20 The pulmonary vasculature resistance is a
21 biologic marker of what this disease is itself. And
22 our consensus guidelines support that right heart

1 catheterization is necessary for us to diagnosis the
2 disease and assess how patients are doing when we
3 initiate treatment.
4 So let's look at what this disease is and
5 turn to the pathology. Shown on the left side of the
6 slide is a normal thin wall pulmonary arterial. The
7 vascular lumen is exceedingly open, and it's
8 relatively easy for blood to flow through here.
9 Because the lumen is very open, the pressure required
10 for the right side of the heart to generate a pressure
11 to push blood through the lung is quite low. And our
12 normal pulmonary pressures are 10 to 15.
13 However, if we look at a typical pulmonary
14 arterial in either a child or an adult with pulmonary
15 arterial hypertension and we focus down on the size of
16 the lumen, you will see that the size of the lumen has
17 now narrowed significantly. And based on Ohm's Law,
18 thus although the disease is due to the pulmonary
19 vascular resistance, this results in the right heart
20 having to generate an increased pressure, the
21 resultant pulmonary hypertension, to get adequate
22 blood flow through the lungs. Thus, in this case with

1 PAH, the pulmonary hypertension is secondary to the
2 disease, which is an increased pulmonary vasculature
3 resistance in the lungs.
4 In addition to the pulmonary arterial
5 hypertension being similar from a pathologic
6 standpoint in the lungs in both children and adults,
7 whether the child is still growing, the differences
8 that we have demonstrated in mechanisms of
9 pathobiology have also been the same. The
10 pathobiology of pulmonary arterial hypertension is
11 exceedingly complex. A number of pathways have been
12 demonstrated to have abnormalities in both children
13 and adults.
14 This schematic representation is limited to
15 three pathways at this point because these are the
16 pathways that we've been successful to date in
17 developing drugs for to treat adult PAH. These
18 include the endothelin pathway, the nitric oxide
19 pathway, and the prostacyclin pathway. The
20 abnormalities that we've seen in these three pathways
21 we have also observed in children similar to our
22 observations in adult patients.

1 So how does this disease present and what
2 can we do to make patients feel better? On this
3 schematic representation, shown across the top is a
4 progression of the disease in the pulmonary
5 vasculature going from when the patient is pre-
6 symptomatic because he's compensated. We see further
7 obliteration of the vascular lumen, and then we see
8 complete obliteration of the vascular lumen.
9 There's no time frame put on the X axis
10 because patients can be diagnosed and rapidly
11 deteriorate and die within months or they can live at
12 least several years. What's important is as the
13 disease progresses, it's because it's a disease of
14 obstruction of the pulmonary vasculature that the
15 pulmonary vascular resistance continues to increase
16 correlating with the progression of the disease
17 overall in the lung.
18 We'll get into how these patients present
19 with symptoms which are rather nonspecific and
20 insidious. But to simplify this and as an example,
21 initially, as the pulmonary vascular resistance
22 increases, the right ventricle is able to increase

1 pulmonary artery pressure and maintain an adequate
2 cardiac output. Over time, the right ventricle no
3 longer is able to generate the increased cardiac
4 output, particularly with exercise, and the patient
5 presents with dyspnea on exertion.
6 Further along, the patient is no longer able
7 to generate adequate right ventricular work at rest,
8 and the patient goes into progressive right heart
9 failure, with a decline in cardiac index, increase in
10 right heart filling pressure. And, in fact, even
11 though the patient is getting worse, the pulmonary
12 artery pressure here is falling. Based on this
13 representation, it is clear that pulmonary vascular
14 resistance is exceedingly useful in assessing the
15 disease severity and what's happening in patients.
16 To illustrate some of the issues that we'll
17 be discussing today and how can we assess children and
18 adults with pulmonary hypertension, I'd like to
19 present a case presentation. We have taken care of
20 hundreds of children and adults at our center, but I'm
21 choosing a young child to illustrate some of the
22 particular challenges we have when we're faced with a

1 young child, particularly a child who's unable to
2 perform exercise testing.
3 This 2-year-old child presented with cough
4 and unexplained dyspnea on exertion while playing.
5 She was diagnosed as having asthma, but did not
6 improve with treatment. Her unexplained dyspnea
7 continued. Her workup was unremarkable except for
8 suspected pulmonary hypertension. Pulmonary artery
9 hypertension was confirmed by right heart
10 catheterization, and based on the results of the right
11 heart catheterization, treatment was initiated.
12 Our standard of care for all children,
13 regardless of age, and for all adults, includes serial
14 evaluation, which includes repeated right heart
15 catheterizations to assess response to therapy. We
16 certainly also put significant impact on an ability to
17 exercise and feel better, and we can do that in
18 virtually all of the adults that we take care of and
19 we see. However, as we will discuss shortly, we
20 really are only able to do that in approximately in
21 one-third of children who we could consider
22 appropriate to enroll in a controlled trial.

1 This slide shows this 3-year-old's
2 hemodynamics at the time of diagnosis. Her main
3 pulmonary artery pressure was quite high. Her
4 pulmonary vascular resistance was over 1,000 dynes.
5 She was too young to perform exercise testing.
6 However, based on the results of her cardiac
7 catheterization, we initiated monotherapy, a drug that
8 had been approved for adult PAH. Our routine
9 practice, regardless of what the parents and the child
10 tell us, even though that's very, very important to
11 try to get an assessment from the family, is to
12 perform serial cardiac catheterizations.
13 Her catheterizations at 4 and 6 are shown on
14 this slide, which were consistent with her reported
15 clinical improvement and her pulmonary vascular
16 resistance now having decreased to less than 500
17 dynes.
18 Based on this, we continued the monotherapy.
19 Over the ensuing year, her parents were unsure if she
20 now was becoming slightly symptomatic again or she no
21 longer liked to play soccer, but she would just rather
22 sit inside and paint. Nevertheless, regardless of

1 what the parents or the child had told us -- because
2 sometimes even when they say everything is fine,
3 everything may not be fine -- her repeat cardiac
4 catheterization at age 7 demonstrated she had had
5 significant deterioration in her pulmonary arterial
6 pressure.
7 Her pulmonary vascular resistance was now
8 greater than 1500 dynes, and her main pulmonary artery
9 pressure had significantly increased. However, as we
10 will see when we look at children overall,
11 particularly young children, her cardiac index at rest
12 remains normal.
13 Based on that follow-up evaluation, we
14 initiated additional PH therapy, using an off label
15 that has been approved for adults. She improved, and
16 this young lady continues to be followed at the
17 pulmonary hypertension center with adjustments in her
18 medical therapy based on follow-up cardiac
19 catheterizations and, as she got older, follow-up
20 exercise studies.
21 At age 7, this was the first time that we
22 tried to exercise this young lady. Her six-minute

1 walk was within normal limits for a child of her age
2 and gender and height; not surprising, since her
3 cardiac index was normal at rest or even on the high
4 side.
5 We then performed cardiopulmonary exercise
6 testing which we believe gives us a better assessment,
7 even in children who say they feel relatively
8 asymptomatic. And, in fact, her peak oxygen
9 consumption was significantly decreased. And with
10 effective therapy, that improved over time.
11 So let's use that one example and look at an
12 overall cohort of children and adults who were
13 diagnosed with PAH. These are data from the U.S.
14 current REVEAL Registry. And these are the
15 hemodynamics in both cohorts at the time of diagnosis.
16 Both the children and adults have similar elevation in
17 pulmonary artery pressure in the 50s and, similarly,
18 severe elevation in pulmonary vascular resistance over
19 1500 dynes. However, as the young child demonstrated,
20 the resting cardiac index for these children overall
21 is normal, with the resting cardiac index for the
22 adults slightly decreased.

1 The symptoms at the time of diagnosis in
2 these same children and adults are shown on this
3 slide. The most frequent presenting symptom in both
4 children and adults is dyspnea on exertion. However,
5 it's important to note that even though these children
6 had severe hemodynamic impairment, only 43 percent of
7 the children had dyspnea on exertion either reported
8 by their parents, their teachers, their siblings or
9 themselves. Thirty-two percent of the children
10 presented with syncope.
11 It is our belief that this is because
12 children, especially young children, do not understand
13 the philosophy of self limitation. As opposed to an
14 adult, if we begin to feel breathless, we probably
15 will sit down; or if we begin to feel light-headed
16 walking up stairs, we'll probably sit down right away.
17 Children don't do this.
18 Fatigue is significantly seen in both
19 children and adults, a nonspecific finding. And if we
20 look at peripheral edema, a reflection of clinical
21 right heart failure, these data are consistent with
22 the hemodynamics at the time of diagnosis in that the

1 overall cardiac index at rest was slightly low in the
2 adults, consistent with peripheral edema, a sign of
3 clinical right heart failure at the time of diagnosis.
4 However, I want to get back to the point
5 that merely because their presenting symptoms may be
6 somewhat different at the time of diagnosis, it should
7 not be not inferred that this means the disease is not
8 similar.
9 Let's look at another example of a pulmonary
10 disease, asthma. Asthma is considered the same
11 disease in children and adults. However, children
12 present with cough and adults present with wheezing.
13 It doesn't mean the disease is not the same. It just
14 means that the symptoms at presentation aren't the
15 same. And there are a whole host of other diseases
16 that we see that with.
17 The consensus amongst the PAH community
18 overall is that the pathobiology and pathophysiology
19 are the same in children and adults. Furthermore, the
20 consensus is that the pulmonary hypertension
21 diagnostic workup and therapeutic algorithm proposed
22 for adults should also be considered in children.

1 In the case presentation that we briefly
2 discussed, treating this young child with PAH drugs
3 that have been approved for adults off label certainly
4 appeared to improve her clinically and from a
5 hemodynamic standpoint.
6 However, are we treating this child the best
7 we can? We don't know the answer to that. One of the
8 reasons and a significant reason for that is we do not
9 have controlled data in these children. And despite
10 the challenges in new drug development in pulmonary
11 arterial hypertension, this is a serious unmet medical
12 need. We need to obtain the necessary data to make
13 sure we are dosing these children properly and giving
14 them the optimal therapy they deserve.
15 As was so eloquently discussed earlier,
16 there are a number of challenges in pediatric research
17 overall. In addition, there's specific challenges in
18 pediatric PAH research. We've used exercise endpoints
19 successfully in all of our registration studies to
20 date. However, exercise endpoints are often not
21 useful in children. A significant proportion of
22 children with PAH are not exercise limited. In

1 addition, a significant proportion of children are
2 unable to undergo formal exercise testing regardless
3 of their age.
4 These studies are very difficult to enroll.
5 The disease is rare in adults, and the prevalence is
6 much rarer even in children. And physicians often
7 prescribe drugs approved for PAH use in adults to
8 children with PAH off label. Parents are reluctant to
9 enroll children with a serious disabling and
10 progressive disease in a clinical trial in which they
11 may receive placebo.
12 What I'm showing on this slide are the
13 clinically relevant potential endpoints that we could
14 consider using in children. And I've listed the
15 endpoints that we have been successful with using in
16 adults, the exercise test and functional class quality
17 of life, et cetera. Six-minute walk has been the
18 primary endpoint or co-primary endpoint for all of our
19 studies that currently are approved in the U.S.
20 Unfortunately, the six-minute walk test will
21 only be abnormal in a minority of developmentally able
22 children. Many children who perform the six-minute

1 walk test will have a normal six-minute walk test, as
2 this child had. Perhaps if we standardized a 12-
3 minute run test, we may be able to see abnormalities.
4 But that's not something we have.
5 Cardiopulmonary exercise testing, as you
6 will see by the presentation from the sponsor, we
7 utilized as the primary endpoint, and we selected this
8 because we felt at least we would be able to obtain
9 accurate data in children who could perform the
10 exercise test reliably as long as they had exercise
11 intolerance. But again, cardiopulmonary exercise
12 testing has turned out to be only applicable in
13 children who, number one, are developmentally able,
14 have exercise intolerance and do not have a history of
15 syncope. And if we put these three exclusions
16 together, we're left with approximately one-third of
17 children in whom we can do formal exercise testing, at
18 best.
19 Functional class and quality of life
20 assessments have been validated in adult PAH studies.
21 However, they're very difficult to assess in young
22 children. Morbidity and mortality is currently being

1 used as a primary endpoint in some of our ongoing
2 adult clinical trials. However, this is not feasible
3 in pediatric PAH. The event rate is very low in
4 children. It would require a very large and prolonged
5 trial, and the recruitment issues in pediatrics are
6 much more difficult, as we discussed earlier, than in
7 adult patients.
8 Hemodynamic variables, pulmonary arterial
9 hypertension is a hemodynamic disease. We require
10 right heart catheterization to confirm the diagnosis
11 of PAH. We utilize repeat hemodynamic assessment to
12 assess response to treatment, to changed treatment,
13 and to assess disease severity. It's a parameter that
14 we can perform in patients of all ages, children of
15 all ages as well as adults of all ages. When we
16 perform this in experienced centers, there is a very
17 low morbidity and mortality in both the pediatric and
18 adult pulmonary hypertension centers.
19 This shows the hemodynamic assessment by
20 right heart catheterization that the PAH community has
21 considered a very important measure of efficacy in
22 adult PAH. What's shown on the left side of the slide

1 are the eight drugs that are currently approved to
2 treat adult PAH. The primary endpoint for the
3 registration studies in all of these was six-minute
4 walk or as a co-primary. Shown on the far right is
5 that hemodynamic evaluation was included in the drug
6 development programs for all of these studies.
7 Having participated in all of these studies,
8 either as a principal investigator, data safety
9 monitoring board member, steering committee member or
10 scientific advisory board member, we supported that it
11 was exceedingly important that the sponsor utilize and
12 allow us to assess hemodynamics regardless of whether
13 it was going to be considered a primary endpoint.
14 So if we return briefly to the schematic
15 representation, the reason we believe that pulmonary
16 vascular resistance is exceedingly useful is that it's
17 something that we can measure accurately and it is the
18 one parameter that encompasses everything that is
19 going on in the pulmonary circulation. And whether
20 the right heart function is good or bad, it tells us
21 what the disease is doing and is the disease severity
22 improving or not.

1 In conclusion, pulmonary arterial
2 hypertension is defined hemodynamically in children
3 and adults. Serial hemodynamic assessments are
4 central to assessing the response to treatment and the
5 presence of disease progression. Exercise testing as
6 an endpoint is only applicable in approximately one-
7 third of children with pulmonary arterial
8 hypertension.
9 Morbidity and mortality trials are
10 unrealistic in this patient population. Hemodynamic
11 assessments can be performed in children and adults of
12 all ages. Hemodynamic assessment, specifically PVRI,
13 have been frequently included as an efficacy variable
14 in our adult PAH trials. And hemodynamic assessments,
15 specifically PVRI, are an appropriate measure that we
16 would like you to consider today as a clinically
17 relevant endpoint to consider for future pediatric
18 trials with PAH. Thank you.
19 DR. KAUL: Thank you, Dr. Barst, for a very
20 erudite and informative presentation.
21 Questions from the committee? Dr. Halperin?
22 DR. HALPERIN: Just as a matter of

1 information, of the serial measurement of PVRI over
2 time in these children who may be prone either to
3 weight loss as a result of cachaxia or to weight gain
4 as a result of edema, how do you establish comparative
5 values?
6 DR. BARST: The hemodynamics do not --
7 they're unaffected with a child who is getting better
8 or not based on their therapy if they have weight gain
9 or weight loss. It's unaffected by that.
10 DR. HALPERIN: So the calculation that's
11 based on body surface area would not be influenced by
12 weight.
13 DR. BARST: It's not significantly
14 influenced by weight. We certainly look at this from
15 the standpoint of PVR and PRVI based with the
16 children. But that has never been an issue
17 whatsoever. Their height is not affected by the
18 disease severity. There are some preliminary data
19 from the United Kingdom that in very, very sick
20 children, they look at disease scores and that appears
21 to be a poor prognostic parameter. That's not the
22 experience in other countries. And even in those very

1 sick children, when they improve, their weight has not
2 significantly increased. So their body surface area
3 has not changed.
4 DR. KAUL: Dr. Coukell?
5 DR. COUKELL: Thank you.
6 Two quick questions. One is to help me
7 understand. You're saying that measuring exercise
8 endpoints in children is not useful or not possible.
9 And then secondly, you said regardless of what the
10 parents or the children tell us, essentially, we treat
11 the number. So what's the outcome? What does it mean
12 to treat that number?
13 DR. BARST: Very good question, I'm glad you
14 asked. We can have children that become asymptomatic
15 based on the child telling us or the parents or the
16 teachers. And we can then repeat a cardiac
17 catheterization, and the pulmonary vascular resistance
18 can be just as high as it was before or slightly
19 lower. And we're left with a child who, in fact, has a
20 potential ticking bomb inside that child.
21 For good or bad, having treated many
22 children and adults from 1978 until we had our first

1 drug approved in 1995, I had the very difficult
2 experience of observing personally the natural history
3 of many, many children and adults and seeing those
4 patients die with little that we could offer them.
5 The only treatment we did have to offer at
6 that point was consideration of lung transplantation,
7 because that's such a serious consideration that if we
8 wanted to go that next step, we would do serial
9 catheterizations to really determine do we think this
10 child has a likelihood of living two years or not.
11 And we sort of focused that into when a child should
12 be transplanted.
13 So unfortunately, we were able to see the
14 natural progression of severe elevations in pulmonary
15 vascular resistance. And we would see that in
16 children very often get worse before the children
17 became very symptomatic, particularly young children,
18 who can die suddenly from a syncopal episode when
19 their normal daily activities may be fine walking
20 around the house.
21 So that's one thing that's very important.
22 We do believe that hemodynamics are the gold standard

1 to assess disease severity. We do see that when we
2 treat patients effectively and they feel better, their
3 pulmonary vascular resistance invariably decreases.
4 And it's inappropriate, in my opinion, that if we
5 follow children to wait until a child or their parents
6 says they're symptomatic for us to reassess them,
7 because we have data now that initiating treatment
8 earlier appears to be more effective.
9 However, I think exercise testing is
10 exceedingly important when we can do it. We do adult
11 studies, and I am in total support that our primary
12 endpoint has been exercise. We do secondary endpoints
13 of hemodynamics, because to me personally, both of
14 those are very useful in assessing how an adult
15 patient is doing.
16 But at least exercise can be equated to feel
17 better, because we can look for "do I feel better" in
18 all the adults. I recommend and I support that we do
19 use a parameter such as exercise capacity in adults or
20 we use a parameter such as clinical disease
21 progression.
22 However, in children, even though I would

1 like to be able to exercise all children -- and
2 certainly, at our center, we exercise all children
3 once they're able to, and it usually will take several
4 years. If we start to try to put them on the bike at
5 age 5, usually by age 7 or 8, it's reliable. When we
6 look at how many children we could exercise to enroll
7 in a study, it comes down to only a third.
8 As you will see, subsequently, when we were
9 designing the pediatric sildenafil clinical trial, we
10 anticipated that virtually all children over 7 years
11 of age would be able to exercise. And so we
12 anticipated that probably half the patients we
13 enrolled would not be able to exercise.
14 As you will hear, it turned out to be a much
15 greater percentage of children who could not exercise
16 for two reasons. A number of children who are over 7
17 still are not developmentally able to understand how
18 to maintain and perform a full effort and the
19 importance of the exercise test. And a second reason
20 is because we want to see what we consider a
21 clinically relevant treatment effect with exercise
22 testing and we selected peak oxygen consumption as the

1 primary endpoint, we included upper and lower limits
2 for enrollment in order that we would be enrolling
3 children that if they got better, we would see an
4 improvement.
5 What this resulted is a number of children
6 who came to the centers who we screened and thought
7 they would be appropriate to enroll in the study
8 because we knew they had severe hemodynamic impairment
9 and severe elevation in the pulmonary vascular
10 resistance, but from their exercise testing, their
11 peak oxygen consumption was too high for us to be able
12 to enroll them since that was our primary endpoint.
13 So I would love to do exercise testing in
14 all the patients, but I think for controlled data,
15 it's important that we look at a parameter that is
16 accurate and that we can measure in every single
17 child, and then also perform exercise testing in all
18 the children we can, which will turn out to be a
19 minority, but still have those data that we can use as
20 supportive secondary endpoints.
21 DR. KAUL: Thank you, Dr. Barst. The
22 committee would appreciate if you can keep your

1 answers brief so as to accommodate questions from
2 other committee members.
3 DR. BARST: My apologies, I apologize.
4 DR. KAUL: Dr. Neaton?
5 DR. NEATON: Two questions.
6 So you pointed out two problems with using
7 the exercise tests; one, that some kids just can't do
8 it. Another is that the kids are not exercise
9 limited. So that suggests to me that the relationship
10 between, for example, changes in six-minute walk and
11 perhaps, also, changes in peak oxygen consumption as
12 they relate to the changes in the hemodynamic measures
13 may be different in children than they are in adults.
14 Can you comment on that?
15 Then the second question is, can you advise,
16 based on your experience in either the trials or
17 clinic, what's a reasonable follow-up period,
18 frequency of measuring the hemodynamics measurements
19 in a study; how long after initiating treatment and
20 the number of measurements?
21 DR. BARST: I will try to be brief. But now
22 I need you to reask me the first question.

1 DR. NEATON: So is the relationship
2 between --
3 DR. BARST: Thank you. The difficulty with
4 the six-minute walk is because the majority of
5 children have good right heart function and they can
6 walk six minutes just fine, but they may have a
7 pulmonary vascular resistance of 1,500. They have
8 severe disease, but they can do a normal six-minute
9 walk. So if we use that as the test, we wouldn't see
10 a treatment effect. In fact, in our adult studies, we
11 put an upper limit on for that very reason.
12 However, with the CPET for the children who
13 can do it, it is very useful, and, in fact, we will
14 see a low peak VO2 and other abnormal parameters of
15 cardiopulmonary exercise testing in children who have
16 significant PAH, even though their six-minute walk is
17 normal. And you will see data presented that there is
18 a correlation.
19 There are two different exercise tests.
20 They both demonstrate exercise capacity. We just need
21 to use something that requires more exercise capacity
22 to demonstrate the abnormalities in children.

1 DR. NEATON: Maybe we'll see it in the
2 future data, but so that there's a stronger
3 relationship between peak VO2 changes and hemodynamic
4 changes or that they're at the concordance of that
5 relationship in children and adults, you would expect
6 it to be strong, more similar than between six-minute
7 walk changes.
8 DR. BARST: Yes. And there certainly is
9 significant data in adults that demonstrate a good
10 correlation between peak VO2 and six-minute walk,
11 which is useful and provides comfort to us in the
12 sense that the six-minute walk we've used in adults
13 does correlate with peak VO2, because those patients
14 are limited in their six-minute walk distance. So
15 therefore, in children, even if they're not limited by
16 their six-minute walk, their limitation in peak
17 VO2 also correlates with how they're doing.
18 DR. NEATON: How often do you catheterize
19 and do the measurements?
20 DR. BARST: Our standard of care unrelated
21 to a clinical trial -- and I think this is really
22 important, and it's always been this way. Our

1 standard of care is we do a catheterization at
2 diagnosis. Before 2001, when we had therapies in
3 addition to Flolan, we may have not done as many
4 serial cardiac catheterizations, because we put the
5 children on intravenous epoprostenol and we would
6 catheterize them really only if we were concerned
7 about transplantation. However, now that we
8 have eight drugs approved, our standard of care is
9 that we better make sure we're treating the child with
10 the best drug possible. So we do a baseline
11 catheterization. We start a drug, and we routinely
12 repeat a right heart catheterization after three or
13 four months to make sure that even if the child feels
14 better, their hemodynamics are better. And if their
15 pulmonary vascular resistance is still very elevated
16 or hasn't significantly decreased, even if the child
17 says they feel great, we augment therapy based on
18 that.
19 DR. KAUL: Thank you, Dr. Barst.
20 We have 10 minutes, and we have seven
21 individuals that are willing to ask questions. So
22 once again, the committee would appreciate it if you

1 can keep your answers succinct.

2 Dr. Newman?

3 DR. NEWMAN: For the committee, would you

4 review -- and maybe those of you that were there --

5 the decision by the FDA in concert with the

6 pharmaceutical companies years ago to use the six-

7 minute walk as the endpoint in studies rather than

8 hemodynamics? Because I think that some of the

9 confusion about the relationship that arises from that

10 distinction, which is partly artificial. I think it's

11 partly the issue here at hand today, which is can you

12 extrapolate one from the other, what's the

13 relationship and how firm is that relationship in

14 predicting outcomes. Can you just review that for a

15 minute for us? And then I have a second question.

16 DR. BARST: Could I ask either

17 Dr. Stockbridge or Dr. Temple to answer that question?

18 DR. STOCKBRIDGE: I don't think the issue of

19 surrogate endpoint even came up in early discussions

20 about developing drugs in adults here. They were

21 symptomatic. It was clear people could do something

22 to establish the benefit.

1 We didn't particularly endorse the six-
2 minute walk. The industry sort of adopted it, and it
3 got replicated through various development programs.
4 But we have a general distrust of surrogate endpoints.
5 That's been developed through other cardiovascular
6 disease experience. And so it was fairly natural to
7 assume that we'd want some kind of clinical benefit
8 demonstrated in the adult studies.
9 DR. KAUL: Dr. Temple?
10 DR. TEMPLE: My dim recollection is that the
11 stress tests, which generally involved a rising level
12 of stress, were just not doable by a lot of adults.
13 Obviously, they can be done by some, but the six-
14 minute walk is less of a stretch. You're walking at
15 your -- but this was a while ago, and I'm not really
16 sure of that.
17 DR. KAUL: Perhaps Dr. Rich can weigh in
18 since he was there.
19 DR. RICH: Very briefly, we did discuss with
20 Rap Lipicki using a surrogate hemodynamic, and it was
21 rejected. And so it was decided to use some measure
22 of exercise tolerance.

1 The cardiologists in the advisory group
2 wanted a treadmill test, which was kind of the
3 standard in heart failure trials. But pulmonary
4 physicians didn't want to work with their
5 cardiologists. We were outnumbered. It was a hand
6 vote. I think it was six to five of six-minute walk
7 over treadmill tests. There was not a shred of data
8 at the time that a six-minute walk had any efficacy or
9 representation of the disease, but that's where we
10 started from. And because the first trial was
11 successful, I think all subsequent trials just adopted
12 the same primary endpoint.
13 DR. BARST: And it's been successful to date
14 with adult patients who are exercise limited by their
15 six-minute walk.
16 DR. KAUL: Let me just ask Dr. Rich this
17 question.
18 If there was no shred of data at that time,
19 has anything changed in the interim? Is six-minute
20 walk distance a validated surrogate endpoint?
21 DR. RICH: Well, it's probably going to come
22 up this afternoon. If, in fact --

1 DR. STOCKBRIDGE: No, no, wait. That's not
2 a surrogate endpoint at all.
3 DR. RICH: Correct.
4 DR. STOCKBRIDGE: Exercise is not a
5 surrogate endpoint.
6 DR. TEMPLE: We think of it as a more formal
7 representation of the clinical problem. You can get
8 debates on this, but on the whole, that's not what we
9 mean. It's the hemodynamic measure that we think is
10 not as well --
11 DR. RICH: The six-minute walk is what it
12 is. It measures your exercise tolerance in six
13 minutes. And to that extent, the fact that the
14 approved drug showed an improvement in six-minute
15 walk, it is successful.
16 The issue that has arisen is the implication
17 of a change in six-minute walk with respect to long-
18 term outcomes. And that's been a failure, because no
19 one has shown that the change in six-minute walk in
20 clinical trials affects outcome at all, and that may
21 come up when we talk about it this afternoon.
22 DR. TEMPLE: There's actually one other

1 thing. These treadmill exercise tests usually involve
2 your failing when they change the slope, the pitch,
3 and you get a finding of a 15-second difference. I
4 think the six-minute walk sounds more real, a little
5 bit, even though in the angina and heart failure
6 setting, we persist in using stress testing of the
7 other kind. It has a "can you get around" quality to
8 it, and the difference can be more than 10 seconds.
9 With the standard test, you sort of fail as soon as
10 they change the slope.
11 DR. BARST: And we explicitly used cycle
12 cardiopulmonary exercise testing in children for those
13 very reasons that Dr. Temple just discussed. In
14 addition, it’s weight independent. So if you’re doing
15 something with children, it’s very important to be
16 weight independent and why we use cyclometry.
17 Dr. Newman, you weren’t allowed to ask your
18 question.
19 DR. NEWMAN: So the reason I asked my
20 question was to make the point, which is that the six-
21 minute walk was empirically derived as a measure of
22 outcome, not scientifically tested against hemodynamic

1 testing originally.

2 For the committee, those people that don't

3 do pulmonary hypertension work, you need to understand

4 that measuring things against the six-minute walk is

5 measuring something against something that was

6 empirically discovered or decided upon initially. So

7 there's a lot of softness in the assumptions

8 underlying this.

9 My second question is this, the

10 extrapolation issue. A lot of your children have

11 congenital heart disease, some ASD, some Down

12 syndrome, that we know that patients with ASD tend to

13 live longer. Do we have evidence that extrapolation

14 will work to the children with congenital heart

15 disease?

16 DR. KAUL: Thank you.

17 Dr. Veltri?

18 DR. VELTRI: This is a question. We're

19 dancing around the surrogate endpoint versus endpoint.

20 It sounds like, from your discussion this morning,

21 that you believe that the hemodynamic variable is part

22 and parcel of the disease and that you are actually

1 using that clinically both in clinical trials, as well
2 as management of patients.
3 We have validated surrogates, if you will,
4 LDL cholesterol, blood pressure, hemoglobin A1C for
5 microvascular disease. So my question is, from a
6 regulatory perspective, I understand we're trying to
7 say this is a surrogate endpoint, but in your opinion,
8 is this indeed the disease and the clinical endpoint?
9 DR. BARST: Thank you very much for asking
10 that. It's my belief and those of my colleagues,
11 particularly the pediatric and the adult PAH
12 community, that pulmonary vascular resistance
13 measurements are the disease. And even though the
14 symptoms are based on the secondary effects of that
15 increased pulmonary vascular resistance, increasing PA
16 pressure and, therefore, increasing right ventricular
17 work, the treatment, if we're most effective, is to
18 decrease the pulmonary vascular resistance.
19 DR. KAUL: Thank you.
20 Dr. Rosenthal?
21 DR. ROSENTHAL: I just have a few quick
22 questions and most of them can probably be answered

1 just numerically. I'm wondering, Dr. Barst, if you
2 can help me understand the current median survival for
3 children diagnosed with PAH. And then I've got a
4 couple of questions about risk of cath in different
5 situations.
6 DR. BARST: For clarification, the current
7 median survival with our using the adult drugs off
8 label?
9 DR. ROSENTHAL: However you would describe
10 the current median survival with a person's own
11 organs.
12 DR. BARST: The current five-year survival
13 for children, from a number of registries from Europe
14 and from the U.S., is approximately 70 percent, which
15 is consistent with an improvement on the therapies
16 that are available.
17 DR. ROSENTHAL: And the natural history,
18 getting at your point about --
19 DR. BARST: The natural history was a median
20 survival of one to two years and a five-year survival
21 of less than 30 percent.
22 DR. ROSENTHAL: Okay. And then moving over

1 to the risks of cardiac catheterization, you made
2 reference to caths being done in centers with
3 experience, and the implication is that not all
4 centers have that experience. I'm wondering if you
5 can help me understand what the risk of cardiac
6 catheterization is for a patient with pulmonary
7 hypertension in an experienced center and then what it
8 might be in an inexperienced center.
9 DR. BARST: Thank you. The risks for
10 cardiac catheterization for both morbidity and
11 mortality have decreased significantly since I've been
12 in the field. Where in the 1980s and early 1990s at a
13 center that we thought had a lot of experience, our
14 center, we had a mortality rate of approximately 1 and
15 a half percent. Over the past 10 years at Columbia,
16 performing 1,500 cardiac catheterizations on children
17 with PAH, we've had no deaths. During that time, we
18 had one child who arrested during the procedure and
19 was successfully resuscitated.
20 There are recent data that are in
21 publication from similar centers of experience where
22 there are also being reported no deaths. There

1 certainly appears to be an increase in morbidity and
2 mortality from less experienced centers, although the
3 best data that is available is that the mortality from
4 those centers is still less than 2 to 3 percent.
5 DR. KAUL: Thank you.
6 Dr. McGuire, a brief question, a brief
7 answer, please.
8 DR. MCGUIRE: Okay. This should be fairly
9 brief. I'm concerned at the conspicuous absence of PA
10 saturation in all of this data analysis. PVR is
11 notoriously inaccurate and violates almost every
12 assumption of Ohm's Law, although it's probably
13 precise, not very accurate. So the question becomes
14 what are the challenges of PVR versus some other more
15 simple and directly measured hemodynamic parameter or
16 measure of performance.
17 DR. BARST: We certainly measure mixed
18 phenol saturation and we measure the complete cohort
19 of pulmonary and systemic hemodynamics in all of these
20 patients. I just limited what I was showing you for
21 simplicity. It is much more difficult because we
22 particularly wanted to include children with

1 congenital heart disease associated with pulmonary
2 hypertension, because there are a lot of those
3 children, and we wanted to include children who were
4 who were unrepaired, as well.
5 In that cohort, we must do fit calculations,
6 and we must get oxygen saturations from all the
7 appropriate sample sizes. And that has been done,
8 and, in fact, we looked at every single CRF to make
9 sure that that was done appropriately.
10 DR. KAUL: Thank you.
11 We'll take one last question from the
12 committee before the FDA presentation.
13 Dr. Rich?
14 DR. RICH: I really want to take issue with
15 one of the statements in one of your slides, and that
16 had to do with the clinically relevant outcomes. No
17 one is making any claim with any of the drugs of a
18 survival benefit. It's really whether it's halt
19 progression, cause regression, improve ventral side
20 performance, quality of life, et cetera.
21 The notion that time to clinical worsening
22 is unrealistic in children, I totally disagree,

1 because if your statement is that the children don't
2 worsen, then what's the point, the actual history?
3 And if the children do worsen, then we can measure
4 that, and that is something that would be something
5 truly applicable.
6 I think it will come up later, but it speaks
7 to the fact that children with congenital heart
8 disease have a much different survival pattern than
9 children with idiopathic pulmonary hypertension.
10 DR. KAUL: So, Dr. Rich, that was a comment
11 not a question, correct?
12 DR. BARST: Could I respond to it, though?
13 DR. KAUL: Please.
14 DR. BARST: Thank you. I beg to disagree on
15 every point you made, Dr. Rich. It's been our
16 longstanding -- we've thought long and hard that the
17 natural history of congenital heart disease has a much
18 better long-term outcome than that of patients with
19 IPAH or familial PAH. However, in the current era, we
20 have looked at data, and with treatment we see now
21 identical two-year survival and five-year survival.
22 Whether that is because we're being much

1 aggressive treating the IPAH and less aggressive with
2 the congenital heart disease or are we closing some of
3 the holes that maybe we shouldn't, I don't know. But
4 the survival is the same, number one.
5 Number two, regarding using outcome,
6 morbidity and mortality in the survival study as an
7 endpoint, I completely disagree. I would love to have
8 survival data, but it's unethical. And I gave an
9 estimate of what the overall survival was from
10 pediatric data around the world, which, at five years,
11 was approximately 70 percent; however, there are
12 significant differences.
13 Our five-year survival at Columbia was 89
14 percent. We had a 10-year survival of 81 percent.
15 And similar data are from the University of Colorado.
16 If we're going to do a survival study and we have a
17 10-year survival of 81 percent, we're not going to be
18 able to do that study in any time when we want to get
19 a drug approved.
20 DR. KAUL: Thank you, Dr. Barst.
21 We have to move on. We'll get back to this
22 in the afternoon in greater details. I'd like to call

1 upon Dr. Brar to give his presentation.
2 DR. BRAR: Good morning, AC committee
3 members, Dr. Stockbridge, Dr. Temple, and the public.
4 I'd like to thank you-all for gathering here today.
5 Today I'm going to present an investigation
6 and the conclusions of our investigation stating that
7 delta PVRI or change from baseline in pulmonary
8 vascular resistance index should be used as an
9 endpoint in pediatric PAH trials for drugs that are
10 already approved in adults.
11 Prior to getting involved in the
12 investigation, I'd like to give you some information
13 about why we conducted this study. So the premise for
14 the investigation is, one, the exercise capacity
15 tests, such as the six-minute walk distance, are often
16 not feasible in pediatric patients with PAH.
17 Therefore, we need to find a measure to use to monitor
18 disease severity and to assess treatment efficacy.
19 As Dr. Barst already stated, the pediatric
20 disease is similar to adults. Therefore, we are using
21 the adult trial information to explore a particular
22 measure for pediatric patients. With the conclusions

1 of our results, our intent is primarily to use
2 hemodynamics as a basis of approval in pediatric
3 patients for PAH therapy for drugs that are already
4 approved in adults.
5 Now, I'd like to go over the background on
6 why we're looking at hemodynamics. As we are all
7 familiar with now, pulmonary arterial hypertension is
8 very severe disease. The hallmark of the disease is
9 that we have an increase in resistance and pressure
10 within the pulmonary arteries. Now, the clinical
11 manifestation of this increase in resistance and
12 pressure is we get symptoms such as dyspnea on
13 exertion. We have chest pain.
14 In addition, we have a decreased or
15 diminished physical activity, which could also -- we
16 say we have a decrease in exercise capacity. Now,
17 this exercise capacity measure is looked at in the
18 clinics currently to assess treatment effect and
19 disease progression. And one of the primary measures
20 that is used is what's called a six-minute walk
21 distance. What's primarily used is the six-minute
22 walk distance.

1 This is the primary endpoint that's used for
2 regulatory approval in adults. In addition and
3 unfortunately, we're unable to conduct this test in
4 pediatric patients because it's not feasible, and in
5 addition, the interpretability in pediatrics is a bit
6 contentious.
7 Therefore, we think keeping this schematic
8 in mind, that the next logical step to look at would
9 be this increase in resistance and pressure within the
10 pulmonary arteries. And one way to do this is to look
11 at cardiopulmonary hemodynamics. One, first and
12 foremost, is it's the gold standard for diagnosis in
13 both adults and pediatrics. Also, it characterizes
14 the disease progression. It represents severity and
15 predicts survival. Also, it's the closest measure to
16 the physiological target of PAH therapies.
17 So in our investigation, we had several
18 questions we wanted to answer to explore the utility
19 of hemodynamics. But I will summarize them in three
20 questions. And of note, I'm going to focus on delta
21 PVRI or change from baseline in pulmonary vascular
22 resistance index as our measure of interest. Of note,

1 we looked at many other hemodynamic measures for a
2 relationship with exercise capacity, but I will
3 present our top-line results, which is based on delta
4 PVRI.
5 One of the first questions we wanted to ask
6 is: Do treatment-induced effects on hemodynamics
7 explain treatment-induced effects on exercise
8 capacity? Now, when I generated this question, it took
9 me a little bit of time to actually understand what
10 this question means. In basic, simple terms,
11 accounting for the placebo, if we see an effect on
12 hemodynamics, does it translate to the effect seen on
13 exercise capacity?
14 In addition, we wanted to look more on the
15 pooled analysis on a trial level to see, one, is there
16 a relationship between hemodynamics and exercise
17 capacity in adults? And this is to establish some
18 internal consistency.
19 With all this information, we also want to
20 determine then how could we use this adult hemodynamic
21 and exercise capacity information to design pediatric
22 clinical trials. So our investigation involved the

1 analysis of hemodynamic and six-minute walk distance
2 data from 13 randomized double-blind placebo- or
3 active-control studies from seven different therapies.
4 And the seven different therapies fell into three
5 categories of mechanisms of action, including the PDE5
6 inhibitors, the prostacyclins, and endothelin receptor
7 antagonists. And of note, what we used within these
8 13 randomized trials is a subset population of WHO,
9 Group 1, idiopathic familial PAH patients, presumably
10 because the idiopathic familial PAH is similar to
11 what's seen in the etiology in the pediatric patients.
12 Our analysis included a total of 1,096
13 subjects that had hemodynamic and six-minute walk
14 distance data. The hemodynamic measures were
15 evaluated on a univariate measure, and also
16 combinations were mean arterial pressure, mean
17 pulmonary arterial pressure, pulmonary capillary wedge
18 pressure, cardiac index, and right atrial pressure.
19 In addition, we looked at composite measures
20 such as pulmonary vascular resistance index and
21 systemic vascular resistance index to see if they
22 related with six-minute walk distance. In addition,

1 our analysis included looking at the absolute number,
2 meaning for a given hemodynamic number, what does it
3 relate to a given six-minute walk distance. In
4 addition, we looked at the change from baseline at
5 both the delta and percent change from baseline.
6 So I've included in the background an
7 addendum looking at the percent change from baseline,
8 but for this presentation, I will only be presenting
9 the delta change. I just want to let you know that
10 the conclusions that I deduce from the delta change
11 are also applicable to the percent change from
12 baseline.
13 Our database of 1,096 subjects included a
14 wide age range ranging from 18 to 83, with a majority
15 of the patients being female. What I want you to
16 gather from this database is that we have patients of
17 different disease severity, of New York Heart
18 Association class, functional class, ranging from 1,
19 2, 3 and 4, where 4 is the most severe state. What I
20 want you to gather is that most of the patients were
21 NYHA Class 2 and 3, representing moderate disease.
22 In addition, the trial design, we have

1 patients in our database that were randomized to
2 either control or active treatment. Control can
3 either be pure placebo or it could be also placebo on
4 top of stabilized background therapy, where we have
5 approximately, in our database, a total of about 40
6 percent of the population that was randomized to
7 control.
8 In addition, the trials that the patients
9 were involved in were of different durations ranging
10 from 12 weeks, 16 weeks and 24 weeks. So our database
11 included a few things. One is that the trials
12 involved seven different therapies of three different
13 mechanisms of action. In addition, we have different
14 disease severities. Also, patients that are
15 randomized to control or an active treatment, and
16 there are different trial durations.
17 The first question we wanted to ask is: Do
18 treatment-induced effects on hemodynamics explain the
19 treatment-inducted effects on exercise capacity? And
20 again, in simple terms, accounting for the placebo, if
21 we see a change in hemodynamics, does that translate
22 to a change in exercise capacity?

1 Before I get involved with the results, I'd
2 like to orient you to the type of analysis that was
3 conducted to answer this question. We are looking at
4 what's called a double delta plot, where the first
5 delta is the change from baseline and the second delta
6 represents active minus control. So we're accounting
7 for the placebo. And what we have on the X axis is
8 the double delta PVRI, meaning the difference in the
9 change from baseline between active and control. And
10 on the Y axis, we're looking at the double delta six-
11 minute walk distance.
12 Upon looking at this grid here, if you're
13 not to see a relationship, you would essentially see
14 no systematic trend with points spanning across the
15 quadrants. In addition, upon looking at these
16 quadrants, I want you to gather the expected
17 physiology of these measures. The delta PVRI, if it's
18 to the right of the Y axis, it means that we're having
19 a worsening in PVRI. To the left of the Y axis, it
20 means we're improving PRVI. And alternatively, on the
21 Y axis, for six-minute walk distance, if we're above
22 the X axis, we're improving six-minute walk distance

1 or exercise capacity and below is a worsening.

2 So looking at the individual quadrants, up

3 on the right-hand quadrant, if the data points were to

4 fall into that range, we would see a worsening

5 pressure, but an improvement in exercise; on the lower

6 right-hand quadrant, a worsening pressure or a

7 worsening exercise; on the lower left-hand quadrant,

8 an improvement in pressure would yield a worsening

9 exercise; and, on the upper left-hand quadrant,

10 improvement in pressure would yield an improvement in

11 exercise.

12 So keeping the physiology in mind, I would

13 like for you to look at our results. One, we found

14 that the treatment-induced effect on delta PVRI

15 explains the treatment-induced effect on six-minute

16 walk distance. Here, we have on the X axis the double

17 delta PVRI; on the Y axis, double delta six-minute

18 walk distance.

19 What I have for you here are observations, a

20 total of 18 observations representing the dose group

21 for each of the 13 trials. And each bubble represents

22 the dose group and the size of the bubble represents

1 the number of subjects that were evaluated. So
2 essentially, the size of the bubble is proportional to
3 the number of subjects that were evaluated.
4 In addition, I've denoted, as well, the
5 mechanisms of action for each bubble just for
6 reference. First and foremost, qualitatively, you
7 could see that -- and, of course, I've cut off the
8 rest of the quadrants, but the majority of the trials
9 fall into this upper left-hand quadrant, showing that
10 over placebo, an improvement of PVRI translates to an
11 improvement over six-minute walk distance.
12 In addition, looking at this more
13 quantitatively, we ran a linear regression, a weighted
14 linear regression, showing there is a statistically
15 significant relationship between double delta PVRI and
16 double delta six-minute walk distance.
17 But I would like for you to keep in mind
18 that this is physiologically plausible, where we have
19 an increase over placebo in PVRI, meaning a reduction
20 in PVRI, meaning an improvement of PVRI, we see an
21 improvement of six-minute walk distance.
22 The next question we wanted to ask was more

1 on a trial level. Is there a relationship between
2 hemodynamics and exercise capacity in adults? We
3 looked at the pooled analysis, and we looked at our
4 trial-level analysis to establish some internal
5 consistency. And as I stated earlier, we looked at
6 all of the hemodynamics for a particular relation with
7 six-minute walk distance.
8 We found that, first and foremost, that
9 delta PVRI is a significant predictor of delta six-
10 minute walk distance, where on the X axis, we have
11 delta PVRI change from baseline in PVRI, on the Y
12 axis, we have change in six-minute walk distance. And
13 I have binned the observations for 1,096 observations,
14 both active and control patients, into 10 different
15 bins, where each bin represents 100 subjects and each
16 point represents the median delta PVRI for that bin
17 and its corresponding mean delta six-minute walk
18 distance for that bin.
19 The arrow bars represent the 95 percent
20 confidence bound about the bin, and I also have a
21 regression showing that there is a relationship on the
22 regression, the linear regression. There is a

1 significant relationship, and the linear regression is
2 about all 1,096 subjects. It's not only the bins.
3 It's about all 1,096 subjects, showing that there is,
4 on average, a relationship. In addition, the
5 relationship is physiologically plausible. Where we
6 have an improvement of PVRI or a decrease in PVRI, we
7 see an improvement in exercise capacity.
8 We then want to evaluate this on a trial
9 level. What I have shown you here is a forest plot
10 looking at the 13 individual trials for the slope of
11 the delta six-minute walk distance versus delta PVRI.
12 Looking at the slope estimates, the black dot, and its
13 corresponding 95 percent confidence bound. On this, I
14 guess you could say this Y axis, it shows the number
15 of subjects that were evaluated in each of the trials.
16 In addition, I have demarcated a black line showing a
17 zero slope. And for reference, I've kept the pooled
18 analysis, the estimate and the 95 confidence bound for
19 the pooled analysis up at the top.
20 Qualitatively, looking at this, you could
21 see that the direction within all 13 trials is the
22 same, meaning than an improvement in PVRI, we see an

1 improvement in six-minute walk distance. In addition,
2 you could look quantitatively, that for the most part,
3 the 95 percent confidence bounds are overlapping,
4 suggesting that the slopes are indistinguishable.
5 In addition, looking at it more through a
6 therapeutic mechanism of action, I've also categorized
7 these looking at the prostacyclins, endothelin
8 receptor antagonists, PDE5 inhibitors. In addition,
9 the patients are randomized to control. Also, for
10 reference, the pooled analysis, looking at the slope
11 estimate and its 95 percent confidence interval about
12 that slope estimate, again, qualitatively, you could
13 see that they're falling, on average, in the same
14 direction. Where we have the improvement in PVRI, we
15 see the improvement in six-minute walk distance.
16 In addition, for the most part, the 95
17 percent confidence intervals are overlapping,
18 suggesting that this relationship holds despite the
19 mechanism of action, despite treatment. Regardless of
20 the treatment that's given, this relationship still
21 holds.
22 So the conclusions of our analysis is we

1 think, one, that the treatment-induced changes in PVRI
2 is able to explain the treatment-induced changes in
3 delta six-minute walk distance. In addition, we see,
4 on average, that delta PVRI shows a significant and
5 consistent relationship with exercise capacity in
6 adults, and it's amongst all 13 trials, seven
7 different drugs, three different drug classes.
8 In addition and I think what's most
9 important is that the relationships are
10 physiologically plausible. Where we see an
11 improvement in PVRI, we see an improvement in six-
12 minute walk distance.
13 The final question we wanted to ask is,
14 okay, what do we do with this information that we
15 have. How can we use the adult hemodynamic and
16 exercise capacity information to design pediatric
17 clinical trials? First and foremost, we think that
18 the PVRI measure can be used for a basis of approval
19 in pediatric trials.
20 Let me stipulate we want to use this for PAH
21 therapies that are already approved in adults, not
22 only because we saw that the delta PVRI shows a

1 relationship to exercise capacity in adult patients,
2 but, in addition, PVRI is used for diagnosis of PAH in
3 both adults and pediatrics. PVRI is a significant
4 predictor of survival in adults based on the REVEAL
5 registry. Also, the pulmonary vasculature is the
6 target for PAH therapies as PDE5 enzymes within the
7 pulmonary vasculature, we have also the prostacyclin
8 receptors and the endothelin receptors that are
9 involved within the pulmonary vasculature.
10 So, one, we think that the delta PVRI
11 measure should be used for pediatric patients. In
12 addition, we think we could use the relationship, the
13 adult relationship, to target a particular PVRI effect
14 size. For instance, if we have a particular meter
15 difference that we are trying to target over placebo,
16 what would the corresponding relationship -- using
17 this relationship, what would the corresponding PVRI
18 over placebo, what we would need?
19 In essence, as well, on the next slide, I
20 have just -- for discussion later, we could look at
21 different effect sizes that we're trying to target for
22 six-minute walk distance and its corresponding effect

1 size that we would see for PVRI. For instance, if we
2 were trying to target a 10-meter difference over
3 placebo, our corresponding PVRI that we're trying to
4 target would be around 212.
5 In addition, I also want you to know that we
6 could use this relationship based on the percent
7 scale. Again, I've included an addendum to the
8 backgrounder showing that the relationship still holds
9 if we're looking at the percent change from baseline
10 in PVRI versus percent change in baseline for six-
11 minute walk distance. We still see a significant
12 relationship on the double delta plot, and, using this
13 relationship, we can come up with a particular target.
14 For instance, if we're trying to target a 10 percent
15 in baseline over placebo, we would need about a 23
16 percent change over placebo in PVRI.
17 So what else can we use this relationship
18 for? We think that the relationship can be used to
19 guide pediatric drug development. And how? In adult
20 registration trials, we suggest, and it's already
21 done, that six-minute walk distance information and,
22 also, delta PVRI information be collected. And within

1 the adult trial, establish the relationship in the
2 adults, then we essentially specify -- using the
3 relationship, specify a particular target for PVRI
4 that we need.
5 Using that target, we can power our study
6 prospectively to look at, in a pediatric study, what
7 our target should be. And in our pediatric study, we
8 would run placebo-controlled dose-ranging studies to
9 perform to achieve different degrees of hemodynamic
10 benefit. And we could essentially come back to the
11 relationship to derive dosing based on the desired
12 benefit in exercise capacity.
13 So I'd like to acknowledge a few people that
14 were involved with this project and gave me some input
15 and scientific input. And I'd like to accept any
16 questions. Thank you for your time.
17 DR. KAUL: Thank you, Dr. Brar.
18 We have 10 minutes for questions.
19 Dr. D'Agostino?
20 DR. D'AGOSTINO: That was very nicely
21 developed and presented. I do have one comment that
22 you may want to consider. I don't know if it'll

1 change the results too much, but all your analysis is
2 sort of internally fulfilling because you never let
3 one study say how well it would do in the other study.
4 You may want to go back and do some of the analysis
5 where you take the 13 studies, for example, drop one
6 study, see what function you get with the 12 studies,
7 how well does it predict the 13th study and just run
8 around that, keep dropping one study out at a time.
9 It's a fairly standard validation technique, and I
10 think it would reinforce what you have here. It would
11 also give you a better sense of the variability that
12 some of it's carrying here, because this is, as I say,
13 very much wish-fulfilling and it over-fits the data,
14 possibly. But if you're willing to do --
15 DR. BRAR: So you're suggesting to do
16 something like a sensitivity analysis.
17 DR. D'AGOSTINO: Well, it's actually even a
18 developmental analysis. You may want to develop the
19 function in this fashion.
20 DR. STOCKBRIDGE: Doesn't slide 12 address
21 your concern?
22 Can you put slide 12 back up?

1 DR. D'AGOSTINO: No, because, you see, this
2 is always taking the studies that you have and seeing
3 how well they fit themselves.
4 DR. STOCKBRIDGE: It's the next slide. Look
5 at the next slide. That's each individual study.
6 DR. D'AGOSTINO: But again, the overall
7 combines them all. It doesn't say how well the first
8 12 predict the 13th. You can easily do it. This
9 gives you a lot of encouragement that what you're
10 doing is exactly right on target. It's to actually
11 get this sort of validation. You do find -- I'm
12 sorry. You were saying?
13 DR. NEATON: I totally agree with Ralph.
14 This is helpful. This is at the individual patient
15 data. Go back to the delta-delta slide. That's kind
16 of, I think, what Ralph is referring to. The slide
17 with --
18 DR. BRAR: The double delta?
19 DR. NEATON: The double delta.
20 So I think the typical -- this would give
21 you some idea of its application. So drop one of
22 these studies at a time, refit this model, and then

1 apply it to the study and see how it compares with
2 what you observed, because if you repeatedly do that,
3 that will give you some notion of how well your model
4 is going to work and, also, the confidence around, the
5 predicted confidence level.
6 DR. D'AGOSTINO: Again, these are all --
7 you're looking at it internally, but all of these
8 predictive models and what have you, this is what
9 we're saying is just very standard methodology.
10 There's nothing clever about it.
11 DR. KAUL: The technical term is
12 calibration. So you want to make sure that your
13 predicted variables fit well with the observed
14 variables.
15 I am next in asking the questions.
16 So did you have information about the other index
17 of exercise capacity, which is the VO2 peak in adults,
18 and did you construct a similar relationship? Because
19 the key issue at hand is that we have the VO2 peak
20 data in children and to see how well we can
21 extrapolate this relationship that we observe in the
22 adults to the children.

1 DR. BRAR: From the entirety of data that we
2 have at the FDA, I could only recall a very few number
3 of trials that actually looked at peak VO2 in adults.
4 Most of the information I saw was based on six-minute
5 walk distance, and because that is the primary
6 endpoint that's used in PAH trials, that is the one
7 that we chose. But we do have -- I think it's limited
8 data on peak VO2 information.
9 DR. KAUL: Thank you.
10 Dr. McGuire?
11 DR. MCGUIRE: I wonder if you might comment
12 on how much this association you've observed may be
13 biased by the exclusion of data from study drugs that
14 did not meet approval criteria. That is, in reviewing
15 these drugs, they've all had to show both improvements
16 in hemodynamics and performance. And so you're
17 effectively contriving this association, and it's
18 represented here by the complete absence in any of the
19 other three quadrants. So to come to market, you
20 would have to have both hemodynamic and performance
21 measures met.
22 I wonder if there are data from drugs

1 developed, but not approved, where a discordance
2 existed; and if that's the case, that would be a
3 strong disincentive to accept this as an intermediate
4 marker of surrogacy.
5 DR. BRAR: I agree. With the data that I've
6 seen thus far in the large trials that have this type
7 of hemodynamic and six-minute walk distance
8 information, we only have some data coming in from the
9 failed trials, the big, large failed trials that
10 evaluated six-minute walk distance and hemodynamics.
11 So I will take a look at that.
12 DR. MCGUIRE: And just very quickly, have
13 you observed any disconnects?
14 DR. BRAR: Thus far, no, I have not. And I
15 think also what I'd like to show you maybe will give
16 you some information about this, is looking at the
17 control patients; the control patients who did not see
18 a benefit in either exercise capacity or hemodynamic
19 information, where essentially the slope relation with
20 the control patients is similar to that of the active.
21 DR. KAUL: Thank you.
22 Dr. Veltri?

1 DR. VELTRI: Very nice work. A quick
2 methodologic question. I understand this is really a
3 completer's analysis, and last observation carried
4 forward kind of excluding. And I noticed in a
5 briefing document, you started about 2,000 patients
6 and you ended up with 1,000. Some of those were non-
7 WHO Group 1.
8 DR. BRAR: Correct.
9 DR. VELTRI: So did you do a sensitivity
10 analysis? Because there could have been some reason
11 why -- even if you had paired readings, but they
12 didn't get to a completers -- that could help or
13 dissuade.
14 DR. BRAR: Unfortunately, a lot of the
15 trials that we looked at -- so there's a total of
16 about 42 trials that we have at the FDA that had
17 information. Unfortunately, not all of them have
18 hemodynamic measures. Most of these use one point in
19 time, which is at baseline and end of therapy.
20 So if the patients did not have an end-of-
21 therapy measure, I did not want to extrapolate from
22 baseline up to -- essentially from baseline. So this

1 is essentially completer information, and we want to
2 see more physiologically. Without extrapolation,
3 we're using last observation carried forward, if this
4 relationship holds physiologically. That was our
5 intent.
6 DR. KAUL: Thank you.
7 Dr. Rich?
8 DR. RICH: Yes. Can you go back to your
9 slide 12? So am I interpreting this correctly that
10 you have here an improvement in six-minute walk in
11 subjects where the PVRI actually went up? Am I
12 interpreting this correctly?
13 DR. BRAR: The PVRI --
14 DR. RICH: The delta PVRI, you're saying
15 that a positive value going to the right of zero.
16 DR. BRAR: Okay. To the right of zero.
17 DR. RICH: Yet the six-minute walk still
18 improved.
19 DR. BRAR: Yes. So you're asking about kind
20 of like what's happening here with this intercept,
21 correct?
22 DR. RICH: Right. Well, I see it's saying

1 that there were cases where the PVRI was actually
2 worse, when we say higher, and yet the six-minute walk
3 still improved.
4 DR. BRAR: And I could attribute this to a
5 training effect. So what I think -- and I'm putting
6 it in my terms -- where we actually see a positive
7 intercept on this relationship, a positive Y
8 intercept, where if we don't see a change in PVRI, we
9 actually have a change in six-minute walk distance.
10 And what I want you to gather is that this is active
11 and control patients all combined together, where
12 we're looking at here is essentially somewhat of a
13 training effect that's only seen in six-minute walk
14 distance.
15 Upon looking at the double delta plot, if
16 you could see the relationship, we have a zero
17 intercept accounting for placebo and I think also
18 accounting for the training effect that's seen.
19 DR. KAUL: Thank you.
20 Dr. Kawut?
21 DR. KAWUT: Very nice presentation. I
22 wanted to know if you looked at some traditional

1 measures of surrogacy such as the proportion of
2 treatment effect --
3 DR. BRAR: Proportion explained?
4 DR. KAWUT: -- accounted for by the
5 surrogate. And then a second question is, it strikes
6 me as a little funny that we're looking at a surrogate
7 to predict an intermediate endpoint rather than using
8 a surrogate to look at a definitive endpoint, such as
9 time to lung transplantation or time to death.
10 Have you done that work, as well?
11 DR. BRAR: I have not looked at the
12 evaluation of these hemodynamics as it relates to
13 harder endpoints such as death or transplant.
14 Unfortunately, the number of trials that we've had
15 that had this information, the PVRI information,
16 essentially, the information that we have would not
17 conclude any significant results based on the data
18 that we have.
19 DR. KAUL: Thank you.
20 Dr. Krantz?
21 DR. KRANTZ: I loved your presentation. I
22 particularly liked the delta-delta. It reminds me of

1 TQT studies. But one quick question in terms of the
2 sensitivity analysis. Did you look at just the
3 studies that were double-blind, randomized, controlled
4 and look at that and was it consistent?
5 DR. BRAR: Yes.
6 DR. KRANTZ: And then the second question is
7 in terms of the TQT, did you look at proportional
8 thresholds in terms of those that had a meaningful
9 increase in six-minute walk as an analysis?
10 DR. BRAR: You know what? First and
11 foremost is trying to figure out what that meaningful
12 change is. I think amongst the PAH community, trying
13 to figure out what a meaningful change in six-minute
14 walk distance means, also how it relates to PVRI.
15 That's one thing I think we should also discuss is
16 this particular treatment effect size.
17 So to answer your question, essentially, is
18 to look at what is that threshold that we're trying to
19 target. And I kind of also want to discuss today what
20 we should be looking at in terms of that threshold.
21 Once we come up with some consensus on that
22 threshold, then I would run some type of analysis on

1 it.

2 DR. KAUL: Thank you. We will deliberate on

3 that this afternoon.

4 One last question before the sponsor's next

5 presentation.

6 Dr. Neaton?

7 DR. NEATON: Thank you. Nice presentation.

8 I have several questions we'll come back to this

9 morning, but one simple one. If you were to make a

10 decision based on a nominal significance level of .05,

11 what concordance is there in these 13 trials between

12 using these two outcomes?

13 DR. BRAR: So doing --

14 DR. NEATON: Suppose your endpoint was

15 change in PVRI versus change in six-minute walk,

16 what's the level of concordance in that decision-

17 making process for the trials that you looked at here?

18 DR. BRAR: Based on the trials that we have,

19 you're talking about the approvability concordance?

20 DR. NEATON: Typically, faced with the trial

21 that's kind of set up with a design around a nominal

22 significance level of .05, had you applied that level

1 to these trials and used six-minute walk as the
2 outcome versus using change in PVRI as an outcome?
3 What's the level of concordance? Would you have made
4 the decision the same in all the trials?
5 DR. BRAR: Okay. So I did somewhat of an
6 analysis looking at the individual doses, essentially,
7 the final results from each of the trials, and
8 compared them to the results that we see on this
9 double delta plot. And essentially, there was
10 concordance between what was originally stated in the
11 label and what we see essentially on here. Is that
12 what you mean by the concordance?
13 DR. NEATON: Is the difference in treatment
14 groups and change in PVRI significant at the .05
15 levels in all the trials?
16 DR. BRAR: In all trials, they are. In all
17 trials, they are.
18 DR. KAUL: For both the variables?
19 DR. BRAR: For both variables.
20 DR. KAUL: Thank you.
21 At this point, I'd like to invite Nancy
22 McKay to give her presentation.

1 MS. MCKAY: Good morning. I'd like to start
2 our sponsor presentation today by thanking the FDA and
3 their advisory committee for inviting Pfizer to
4 present sildenafil data at today's meeting.
5 My name is Nancy McKay. I'm the U.S.
6 regulatory lead for Revatio, and I'm going to give an
7 introduction of regulatory history beginning to
8 describe some of the learnings we've had along the way
9 during the sildenafil development program.
10 My introduction will be followed by a
11 presentation given by Dr. Colin Ewen, who will present
12 the sildenafil adult and pediatric PAH development
13 program. Dr. Ewen's presentation will be followed by
14 Dr. Lutz Harnisch, who will present a model-based
15 approach to the integration of adults and pediatric
16 data with sildenafil. Dr. Ewen will return for
17 closing remarks.
18 We're delighted to be here today to
19 contribute to the discussions of the treatment of
20 children with PAH. As Dr. Barst mentioned in her
21 presentation, there are no currently approved
22 treatments in PAH for children. This is partly

1 because there are no agreed endpoints for clinical
2 trials.
3 We're here today to show you data from our
4 adult sildenafil program which resulted in approval
5 based on exercise capacity and has contributed to our
6 understanding of sildenafil use in children with PAH.
7 We'd also like to describe for you the first pediatric
8 development program in children with PAH, which
9 includes a randomized controlled trial in children.
10 The study of sildenafil in children has been
11 a learning process for us at Pfizer, and we'd like to
12 acknowledge our continued collaboration with FDA
13 during the process to help suggest potential ways
14 forward during the development.
15 I'd like to walk you through a brief
16 regulatory history for Revatio, which is a PDE5
17 inhibitor for the treatment for PAH. The IND for
18 Revatio was first submitted in August of 2001. We
19 thought it was important to study children with PAH
20 early during the development program, and FDA issued a
21 pediatric written request in December of 2001. The
22 adult development program for sildenafil, which was

1 conducted in parallel, initiated in October of 2002.
2 The pediatric study A1481131, which is the main topic
3 of our sponsor presentation today, began in August of
4 2003. In the meantime, adult data continued to
5 accrue. We submitted an NDA for adults, which received
6 approval based on exercise capacity in June of 2005.
7 With the continued study of Revatio, the
8 addition of a delay in clinical worsening claim was
9 added to the labeling in May of 2009. With that
10 addition of delay in clinical worsening claim, we
11 thought it was important to look at alternative
12 formulations for sildenafil for patients who are
13 temporarily unable to take tablets. That IV
14 formulation was approved in November of 2009.
15 The study of sildenafil in children has been
16 a learning process for us, and sildenafil has become
17 the standard of care in adults with PAH, with over
18 60,000 patients treated to date.
19 During the development program for
20 sildenafil, we've worked very closely with FDA, and
21 we've learned quite a lot over the years of
22 development. We look forward to the submission of our

1 pediatric NDA, which is currently under preparation.
2 The adult information I described in the
3 previous slide has contributed to the Revatio labeling
4 and the indication you see here on the screen.
5 Revatio is indicated for the treatment of PAH Who
6 Group 1 to improve exercise ability and delay clinical
7 worsening. The delay in clinical worsening was
8 demonstrated when Revatio was added to background
9 epoprostenol therapy.
10 As mentioned in Dr. Stockbridge's
11 presentation, the original sildenafil development
12 program for children and, therefore, the original
13 written request, consisted of a full-blown development
14 program. This was because we had not yet studied
15 sildenafil in adults, and so very little was known
16 about the clinical benefits of sildenafil in PAH at
17 that time.
18 The program consisted of the studies you see
19 here, a study for chronic treatment of PAH with a
20 long-term extension; a placebo-controlled withdrawal
21 study to show durability of treatment effect; and, two
22 specialty studies, one for postoperative congenital

1 heart disease and one for persistent pulmonary
2 hypertension of the newborn, PPHN.
3 Changes often occur during development
4 programs, and for pediatric programs, that means
5 changes are needed to written requests, as
6 Dr. Stockbridge mentioned. That was certainly the
7 case for sildenafil. So I'd like to describe for you
8 the clinical amendments to the sildenafil written
9 request.
10 If I can focus you on the bottom of the
11 screen, you'll see the two specialty studies I
12 mentioned for postoperative congenital heart disease
13 and PPHN were removed from the sildenafil written
14 request in 2005 by agreement between FDA and Pfizer.
15 This was due to a change in treatment paradigm that
16 resulted in difficulties enrolling patients.
17 Moving up the screen, the need for placebo-
18 controlled withdrawal study was satisfied when we
19 submitted and received approval for a time to clinical
20 worsening claim for Revatio in 2009.
21 That still left us with the largest
22 pediatric program ever conducted in this patient

1 population. The A1481131 study and its long-term
2 extension was a difficult study to conduct. We
3 conducted this study in 16 countries, and it took us
4 almost five years to do it. There are 234 patients in
5 this study, and it's the only randomized controlled
6 trial in this patient population.
7 It's Pfizer's belief that we've conducted a
8 study that informs the treatment of children with PAH
9 with this study. We look forward to the discussions
10 at the meeting today to help inform future discussions
11 with FDA toward the appropriate amendment of the
12 sildenafil written request.
13 Specific to today's discussions on
14 hemodynamics as an efficacy endpoint, it's important
15 to remember that adult and pediatric Revatio programs
16 were designed to evaluate sildenafil efficacy using
17 exercise capacity and hemodynamic measures including
18 PVRI. We believe that PAH is a similar disease in
19 adults and children.
20 The presentation of data that follows this
21 one will show that changes in exercise capacity are
22 associated with changes in hemodynamics, particularly

1 PVRI, and the data will support the use of PVRI as an
2 endpoint in children with PAH to inform labeling where
3 a drug has documented to improve exercise capacity in
4 adults. These data support inclusion of hemodynamics
5 in the sildenafil written request.
6 I'd now like to introduce Dr. Colin Ewen,
7 who will give a presentation on the sildenafil adult
8 and pediatric PAH program.
9 Dr. Ewen?
10 DR. EWEN: Good morning, ladies and
11 gentlemen. My name is Dr. Colin Ewen. I'm an
12 executive director in the specialty care business unit
13 in Pfizer, and I'm located at Pfizer Laboratories in
14 Sandwich in the United Kingdom.
15 I've had the honor and the privilege of
16 being the development team leader in the sildenafil
17 pulmonary arterial hypertension program since we
18 initiated the full development program in 2001. And I
19 hope that the data I'm going to show you will be
20 informative for today's discussions.
21 So far, I think we've heard that using adult
22 data to inform treatment in children is precedented in

1 a number of disease areas. I think we've also heard
2 that changing a written request is possible and,
3 indeed, may be necessary as new information becomes
4 available. We've also heard from Dr. Barst that not
5 all children can undertake exercise testing and that
6 the hemodynamics is, however, used in the prognosis,
7 diagnosis and evaluation of all children of all ages
8 with pulmonary arterial hypertension. And we've just
9 heard from Dr. Brar that in adults a correlation
10 exists between improvements in exercise capacity and
11 pulmonary vascular resistance.
12 The question before us is how can these data
13 be used to inform the treatment of pediatric PAH
14 patients. So the objectives of my presentation are,
15 first of all, I'd like to review the key exercise and
16 hemodynamic data from the adult sildenafil program,
17 demonstrating the relationship between endpoints in
18 terms of exercise capacity and pulmonary hemodynamics,
19 and I hope to set the context for the later discussion
20 around the pediatric data.
21 I'm then going to move on to talk about the
22 exercise and hemodynamic data from the pediatric

1 program, again, demonstrating the relationship between
2 these two endpoints, before spending the last few
3 minutes of the presentation talking about the
4 consistency of treatment effects and the relationship
5 between exercise, hemodynamics and exposure in adults
6 and children with pulmonary arterial hypertension.
7 The initial studies with sildenafil and the
8 treatment of pulmonary arterial hypertension were
9 started in 1998, and in 2001, we initiated the full
10 development program. And this resulted in the initial
11 approval of sildenafil from proven in exercise
12 capacity in adults with pulmonary arterial
13 hypertension in 2005, and the indication was updated
14 further in 2009.
15 At the same time as we initiated the adult
16 development program and in response to an FDA written
17 request, Pfizer initiated a comprehensive pediatric
18 development program in 2002. We received the written
19 request in late December 2001 and began planning for
20 the program in 2002. And as was stated by Ms. McKay,
21 this included the first placebo-controlled, indeed,
22 the only placebo-controlled randomized study in

1 pediatric PAH.

2 The pediatric program has now completed

3 recruitment, and I hope to provide informative data on

4 the use of sildenafil in children with PAH. And I

5 think overall, the sildenafil PAH program informs the

6 discussion about the potential utility of PVRI as an

7 endpoint in pediatric PAH.

8 Just a minute or two on the mechanism of

9 action of sildenafil and as it relates to pulmonary

10 arterial hypertension, following oxygenation, alveolar

11 ventilation, nitric oxide synthase increases levels of

12 nitric oxide, which in turn results in increased

13 levels of CGMP. CGMP initiates pulmonary

14 vasodilatation and results in the reduction of

15 pulmonary vascular resistance and other hemodynamic

16 improvements in the lung.

17 Levels of CGMP are regulated by

18 phosphodiesterase 5, which acts to rapidly break down

19 CGMP, and the role of sildenafil, a phosphodiesterase

20 5 inhibitor, is to inhibit this degradation,

21 therefore, maintaining levels of CGMP and maintaining

22 pulmonary vasodilatation.

1 We've conducted a number of studies in the
2 sildenafil development program, but I'm just going to
3 concentrate today on three studies. Two of these
4 studies were conducted in adults, and one of these
5 studies was conducted in children. The two adult
6 studies are shown at the top of this slide. A1481140
7 was conducted in treatment-naïve patients and was the
8 single pivotal study which resulted in the initial
9 approval of sildenafil.
10 We recruited 277 patients into this study.
11 A1481141 was a randomized-controlled study in patients
12 who were already receiving intravenous epoprostenol,
13 and both of these studies had long-term extension
14 studies associated with them. A1481141 recruited 265
15 patients.
16 I'll talk you through some of the key data
17 from these studies before going on to talk to you
18 about the data from A1481131, and this was a study
19 which we conducted in treatment-naïve children with
20 PAH. This study also has a long-term extension study
21 associated with it, and we recruited 234 patients in
22 this study.

1 The endpoints which we used in the
2 sildenafil program are widely accepted within the PAH
3 community and indeed by regulatory agencies as
4 reflecting efficacy of new treatments for pulmonary
5 arterial hypertension. In our program, we've looked
6 at exercise capacity, change in hemodynamics, time to
7 clinical worsening, change in functional class, and
8 quality of life. But for the purposes of today's
9 discussion, I'm just going to concentrate looking at
10 the data on exercise capacity and change in
11 hemodynamics.
12 Exercise capacity has been the primary
13 endpoint for all three studies I've just discussed or
14 just mentioned. For adults, we've used six-minute
15 walk distance as a primary endpoint, and in children,
16 we used cardiopulmonary exercise testing.
17 This next slide shows the data from the
18 original study A1481140 in adults. And you can see
19 here's the changing walk distance assessed at week 4,
20 week 8 and week 12. We studied three doses of
21 sildenafil in the study, sildenafil 20, 40 and 80
22 milligrams TID, and these are reflected in the green,

1 yellow and blue bars. Placebo is shown in red.
2 You can see it here, at the primary
3 endpoint, which is assessed at week 12, a highly
4 statistically significant improvement in exercise
5 capacity in the patients receiving sildenafil.
6 If we go on to look at the corresponding
7 hemodynamic data in terms of improvements in pulmonary
8 vascular resistance and the improvements in mean
9 pulmonary arterial pressure, again, using the same
10 dosing regimen and the same color schemes, you can see
11 that the pulmonary vascular resistance index and
12 pulmonary arterial pressure, you can see important
13 reductions in these parameters in the patients being
14 treated with sildenafil.
15 So in the first, I think we saw improvements
16 in exercise capacity and improvements in pulmonary
17 hemodynamics, specifically pulmonary vascular
18 resistance pulmonary arterial pressure. In the second
19 study, we used similar endpoints, and these are the
20 data from the Study A1481141 in which patients were
21 already receiving IV epoprostenol. Patients were
22 randomized to receive placebo or epoprostenol plus

1 sildenafil. And patients in this study were up
2 titrated to receive 80 milligrams TID of sildenafil.
3 The primary endpoint was, again, improvement
4 in exercise capacity using the six-minute walk
5 distance test. And again, you can see at week 16,
6 when the primary endpoint was assessed, a highly
7 statistically significant improvement in exercise
8 capacity. And again, in this study when we look at
9 improvements in hemodynamics, you see a similar
10 picture to that seen in the previous study, A1481140,
11 significant improvements in pulmonary vascular
12 resistance and pulmonary arterial pressure in this
13 study. And in this study, we only had the one dose
14 group to assess, and, therefore, that's why there's
15 only one, if you like, 80-milligram group displayed on
16 this graph.
17 So we now have two studies demonstrating
18 improvements in exercise capacity and improvements in
19 pulmonary vascular resistance index. If you look at
20 these data in a slightly different manner, if you plot
21 mean change in pulmonary vascular resistance against
22 percent change in exercise capacity -- although I'm

1 using percent change in this slide rather than
2 absolute change, because I was going to go on later on
3 in the presentation to compare these data with the
4 pediatric program -- you can see, again, here the
5 placebo group is in red, sildenafil 20, 40 and 80
6 milligram, again, shown in yellow, green and blue.
7 And you can see for the two blue crosses relating to
8 80 milligrams TID, these from the two studies, the two
9 of which I've just described.
10 But importantly, I think you can see the
11 development, if you like, of a relationship or
12 appearance of a relationship between improvement in
13 exercise capacity and improvement in pulmonary
14 vascular resistance index. These two studies led to
15 the indication, which has already been shown to you by
16 Ms. McKay, but what I hope they do is provide some
17 context and some background now for the pediatric data
18 which I'm about to show you.
19 What I'd like to do, just to reiterate, is
20 to review the key exercise and hemodynamic data from
21 the pediatric program and demonstrate to you the
22 relationship between exercise and hemodynamic

1 endpoints in this patient population. This study
2 we're going to discuss is A1481131, a randomized,
3 double-blind, placebo-controlled, dose-ranging,
4 parallel group study in oral sildenafil in treatment-
5 naïve children. It is and remains, I think, the only
6 randomized controlled clinical trial conducted in this
7 pediatric patient population. I think we can regard
8 this as a landmark study. We assessed different
9 doses, and we explored the effects of sildenafil
10 across the whole pediatric patient population age
11 range.
12 This study design is shown on this slide
13 here. Patients underwent screening within 21 days of
14 randomization and then went on to be randomized to one
15 of four treatment groups: placebo, sildenafil low
16 dose, sildenafil medium dose, and sildenafil high
17 dose. The first week of the study, patients received
18 sildenafil low dose before up-titrated as appropriate
19 for their treatment dose, and the primary endpoint was
20 assessed at week 16. Patients completing the study
21 were able to go on to the long-term safety extension
22 study.

1 The patient disposition is shown on this
2 slide. We screened 308 patients during the
3 approximately five years' duration of this study. 234
4 of these patients went on to be treated in this study
5 and, as I said, were allocated to one of four
6 treatment groups: placebo, low, medium and high dose.
7 You can see in the boxes underneath each of these
8 treatment groups the numbers of patients who were
9 treated, the numbers of patients who completed 16
10 weeks of treatment, and the numbers of patients who
11 underwent the primary exercise testing endpoint.
12 The primary endpoint in this study was
13 cardiopulmonary exercise testing, and 115 of the 234
14 children randomized into this study were able to
15 undertake this exercise test, and we termed these
16 children developmentally able. We anticipated at the
17 outset of the study that at least 70 percent of the
18 patients would undertake the primary endpoint.
19 However, as you can see, it's nearer to 50 percent of
20 the children evaluable for the primary endpoint.
21 The primary endpoint was increase in oxygen
22 consumption at peak exercise, otherwise termed percent

1 change in VO2 peak. It was assessed at week 16 and
2 was assessed for the combined doses of sildenafil.
3 At the outset of the study, we were aware of
4 the potential difficulties associated with conducting
5 multi-national, multi-center studies using
6 cardiopulmonary exercise testing, particularly in
7 children. And we were assisted in this using a
8 central laboratory run by Dr. Stuart Russell of Johns
9 Hopkins University, and the central lab played a key
10 role in standardization of protocols, review of data,
11 and ensuring quality and training at all the sites
12 that participated in the study.
13 Just to explore the patient population in a
14 little bit more detail, as I've stated already, less
15 than 50 percent of children recruited to the study
16 were able to perform the exercise test, 115 of the 234
17 patients. We also found that in terms of the patients
18 who were unable to undertake the exercise test, 63
19 were less than 7 years of age. But we also found that
20 56 children, nearly a quarter of the patient
21 population, were older than 7 years of age but had
22 other reasons for being unable to perform the exercise

1 test.

2 I think the difficulties associated with

3 recruitment to this study are shown by the fact that

4 we had 14 active centers in Canada, the United States

5 and Mexico. And during the five years of this study,

6 we were only able to recruit 25 developmentally-able

7 patients in the North American region.

8 These data show the hemodynamic values, if

9 you like, in healthy children and in children

10 recruited into A1481131. We're looking at the

11 hemodynamic and exercise baseline parameters here. In

12 terms of VO2 peak, you can see the normal range for

13 healthy children is 30 to 35 mils per kilogram per

14 minute. The children recruited in this study

15 certainly had significant exercise impairment

16 demonstrated by baseline VO2 peaks of 20 and 18. And

17 in terms of the pulmonary hemodynamics, you can see

18 that in terms of pulmonary arterial pressure and

19 pulmonary vascular resistance index, a considerable

20 elevation over normal values.

21 You can see, looking at these data, that in

22 terms of these parameters, the placebo group appeared

1 to be doing slightly better than the sildenafil-
2 treated group.
3 These data show the primary endpoint, which,
4 as I've stated, was improvement in exercise capacity,
5 percent change in VO2 peak at week 16. The data for
6 all three doses is shown, again, low, medium and high
7 in green, yellow and blue. But I'd like you to just
8 concentrate on the highlighted blue box. You can see
9 here that these are the primary analyses looking at
10 the combined doses where we saw a 7.71 percent
11 increase in VO2 peak at week 16. This just missed
12 conventional measures of significance with a p-value
13 of 0.056.
14 Now, at the outset of the presentation with
15 relation to the pediatric data, I mentioned this was a
16 dose ranging study. And indeed, we've looked in some
17 detail at the doses used in this study and compared
18 the doses or the concentrations, rather, seen in the
19 adult study. If you look at the top box of this
20 slide, you can see the individual average steady state
21 concentrations in nanograms per mil for sildenafil in
22 the adult population. The top boxes are green is 20

1 milligrams TID, yellow is 40 milligrams TID, and blue
2 is 80 milligrams TID. And in the bottom box, you can
3 see the, again, steady state nanograms per mil
4 concentrations for low, medium and high doses in
5 children in the Study A1481131.
6 If I overlay this slide with the
7 pharmacologically active range which we determined at
8 the outset of the pediatric study using in vitro PDE5
9 inhibition data, you can see here that the low dose
10 group in the pediatric population had median
11 concentrations which were below the IC50 of 47
12 nanograms per mil.
13 If you allow us to speculate that these
14 patients and these children, therefore, received
15 suboptimal doses of sildenafil and we go on in a post
16 hoc manner to look at the effects seen in the medium
17 and high doses, you can see here that overall, we see
18 a treatment effect which approaches a 10 percent
19 improvement in VO2 peak, and the 95 percent confidence
20 intervals for this analysis don’t cross the zero line.
21 Now, what I’d like to do is just change
22 gears somewhat and go on to talk about the hemodynamic

1 data that we have generated in this study in children
2 with pulmonary arterial hypertension. As I mentioned,
3 at the outset of this study, we anticipated that not
4 all children would be able to perform the primary
5 endpoint of exercise testing. But in terms of
6 statistical support for this endpoint, we prespecified
7 that the main hemodynamic endpoints would be PVRI and
8 mean pulmonary arterial pressure. And 234 children
9 who were randomized to this study underwent right
10 heart catheterization, and we have week 16 data on 208
11 children. And these data, I think, are informative
12 for today's discussion.
13 When we look at them in terms of the main
14 secondary analysis of this study, at the top of this
15 graph, you can see pulmonary vascular resistance
16 index, at the bottom, the data for mean pulmonary
17 arterial pressure. And again, same presentation of
18 dosage, low, medium and high, and the combined doses,
19 the combined doses are shown in the red line.
20 What you can see is the beginnings of
21 evidence of a dose-response effect for both PVRI and
22 pulmonary arterial pressure. And indeed, these

1 effects on these parameters are very similar in
2 magnitude to those seen in the adult program. And
3 when you look at the combined data, low, medium and
4 high for pulmonary vascular resistance index, you can
5 see the 95 percent confidence interval does not cross
6 the zero line.
7 I also mentioned, when looking at the
8 patient population recruited for this study, that a
9 number of the patients, 25 percent of the patients,
10 were less than 7 years of age and, therefore, were
11 unable to perform the exercise test. And when you
12 look at these data -- and I must emphasize that this
13 is a post hoc exploratory analysis and the
14 interpretation of this study should rely on the
15 totality of the hemodynamic data generated in this
16 study.
17 But in this analysis, you can see that the
18 children less than 7 years of age and children greater
19 than 7 years of age, it would appear to be that
20 there’s a similar improvement in pulmonary
21 hemodynamics in this patient population.
22 Now, you’ve seen this presentation already,

1 or this form of presentation already for the adult
2 data, and this, again, is the same presentation
3 showing change in mean pulmonary vascular resistance
4 plotted against percent change in exercise capacity.
5 And again, placebo in red, low dose in green, medium
6 dose in yellow, and the high dose in blue, and again,
7 I think you can see the beginnings of a relationship
8 here, which is that as you improve pulmonary vascular
9 resistance index, you see concomitant improvements in
10 exercise capacity.
11 So with that, that concludes that data I'm
12 going to review with you, particularly specifically to
13 the pediatric program. I'd now like to just take a
14 few minutes to demonstrate consistency of the
15 treatment effects and consistency of the relationship
16 between exercise capacity, hemodynamics and exposure
17 in adults and children with PAH in our sildenafil
18 development program.
19 These data show the consistent exercise
20 improvements from baseline in the pediatric and the
21 adult patient populations. I've shown here just the
22 data from the two studies, A11481131 in children and

1 A1481140, as these present treatment-naïve patient
2 populations.
3 You can see here the children shown in the
4 orange line and the adults in the blue line, and we've
5 plotted the improvements in exercise capacity as a
6 percent improvement in exercise capacity against the
7 median concentration of sildenafil. And I think you
8 can see from this graph here very similar response for
9 both patient populations.
10 If we do the same analysis for improvements
11 in pulmonary vascular resistance index using the same
12 studies and the same plot of change in PVRI against
13 median concentration, again, I think looking at these
14 data, you can see a consistent effect between the two
15 patient populations.
16 If we go on to examine the data in terms of
17 exercise capacity for the patients in the adult Study
18 1140 who received 20 milligrams TID and the patients
19 in this Study 1131, the pediatric patient group, who
20 received medium and high doses, you can see the
21 percent change from baseline compared to placebo for
22 these doses in these patient populations is very

1 similar.

2 If you go on to perform a similar analysis

3 for PVRI using the same dose groups and the same

4 patients, you can see once again the improvements in

5 PVRI in the region of 20 percent and, again, these

6 bars overlaying each other.

7 These data, again, this is just a

8 combination of the two previous slides I've shown you,

9 where we've overlaid the pediatric data on top of the

10 adult data. And again, I think you can see a

11 consistent relationship between exercise capacity

12 improvement and pulmonary vascular resistance

13 improvement in the two patient populations that we've

14 been discussing.

15 So in conclusion, from the sildenafil

16 program, we've seen that in adults, efficacy of

17 sildenafil was demonstrated by improvements in six-

18 minute walk distance and improvements in pulmonary

19 vascular resistance index. And reflecting the

20 similarity of disease and the effect of sildenafil in

21 adults and children, similar improvements were seen in

22 exercise capacity and pulmonary vascular resistance in

1 the pediatric patient population. And we see evidence
2 of a consistent relationship between exercise capacity
3 and PVRI in both patient populations.
4 What I'd now like to do is hand over to
5 Dr. Lutz Harnisch, who will present further data on
6 this relationship.
7 DR. KAUL: Before you do that, we're going
8 to be breaking for about 15 minutes. We'll reconvene.
9 Actually, how long is this presentation
10 going to take?
11 [No audible response.]
12 DR. KAUL: Ten minutes? Why don't we finish
13 this presentation, and then we'll break. Thank you.
14 DR. HARNISCH: Good morning, ladies and
15 gentlemen. My name is Lutz Harnisch. I'm the lead
16 pharmacometrician of the pediatric and adults
17 sildenafil PAH project. And I'd like to guide or take
18 you today through kind of a model-based integrated
19 analysis which takes the adult sildenafil data we have
20 at hand in the PAH population and put those data in
21 the context of the analysis as you have seen earlier
22 presented by Dr. Brar.

1 I think I should acknowledge at the very
2 beginning that it was a very fruitful collaboration
3 and without actually being able to exchange the models
4 in between us, this analysis wouldn't have been
5 possible in the first place.
6 The objectives, in general, are two-sided.
7 We want to show first that the adult data on the
8 relationship between PVR and six-minute walking
9 distance fit the correlation analysis the FDA has
10 partly presented today. And if we assume actually
11 exchangeability for the VO2 peak exercise capacity in
12 the pediatric population with the six-minute walking
13 distance endpoint in the adult population, then we
14 want to apply this dataset to a similar relationship
15 and ask the question whether they are consistent, as
16 well.
17 Now, the key focus of today's discussion
18 will be what a PVR target response might be to predict
19 an exercise capacity improvement, and we want to see
20 this analysis in light of the adult data we have
21 obtained based on the target responses, response
22 ranges or target response ranges Dr. Satjit Brar has

1 presented earlier, and then, again, ask the question
2 whether the pediatric data fit the same picture,
3 meaning whether the target PVR response seen measured
4 in the pediatric population translates in to a similar
5 VO2 or exercise capacity endpoint response in this
6 population, the pediatric population.
7 I remind you just of a model. It's not
8 exactly the model Dr. Brar has shown you earlier, but
9 I remind you of an alternative model we exchanged
10 about the factual change from baseline in six-minute
11 walking distance and the factual change from baseline
12 in PVR as presented here, and you see the parameter
13 estimates, the regression line we presented, and the
14 95 percent confidence interval, which is always one of
15 the results relating those two endpoints.
16 You can read out from the graph that a
17 change of 20 percent in PVR translates to about a 10
18 percent improvement in exercise capacity.
19 Now, it wouldn't be entirely fair to compare
20 our sildenafil adult data against this model as it
21 stands because the analysis did already include the
22 sildenafil data in the first place. So what we asked

1 kindly the pharmacokinetics group to do for us is
2 actually to provide an analysis where the sildenafil
3 data has been taken out.
4 If we switch to the next slide, then you see
5 that the relationship slightly changes. There is a
6 change in the slope and a slight change in the
7 intercept, but still, we conclude from this
8 relationship that about 20 percent change from
9 baseline in PVR translates to a 10 percent improvement
10 on the exercise capacity scale, measured here by the
11 six-minute walking distance.
12 Now, this regression analysis could be
13 utilized now to construct a relationship between the
14 model and the data in the adult population. And on
15 the next graph, I show you here, again, a similar
16 representation of the data as Dr. Brar has shown you.
17 He binned the data from the two trials at hand, which
18 is 1140 and 1141; 1140, just to remind you, was the
19 dose-response trial; 1141, the background epoprostenol
20 trial.
21 The four dots correspond to four bins
22 representing 25 percent of the data binned by the

1 individual change from baseline in PVR, calculating
2 then the corresponding improvement or change in six-
3 minute walking distance and plotting those four dots
4 for each of the trials onto the regression line.
5 Now, the regression line cannot be compared
6 directly with those four dots for each trial. One
7 would need to construct a prediction interval from the
8 FDA model, and that's what we did. That's the gray
9 area in the background. Utilize the model and
10 construct it for a bin size of about 30 subjects, an
11 interval, and you would conclude, in a way, success or
12 consistency between the model and the data. If you
13 have only eight dots, actually, all of them fall into
14 the interval which is nicely shown here.
15 Now, you can follow the similar
16 methodological approach, assuming, again,
17 exchangeability between the exercise capacity endpoint
18 between pediatrics and adults and introduce the
19 pediatric dataset. And you see here those four dots
20 representing the 1131 trial.
21 Now, since the trial is slightly smaller in
22 the number of subjects where we have corresponding

1 endpoints and exercise capacity and PVR, the bin size
2 is about 24 subjects. Therefore, you would need to
3 enlarge the prediction interval slightly, but you see
4 it's not a big deal. And although the interval
5 changes, all dots would have been found in the smaller
6 interval already.
7 So from this presentation, we would conclude
8 here that the adult data and the pediatric data follow
9 each other, as well as fall in the prediction
10 boundaries or they follow the relationship the FDA has
11 actually assessed.
12 Now, we are going to talk about the target
13 effect size and what actually a minimum PVR target
14 effect size should look like translating into a
15 meaningful improvement on the exercise capacity scale.
16 And Dr. Brar mentioned already that for that purpose,
17 a normalization or a reference to placebo needs to be
18 introduced. So we follow actually the model the FDA
19 has presented earlier on the double delta method by
20 subtracting the placebo response, because from this
21 relationship here, you read only out the change from
22 baseline translating it to a change from baseline.

1 And from the subsequent relationship shown to you
2 earlier, delta versus delta, then you can conclude or
3 construct an improvement over placebo which translates
4 into an exercise capacity improvement.
5 We don't know what our target will be,
6 whether it's 10 percent improvement on exercise
7 capacity, 15 percent or 20 percent. And Dr. Brar
8 showed a table that you can read the various numbers.
9 We just assumed because the number 10 appears in our
10 discussions in multiple places, we construct the
11 relationship on a 10 percent improvement in exercise
12 capacity and calculate the corresponding PVR
13 improvement of about 28 percent reduction. It would
14 take the intercept of the relation out of the
15 equation, then you would come up with the number of
16 23, as Dr. Brar mentioned earlier in his table.
17 The confidence, there's obviously an
18 uncertainty in this relationship, and you could,
19 therefore, constitute or construct a confidence
20 interval which would state that at an improvement of
21 about 20 to 40 percent, it is likely to achieve an
22 improvement of 10 percent on a maximum exercise

1 capacity scale.

2 Now, how do we fit our adult data into this

3 relation? And for kind of statistical correctness, we

4 take out the confidence interval, because we know that

5 the FDA utilized our adult data in their analysis. So

6 what you see here only is the placebo-corrected

7 treatment responses from 1140 and 1141, 20, 40, 80

8 milligram, 1140, 80; and, 1141, the epoprostenol

9 background trial.

10 You, I think, get the impression that all of

11 those four dots follow quite nicely the relationship;

12 but furthermore, the majority of the dots achieve or

13 the majority of the improvements on PVRI actually

14 achieve the target which we would propose or could

15 propose here to discuss on both scales in PVRI, as

16 well as exercise capacity.

17 So if I would have made a decision on one of

18 the endpoints, it would have been likely that the

19 other endpoint decision would have been done on a very

20 similar base.

21 Now, for the pediatric data, the picture

22 changes again a little bit because the pediatric data

1 is not available to the FDA, and so we could construct
2 a prediction interval again. And we do the same kind
3 of presentation here, subtracting the placebo response
4 as measured in 1131 from all the treatment arms and
5 plot the resulting improvement on exercise capacity,
6 as well as PVR improvement into the graph.
7 You see the majority of dots, or nearly all
8 dots, fall into the prediction interval. The low and
9 the medium dose follow quite nicely the relationship
10 under discussion. And most importantly, the
11 distinction between which dose to take forward if I
12 would make a dose recommendation distinction between
13 low and medium dose would come up as the same
14 conclusion, meaning that a medium dose would actually
15 be very well suited -- would fall very well into the
16 target of the PVR reduction, while the low dose
17 wouldn't. And the similar conclusion would be driven
18 using the exercise capacity endpoint, VO2 peak in this
19 trial.
20 Furthermore, if one would have not an
21 exercise capacity endpoint available in this trial,
22 then actually still, a very meaningful conclusion

1 would have been driven from just assessing the PVRI
2 scale on its own, because still I would probably go
3 for a minimum dose which would achieve a PVR target
4 response, and the decision would be very similar as to
5 go with a medium dose forward.
6 Now, with that, I think I would like to
7 conclude and think I have shown you that the adult
8 sildenafil data follow the relationship the FDA has
9 proposed as being between PVRI and six-minute walking
10 distance, and it appears to be very consistent across
11 the adult data and the FDA model.
12 For the pediatric data, assuming, again,
13 exchangeability between the endpoints on exercise
14 capacity, a similar relationship could be shown.
15 Assuming an FDA proposed or promoted a
16 target in the future, then I would guess that the
17 adult sildenafil data follow very nicely into this
18 target. A 20 to 40 percent improvement we would think
19 would be reasonable to go forward with would have been
20 achieved in the trial and would correspond to a 10
21 percent six-minute walking distance improvement.
22 Finally, the target PVRI response which

1 might be promoted or you will deliberate in your
2 discussions later on during the day will hopefully
3 show you that we achieved in our sildenafil trial a
4 very corresponding, meaningful VO2 peak response.
5 Ultimately, I would guess one could conclude
6 here, coming back to kind of the last presented graph,
7 that the inferences or the decisions we would make or
8 would have made on either the adult or the pediatric
9 program taking either or the other endpoint forward
10 would be very similar and, therefore, we think that
11 the two endpoints perform very consistently.
12 With that, I would like to conclude and ask
13 Dr. Colin Ewen to come back.
14 DR. KAUL: Dr. Ewen, why don't we just wrap
15 it up and then we'll take a break?
16 DR. EWEN: So, ladies and gentlemen, just a
17 few concluding remarks. I know that I'm now between
18 everybody and coffee, so I'll be quick.
19 In terms of pulmonary arterial hypertension,
20 the disease, I think we've shown you today that it's a
21 rare, progressive and fatal disease and that the
22 diagnosis and its treatment rely, to a large extent,

1 on pulmonary hemodynamic measurements and assessment.
2 I think we've shown that exercise capacity
3 supported by hemodynamics has been used in all adult
4 PAH development programs and hemodynamics have played
5 an important part in the assessment of the efficacy of
6 all the currently available drugs used in adults. And
7 I think the data presented today demonstrate and
8 describe the relationship between exercise capacity
9 and pulmonary vascular resistance index in adults with
10 pulmonary arterial hypertension.
11 In terms of the conclusions I think we can
12 draw about the pediatric situation and the pediatric
13 data that we have in hand, I think we say that
14 pediatric PAH is certainly considered to be a similar
15 disease in adults and in children and that the
16 baseline hemodynamics are similar in adults and
17 children with PAH and that these hemodynamics show
18 similar response to treatment certainly in the
19 sildenafil program.
20 I think taken together, these findings
21 support the use of pulmonary vascular resistance index
22 as an endpoint in children with PAH to inform labeling

1 where a drug has been documented to improve exercise
2 capacity in adults. And with that, I would like to
3 conclude.
4 DR. KAUL: Thank you. And thank you for
5 finishing ahead of time.
6 I'll take the chair's prerogative to take a
7 break for 20 minutes instead of 10. We'll reconvene
8 at 5 past 11:00, and then we'll have 55 minutes for
9 questions before we break for lunch. So, committee
10 members, please remember that there should be no
11 discussion of the meeting topic during the break
12 amongst yourselves or with any member of the audience.
13 We'll resume at 5 past 11:00. Thank you.
14 (Whereupon, a recess was taken.)
15 DR. KAUL: Welcome back. I'm going to open
16 up the discussions for questions from the committee to
17 either the FDA or to the sponsor or to each other. So
18 feel free. The first one is Dr. Venitz.
19 DR. VENITZ: Thank you. I have a question
20 for Pfizer first. In looking at your background
21 material, you differentiate among the different
22 subgroups in your pediatric study. And I'm looking

1 particularly at figure 12, where you break it down in
2 terms of their response over placebo and you conclude
3 that the patients that have Down syndrome don't show
4 any dose response at all relative to PVRI.
5 How would that affect your overall
6 conclusion of looking at the PVRI as a surrogate
7 marker of cardiovascular function, cardiopulmonary
8 function?
9 DR. EWEN: So that's an important question.
10 And I think before I answer you, I'd like to stress
11 that, as I said in the presentation, you have to look
12 at the totality of the data in terms of hemodynamics.
13 And that those data with regard to Down syndrome, I
14 would regard them, at this stage, exploratory and
15 maybe worthy of consideration for future trial
16 designs, but I don't think it's appropriate and
17 necessary to draw conclusions around those data at
18 this stage.
19 DR. VENITZ: So you're arguing that there's
20 a good chance that they look like the overall
21 population. They're just, by chance, different in the
22 study that you conducted.

1 DR. EWEN: I think we'd have to look at
2 that. I mean, there are some data to suggest that
3 Down's children may behave differently from the
4 literature, but overall, I think we have a consistent
5 reduction in pulmonary vascular resistance index in
6 the population that we've studied in this study.
7 DR. VENITZ: With the exception of the Down
8 patients?
9 DR. EWEN: I'm not sure we can necessarily
10 draw that as it was a post hoc subgroup of a subgroup
11 analysis, but I think it's interesting data.
12 DR. VENITZ: And how large was the sample
13 population, the sample size?
14 DR. EWEN: We ended up, I think, with a
15 little over 50 patients with Down's syndrome.
16 DR. VENITZ: So 50 out of 260?
17 DR. EWEN: Yes, but split by three treatment
18 groups.
19 DR. VENITZ: So about 20 percent. Okay.
20 Thank you.
21 DR. KAUL: Dr. D'Agostino?
22 DR. D'AGOSTINO: I'd like to go to the last

1 presentation, slide 52.

2 DR. EWEN: Slide 52, please.

3 DR. D'AGOSTINO: The comment I have is that

4 -- do we think or do you think that the FDA model is

5 ready for prime time, as they say? When you took the

6 FDA model and removed your data, the slope changed by

7 28 percent. And when you look at this graph here,

8 your prediction interval is about 50 percent of what

9 the scale. You go from 30 to minus 20 in terms of the

10 sort of area or range of interest, and the tolerance

11 or the prediction interval is about 50 percent of

12 that.

13 So like anything that has a sort of downward

14 slope is going to basically fit into that. So the

15 question is, again, do you think you have enough

16 precision or, to not put it in a humorous vein, but do

17 you think you have enough precision in this model to

18 really use it for later predictions in effect size?

19 Because the confidence intervals around these things

20 are going to probably be extremely large.

21 DR. EWEN: Could I ask, is that question

22 addressed to the sponsor or to the agency?

1 DR. D'AGOSTINO: Well, the sponsor used it.
2 Weren't they bothered by the fact that the tolerance,
3 the prediction intervals were so large and, also, to
4 the FDA in terms of the precision that their model
5 actually does carry?
6 DR. EWEN: Could I ask Dr. Harnisch to
7 comment, please?
8 DR. HARNISCH: I think we need to
9 differentiate on this graph the regression line
10 through the mean, which is the white line on the graph
11 and the prediction for an improvement in exercise
12 capacity based on a seen improvement on PVR. So that
13 graph, the grayish area depends on the sample size you
14 see. So if you run a new trial, your new trial would
15 have a spread of PVR changes that are positive or
16 negative. And in a group of subjects of 30, you're
17 very, very unlikely if you see a worsening in PVR of
18 about, let's say, 40 percent, that there will be
19 actually a corresponding large improvement on exercise
20 capacity.
21 On the other side, if you see actually an
22 improvement in the sample size of treatment groups of

1 about 30 subjects of about 40 percent improvement, you
2 can read out from the graph that you basically have no
3 chance to see not an improvement on the exercise
4 capacity scale, so, yes.
5 DR. D'AGOSTINO: The question I'm raising is
6 that anything will fit into that prediction interval.
7 It's just a very large prediction interval. Are you
8 really somehow or other validating the model by this
9 or could you really say that we have enough precision
10 now with the model that the FDA produced to actually
11 use it for setting effect sizes and so forth?
12 DR. HARNISCH: I think you would take -- and
13 I didn't stress it probably too far saying that this
14 is not a strong statistical comparison in a way
15 whether we are similar or different to the FDA model.
16 What I wanted to illustrate is that the data we have
17 at hand appears to be very similar in the changes of
18 the two or the changes of the two variables against
19 each other among our trials and the FDA or the overall
20 response.
21 I'm not saying that you can read out from
22 this graph directly whether 30 subjects per bin is the

1 right one to go forward, 30 subjects per treatment
2 group. You might need 50, but this is a different
3 assessment.
4 DR. KAUL: Can you, for some of us
5 innumerate on the committee, quantify the strength of
6 association? How much of the percent variation in one
7 variable predicts the percent variation in the other
8 variable? I mean, that's how we are used to
9 quantifying the strength of the association. The p-
10 values, to some of us, don't mean much.
11 DR. HARNISCH: I think that's a question the
12 FDA would need to answer.
13 DR. A'GOSTINO: You'd need to sort of ask
14 where and then, also, the standard error estimate to
15 see just how tight you are here.
16 DR. KAUL: Dr. Temple?
17 DR. TEMPLE: Well, I'm certainly not capable
18 of answering that. I just want to make one
19 observation and make sure other people agree with me,
20 which is that what we're focusing on is the slope
21 here. It's perfectly possible that within that slope,
22 one drug could have a slightly bigger effect or more

1 effect on exercise for a given change in PVRI. That's
2 not ruled out, and I thought one of Dr. Brar's slides
3 sort of suggested that.
4 DR. D'AGOSTINO: You don't think the
5 relationship holds? I mean, I thought we were talking
6 about the relation, the delta versus delta, that we
7 thought somehow or other if you'd see a change of
8 delta in the PVRI, that that would correspond to a
9 change of delta in the log test. One drug may be
10 better than the other, but you're basically dealing
11 with basically the same slope.
12 DR. TEMPLE: Well, that's the point. The
13 slope was the same for all of them. But in Dr. Brar's
14 thing with multiple colors for each drug type, you
15 could sort of read it as one of them being a little
16 higher, but there was always the same slope.
17 DR. KAUL: Dr. Brar, would you like -- or
18 Dr. Gobburu, any one of you?
19 DR. GOBBURU: My name is Joga Gobburu. I
20 work with the Division of Pharmacometrics at FDA. I
21 just wanted to respond to Dr. D'Agostino's point about
22 the gray. We're not clear why. We will have to look

1 at the graph that way.

2 The key point is the mean line is the white

3 line that's shown there, and the dotted blue lines are

4 the 94 percent confidence intervals around that

5 regression line. The gray area is prediction

6 interval, which is the 95th percentile to the 5th

7 percentile.

8 DR. D'AGOSTINO: I'm aware of all that.

9 DR. GOBBURU: So the question is about the

10 mean relationship of slope. There will be patients

11 who will have, for a given change of PVRI, different

12 response in terms of the six-minute walk distance. So

13 that's why we have been relying more on the double

14 delta plot.

15 To respond to the chair's question, the

16 variability that is explained according to the double

17 delta plot is 70 percent by the PVRI.

18 DR. KAUL: I think, Dr. Neaton, were you

19 going to make that same point?

20 DR. NEATON: I was going to make the same

21 point. I guess what I want to see is how it fits with

22 the double delta plot, not this one. The fact that

1 these two correlate is kind of one small factor, and
2 so that the important thing would be -- and this is
3 what I think Ralph and I were talking about earlier --
4 going back to your double delta plot, if you remove
5 one study at a time and kind of refit that line and
6 then ask the question what does the predicted six-
7 minute walk kind of look like relative to what was
8 actually observed, then that would add some insight to
9 the --
10 DR. D'AGOSTINO: That's basically the
11 motivation that my question -- how are we going to
12 quantify just how precise these analyses are? And I
13 think the delta delta versus delta delta is the right
14 plot to look at. And these things will tend to be
15 jumping around maybe more than you'd like to see.
16 How tight is that relationship?
17 DR. KAUL: Just to extend that question,
18 either the FDA or the sponsor can answer this
19 question.
20 Are the relationships between these
21 variables consistent across the range of age, lower
22 end and the higher end?

1 DR. BRAR: Yes. I'd like to answer that
2 question. If we can go to my backup slide.
3 To answer your question, yes, it is. And if
4 we can go to my backup slide number 10, in essence
5 I'll just go over the analysis that we did.
6 In essence, from the entire adult
7 population, I binned the age groups into quartiles to
8 essentially look at the relationship of the six-minute
9 walk distance and PVRI. And essentially, what the
10 plot will hopefully show, if it comes up soon, is the
11 forest plot shows that across age groups, we do see
12 that the relationship still holds, meaning
13 qualitatively. And in addition, the 95 percent
14 confidence bounds are essentially overlapping.
15 I could almost say that the slope estimates
16 for all those are essentially the same across age
17 groups, and this is ranging from age 18 to 83. So I
18 binned into four groups. In addition, I binned into
19 half, where I looked at under 50 and over 50, and,
20 also, we see the same relation, as well.
21 DR. KAUL: Did the sponsor also do a similar
22 analysis in their two adult programs?

1 DR. EWEN: Dr. Harnisch?

2 DR. HARNISCH: So this one does not have any

3 exercise capacity for the subjects below 7. So our

4 analysis would be limited to exercise capacity between

5 7 and 17.

6 DR. KAUL: What about your adult program,

7 the two?

8 DR. HARNISCH: In the adult program, we have

9 a different exercise capacity endpoint, so you would

10 kind of split by age and by endpoint.

11 DR. KAUL: That's okay. Whatever exercise

12 index you have, did you observe the same relationship?

13 DR. EWEN: So have we seen an age effect, I

14 think, in the adult patient population?

15 DR. HARNISCH: I mean, effectively, if you

16 overlay the pediatric population, then they are all

17 between 7 and 17, and the rest of the population is

18 from 18 to the maximum age in the sildenafil program.

19 So you cut by trial, you cut by endpoint and you cut

20 by age at the same time.

21 DR. KAUL: Dr. Temple?

22 DR. TEMPLE: I just want to point out, since

1 this slide is up --

2 DR. BRAR: Maybe I can just give a better

3 explanation of this. Again, we're looking at the

4 forest plot, looking at the slope of the six-minute

5 walk distance PVRI relationship across age bins. At

6 the top, I have divided it essentially by median,

7 where we're looking at age group less than 50 or

8 greater than or equal to 50.

9 As you can see, if you bin by median,

10 greater than median or less than median, that the

11 slopes are the same. In addition, below shows if

12 they're binned by quartiles, where we have age 18 to

13 38 in different bins, and, in essence, the

14 relationship holds across those age groups.

15 Just as a reference, and people can say I

16 consider this a young adult, less than 30, I've also

17 binned essentially just showing, again, the

18 relationship still holds. And the expected physiology

19 direction, in addition to the slope estimates, are the

20 same across age groups.

21 DR. KAUL: I assume the percent delta is

22 similar.

1 DR. BRAR: The percent delta is still
2 similar, correct.
3 DR. KAUL: Well, thank you. That's very
4 informative.
5 Dr. Newman?
6 DR. NEWMAN: I have a question on slide 58.
7 DR. EWEN: Can we have slide 58, please?
8 DR. NEWMAN: It shows the delta delta for
9 the three doses. One way to interpret this -- and
10 it's a question about how do you go forward -- is that
11 the low dose had an insufficient PDE5 inhibition to
12 give a large effect, that the medium dose was
13 beneficial. And if the high dose may have resulted in
14 an increased cardiac output at rest, it didn't
15 increase reserve in exercise since there was a bigger
16 reduction in PVR than there was an improvement in six-
17 minute walk. That would be one way to interpret it.
18 You may interpret it differently.
19 But my question is, if you do a study going
20 forward, would it be important to prospectively adjust
21 dose in order to achieve the PDE5 inhibition levels
22 that might be appropriate? So two things, would you

1 respond to my interpretation and then talk about what
2 you might do next?
3 DR. EWEN: So I think if I understand the
4 first part of your comment, are we seeing a sort of
5 flattening off of the exercise response, which isn't
6 being reflected in the changing pulmonary vascular
7 resistance index.
8 DR. NEWMAN: Well, the pulmonary vascular
9 resistance index and the blue dot is way down. So
10 it's a marked improvement, presumably more due to
11 cardiac output than reduction in PA pressure. But
12 that didn't translate into the improvement in exercise
13 capacity. So my question was, is that a resting
14 effect without an increase in cardiac reserve that
15 might occur?
16 DR. EWEN: I'm not sure we necessarily
17 understand this, if you'd like the details of this.
18 But this is a similar effect we've seen in the adults,
19 as well.
20 DR. NEWMAN: So how would you handle this
21 data going forward since the blue dot is slightly out
22 of proportion -- the PVRIs benefited, but the exercise

1 increase is not particularly --

2 DR. EWEN: So I think if I understand your

3 question, if you take the adult data as your guide, if

4 you like, we would have assumed the target drop in

5 PVRI was associated with a 20 milligram TID dose

6 rather than the higher dose, and these data are

7 consistent with that dose prediction for pediatrics.

8 DR. KAUL: Dr. Coukell?

9 DR. COUKELL: Thank you. To understand the

10 role of PVRI, I'm still trying to understand the

11 alternatives. So could you help me to understand the

12 rationale for recruiting patients who are 1, 2, 3, 4,

13 whatever years old into a trial where the primary

14 outcome measure involved riding a bicycle, a

15 cyclometer? And then more importantly, as I

16 understand it, there are performance measures that

17 have been validated in much younger children. What

18 consideration did you give to developing some other

19 physical performance measure?

20 DR. EWEN: So to answer the first part of

21 your question, we anticipated at the outset of the

22 study that, obviously, there would be children who

1 would be too young to exercise, but we thought it was
2 important in discussions with the FDA to at least
3 obtain efficacy data in terms of hemodynamics on these
4 children, because there is no other alternative.
5 With regard to developing different
6 measures, at the moment, I'm not aware of anything we
7 could use at this point for contrast, and we certainly
8 didn't have anything in 2001.
9 DR. COUKELL: So nothing is out there, but
10 have you explored the possibility of developing and
11 validating one.
12 DR. EWEN: We've given it some thought, but
13 it's nowhere near advanced far enough to be utilized
14 anytime soon.
15 DR. KAUL: Dr. Rich?
16 DR. RICH: Can we start with slide 53?
17 DR. EWEN: Can we have slide 53, please?
18 DR. RICH: So just to make sure that I
19 understand, what you've done here, you've just added
20 on in the blue line, blue dots, the pediatric data on
21 top of the adult data, correct?
22 DR. EWEN: I'll ask Dr. Harnisch to comment

1 on that.

2 DR. HARNISCH: Yes.

3 DR. RICH: Correct? Okay. And so what this

4 is showing is that in children, some of the children

5 had a dramatic worsening or increase in PVRI, which

6 was not reflected by any change in their exercise

7 capacity; is that correct?

8 DR. HARNISCH: You have definitely children

9 where the relationship is not based on the

10 presentation such as Dr. Brar gave earlier about the

11 four kind of panels you get into. You're not

12 achieving a perfect correlation and everybody is on

13 the right side.

14 DR. RICH: I'm not asking you about perfect

15 correlation. I'm just asking if I'm understanding the

16 slide correctly. There were patients where the PVRI

17 increased as much as 60 percent, and yet that was not

18 reflected by any meaningful change one way or the

19 other in their exercise capacity.

20 DR. HARNISCH: That's true.

21 DR. RICH: Okay. Could we go now to

22 slide 20?

1 DR. EWEN: Can we have slide 20, please?
2 DR. RICH: So I find a little bit of a
3 dilemma here. This is the adult study, 1140, and I
4 think this is the pivotal trial by which sildenafil
5 got approved in pulmonary hypertension. And it shows
6 the difference in six-minute walk with the three
7 different doses, and because there was no meaningful
8 improvement in six-minute walk at the highest dose,
9 the agency gave approval at the lowest dose. Am I
10 correct?
11 DR. EWEN: Yes.
12 DR. RICH: Okay. So next slide.
13 DR. EWEN: Slide 21, please.
14 DR. RICH: So this is the hemodynamic data
15 from that study, and the hemodynamic data, if we just
16 focus on the left panel of PVRI, did show a dose
17 response effect at least with hemodynamics; that the
18 ones that got the highest dose, in blue, had a much
19 lower PVRI than the ones who got the lowest dose.
20 So then we have this dilemma. If you just
21 jump to slide 24 --
22 DR. EWEN: Slide 24, please.

1 DR. RICH: -- considering, for children, to
2 give them the highest dose, which was the most
3 effective dose in your trials, and deny adults the
4 same benefit because the PVRI was ignored in the
5 adults, so the adults now are stuck with a low dose
6 which didn't change PVRI very much. The children get
7 the benefit of the high dose which changed PVRI a lot,
8 even though we can't show an exercise performance
9 difference.
10 I'm a little bit stuck in the middle here.
11 If we're going to be consistent, then shouldn't we
12 change the dosing for adults to also reflect the PVRI
13 if we truly believe that the PVRI, as a biomarker,
14 really does reflect long-term outcome? And that could
15 be answered, I guess, by you or by Bob or Norman.
16 DR. TEMPLE: Well, I'm no maven on this, but
17 it wouldn't surprise me if six-minute walk is topped
18 out at some point by the fact that these people
19 haven't been exercising very much, they get tired and
20 other stuff that has nothing particular to do with
21 their pulmonary function. So that wouldn't surprise
22 me at all.

1 But you're asking a good question which is
2 maybe the increased difference in PVRI has something
3 to do with other outcomes that are, if anything, even
4 more relevant than how far you can walk, like whether
5 you live or die. I think that's a fair question. The
6 reason we would have done that -- and as Norm was
7 whispering, we asked them to study lower doses as
8 well -- was that we were relying on that as the
9 clinical benefit. That was the primary clinical
10 benefit. We would add other stuff if people would
11 show it, but they hadn't. But I think it's a good
12 question and needs some reflection.
13 DR. RICH: And similarly, if we're being
14 asked to judge whether the disease is the same in
15 children as adults, then I'm bothered by the fact that
16 the PVRI got so much worse in some of the children and
17 you couldn't even see it in the six-minute walk,
18 whereas in the adults we would expect to see it. So
19 I'm just raising some things that are troubling.
20 DR. KAUL: I think the FDA would like to
21 respond.
22 DR. JADHAV: My name is Pravin Jadhav. I'm

1 team leader in pharmacometrics at FDA. And we were
2 actually thinking of the same question, and we do have
3 some explanation. I'm not sure if this is a complete
4 explanation. I think where the difference is, is PVRI
5 being a very sensitive measure. In the overall
6 population, as you pointed out, there's a dose
7 response. A high dose shows a high effect on PVRI,
8 but that doesn't really translate into six-minute walk
9 distance. And you pointed out the disconnect that if
10 we show that the more change in PVRI should lead to
11 more change in six-minute walk distance.
12 The difference is, I think especially if you
13 look at the subset that Dr. Brar looked at it in terms
14 of the WHO Class 1, there is actually a hint of dose
15 response in six-minute walk distance, and it does then
16 open a little bit of a question, saying should we --
17 then there is more benefit in WHO Class 1 on six-
18 minute walk, also. Again, it's a group analysis
19 looking at data more.
20 But what explains the disconnect between the
21 PVRI six-minute walk relationship, where it says the
22 dose response is, I think PVRI being sensitive, it's

1 very easy to see dose response, whereas it's not so
2 easy to see dose response on six-minute walk distance.
3 DR. RICH: Okay. But when we're done with
4 all of this, what we need to do is translate all of
5 this language into clinically meaningful.
6 DR. JADHAV: That's true.
7 DR. KAUL: Steve, before you get to ask your
8 question, I'm going to ask a question of you, and feel
9 free to answer it any which way you want to, with or
10 without regulatory implications in mind.
11 Are there any validated surrogate endpoints
12 for pulmonary arterial hypertension? If so, what are
13 they and do we have any idea about the relative
14 performance of these surrogate endpoints and are they
15 consistent across age groups?
16 DR. KAWUT: So I think the answer to the
17 first question is, no, I don't think there are any
18 validated surrogate endpoints. And I guess it would
19 be helpful to kind of review what goes into making a
20 validated surrogate endpoint.
21 It's got to be a reliable measure. It's got
22 to make sense. It would be great to be in the causal

1 pathway of the disease, but doesn't have to be. It
2 needs to consistently show relationships with
3 outcomes, clinically important outcomes, whether it be
4 exercise or survival. And last, it needs to be looked
5 at within the spectrum or within the context of
6 clinical trials, and it needs to be shown that the
7 effect of the treatment on the ultimate outcome is
8 almost fully or mostly explained by the effect of the
9 treatment on the surrogate.
10 When we go through the first two or three of
11 those criteria, we do have a decent number of markers
12 which meet those criteria. Certain blood biomarkers,
13 hemodynamics certainly meet the reliability, validity
14 causal pathway and epidemiologic association criteria.
15 It's this last criterion which has really been
16 difficult to get to.
17 I think this is an opportunity both for the
18 sponsor and the FDA to get to that, which is do
19 hemodynamics, do PVRI explain the impact of the drug
20 under study on the ultimate outcome. And today it
21 sounds like that six-minute walk distance, but to me,
22 it's probably more time to hospitalization or death.

1 DR. KAUL: Does the six-minute walk test lie
2 in the causal pathway?
3 DR. KAWUT: That's a great question. It
4 doesn't and might be a biomarker, but analyses have
5 been shown -- actually, at the FDA meeting we had a
6 few months ago, one of the industry groups actually
7 looked and did this kind of proportional effects
8 analysis and showed that the impact of the drug on the
9 six-minute walk did not at all explain the impact of
10 the drug on long-term outcomes. So I can, I think,
11 safely say that six-minute walk is not a surrogate
12 endpoint. It might be an intermediate endpoint and
13 may be clinically important, but it is not a surrogate
14 in this disease.
15 DR. KAUL: Dr. Temple?
16 DR. TEMPLE: But we haven't considered it a
17 surrogate for the disease. We considered it a measure
18 of clinical benefit in much the same way exercise
19 ability and heart failure can be, although you want to
20 know the outcome.
21 It's a perfectly fair question of how an
22 improvement in that corresponds to the ultimate

1 outcome. That's a very good question. We're always
2 interested in that. But the question being raised
3 here is whether the change in PVRI is a surrogate that
4 predicts the walking benefit. Whether you could go
5 further, we don't know. And it is getting, as
6 somebody pointed out, much, much, much harder to do
7 outcome studies here and leave people untreated.
8 Nobody wants to do that.
9 But one of the questions raised by some of
10 the previous conversation is suppose you go past the
11 dose -- suppose you go past the dose that gives you
12 your best effect on walking distance, but does improve
13 PVRI? Would that have an outcome effect? Now, that
14 is presumably studyable, and that's an interesting
15 question.
16 DR. KAUL: I think both of you echo the
17 conundrum that we are faced with, trying to figure out
18 whether this is a surrogate which we don't know is
19 really a surrogate.
20 DR. TEMPLE: But the ability to exercise
21 more, whether measured in a treadmill test or in a
22 quality of life assessment or a patient-reported

1 outcome, I don’t think anybody doubts that that isn’t
2 a real benefit. Whether it corresponds to improved
3 survival is an interesting and very important
4 question. But we had felt it was of benefit by itself.
5 DR. KAWUT: And I would respectfully
6 disagree. I don’t at all think -- and I know of no
7 data that correlates changes in VO2 max with how a
8 patient feels, functions or survives. And so that’s
9 where the issue -- and six-minute walk, maybe we can
10 sell that walking farther is better, and that would
11 make sense to a patient.
12 DR. TEMPLE: Actually, in conventional heart
13 failure, not this kind, there is data to that effect,
14 because somebody went to the trouble to develop a
15 very, very, very good heart failure scale. So I’m
16 sure there aren’t those data here, but that doesn’t
17 mean there couldn’t be.
18 DR. KAUL: And there is an example of a
19 trial called STRIDE-1 where there was a disconnect,
20 where the peak VO2 did not track with the six-minute
21 walk test and I’ve heard explanations that there were
22 technical issues with how they measured the VO2 peak,

1 but there's an example of a disconnect. Are there any
2 other such examples of disconnect that any one of you
3 are aware of?
4 DR. KAWUT: Well, in data from Columbia, we
5 looked at our cohort of adult patients looking at VO2
6 max, it actually did not correlate with survival. And
7 there's only one or two studies in pulmonary
8 hypertension where it does. And that was actually
9 going to be my question, which is when we designed
10 this study, was this considered a surrogate or an
11 intermediate endpoint, because, in my mind, there's
12 some data connecting VO2 max to survival. So I would
13 think this is a surrogate endpoint in this study. But
14 it sounds like that wasn't the intent.
15 DR. TEMPLE: I think VO2 max has more
16 properties of a surrogate because you're not actually
17 necessarily walking faster. But we have not --
18 there's debate about definitions, but the view has
19 been generally that the ability to walk longer is not
20 really different from a very good patient-reported
21 outcome that showed you could do more things. But
22 it's easier to quantify, easier to set the conditions

1 of the test and, therefore, more sensitive.

2 I'm sure all of those things could be

3 debated, and there's much more interest now in the

4 living with heart failure scale which everybody thinks

5 is a great advance in heart failure. And they do

6 track pretty well. They even track with New York

7 Heart Association classification.

8 DR. KAUL: Steve, you get to ask a question

9 now.

10 DR. KAWUT: I guess we've seen a lot of

11 analyses, and they're well calibrated. I think

12 someone used that term. And the question is, is that

13 how we want to look at the data, and did you do

14 analyses looking at discrimination.

15 So if you take some increment of change of

16 PVRI, what's the positive and negative pick to value

17 that you'll see some increment of change of six-minute

18 walk, which, if it's calibrated, it should be

19 discriminating? But I wondered if either the sponsor

20 or the FDA had done those analyses.

21 DR. EWEN: So we haven't done those

22 analyses. Perhaps the agency has.

1 DR. BRAR: Is this analysis, the double
2 delta scale, you're saying removal of trials to see if
3 the relationship still holds or are you asking for
4 like a single delta looking at if you take data off,
5 like, say, the ends, for instance, and looking to see
6 if the relationship still holds? We have run that
7 analysis, and this is in the backgrounder, as well.
8 DR. KAUL: If I can extend that, I think
9 what is being asked here is that will a change in your
10 hemodynamic variable predict a clinically meaningful
11 change. So it's a binary decision, and so can it help
12 discriminate those with the outcome of interest from
13 those without the outcome of interest, not a
14 continuous relationship question.
15 DR. BRAR: That's a very good question. And
16 I think, first and foremost, before we could answer
17 that question, is to determine what is the clinically
18 relevant change. And we don't know this is the reason
19 why this analysis has not been done, so I right now
20 would not be able to answer that question.
21 DR. KAUL: Dr. Rich?
22 DR. RICH: So to address this, in a way,

1 when we chose six-minute walk as the primary endpoint
2 in the epoprostenol trial, there was no knowledge of
3 what a clinically meaningful delta would be, and the
4 trial was designed just to show the statistically
5 significant difference between the treatment versus
6 control groups, even if it was 1 meter, as long as it
7 met that test.
8 Since then there's been a lot of reports
9 about what a clinically meaningful change in six-
10 minute walk is. The typical six-minute walk baseline
11 in these trials is about 325 meters. It's remarkably
12 consistent from trial to trial. And a normal,
13 although no one really knows what a normal is, is
14 about 550 to 600. And the typical change -- and what's
15 very interesting is regardless of the trial, the drug,
16 the patients, the dose or the duration, it's always
17 about 40 meters.
18 There is a paper that addressed clinically
19 meaningful in people with lung disease, and they said
20 they needed at least a 55-meter change before the
21 patient could even detect whether they felt better or
22 worse. And another paper came out and said it was in

1 the 70-meter range.

2 So one of the problems we might be facing is

3 that we're looking at a delta in six-minute walk in

4 these trials that while statistically significant,

5 have such little impact on the wellness of the

6 patient, that it's very hard to ascertain whether or

7 not it's truly reflecting the disease process and a

8 beneficial effect.

9 I can say that most of us would agree that

10 walking farther is a good thing in these people,

11 because they can't walk far. And when someone walks

12 150 meters, it's very easy to ascertain, because

13 they're so much better. But I have a lot of patients

14 who walk 30, 40 meters better and they look at me and

15 they're wondering when they are going to get their

16 treatment. So I think it's a relevant issue.

17 DR. KAUL: So you're saying that they cannot

18 -- the change that you see, on average, cannot

19 distinguish a clinically meaningful impact from a

20 learning effect if you were to repeat that test.

21 DR. RICH: There is a training effect --

22 DR. TEMPLE: No, that's not --

1 DR. RICH: -- but I'm not going to
2 discount --
3 DR. TEMPLE: This is corrected for that.
4 This is the double delta.
5 DR. RICH: I think there is a drug effect.
6 The bigger issue is whether the drug is working, and,
7 personally, I don't think it's working on the
8 pulmonary circulation. It could be working on the
9 skeletal muscle. All you need is to improve skeletal
10 muscle blood flow and you can walk 30 meters farther.
11 Then there was another study that's never
12 been mentioned here that was published in Circulation
13 a few years which looked at the effect of an exercise
14 rehab program in patients with pulmonary arterial
15 hypertension, on what's considered maximal medical
16 therapy. And the improvement in six-minute walk was
17 96 meters, which is almost three times what you get
18 with a drug trial, and no one makes the claim that the
19 PVRI was affected at all by being enrolled in a rehab
20 program.
21 So there are really serious issues about the
22 interpretation of the six-minute walk with respect to

1 the underlying disease, pulmonary hypertension.

2 DR. KAUL: Dr. Barst?

3 DR. BARST: In the studies in which we

4 demonstrated the six-minute walk treatment effects of

5 approximately 40 meters in the various trials, we also

6 saw that there was a correlation with the improvement

7 in functional class across the board. It's my belief

8 that an improvement in functional class is feel

9 better, number one.

10 Number two, with regard to the rehab

11 program, which those data came out several years ago

12 from the Giesen group, that, in fact, has been shown

13 that that improves exercise capacity. However,

14 knowing that, our studies have been designed and

15 continue to be designed that a patient who is going to

16 enroll in a study could not have started a rehab

17 program within 12 weeks of enrollment and is precluded

18 from starting a rehab program during the course of the

19 trial.

20 We saw the functional improvement consistent

21 in the pediatric trial, as well, that there was a

22 significant functional class improvement in these

1 children.

2 DR. RICH: To be clear, I didn't want to

3 imply that the change in six-minute walk was not a

4 drug effect. I truly do believe it's a drug effect.

5 The question really is how the drug is working.

6 The issue with functional class, and that's

7 also real, is that there will be people who will

8 perceive whatever the delta is in six-minute walk as

9 feeling better, report a better functional class. But

10 what we don't have is a histogram of the whole spread

11 of change in six-minute walk and then how that

12 correlates, because functional class is, in a sense,

13 binary. They're three and they go to two, for the

14 most part. And so that may be some of the reason for

15 that problem.

16 DR. KAUL: Dr. Temple?

17 DR. TEMPLE: One of the things we've become

18 more interested in recently -- and it's probably not

19 reflected in these analyses -- is not just the mean

20 effect, which is not what really happens to anybody in

21 particular, but what the distribution effect is. So

22 if the mean effect is 40, there's obviously a range.

1 Some people get 20, some people do get something that
2 might be considered important.
3 It's probably more important than we've
4 insisted on to look at the distribution, because you
5 invariably see that there's a difference in the number
6 of people on placebo and drug who have an 80-meter
7 difference, as well as the difference in the mean. So
8 that's probably worth thinking about, too.
9 DR. KAUL: Dr. Neaton?
10 DR. NEATON: Can I just go back to Dr.
11 Brar's presentation, the delta delta graph, slide 9,
12 and just ask the question I asked earlier again?
13 Because I'm not really sure I understand your answer
14 in response to the circles on this slide.
15 My look at this slide is there are a fair
16 number of studies that had fairly large decreases in
17 delta delta PVRI, but minimal changes in six-minute
18 walk. So if I was to do a two-by-two table and
19 basically ask the question, did the pivotal study
20 reach its endpoint based on six-minute walk versus did
21 it reach it on PVRI, I think there's a fair amount of
22 discordance.

1 I say that and also because when I look at
2 the children's study that was presented earlier, you
3 get a different answer with regard to whether the
4 treatment works. If you look at medium dose, there's
5 a disconnect there, because it won on VO2 and lost at
6 the PVRI. And the high dose kind of lost on VO2, but
7 won on PVRI.
8 So that's just a very simplistic but
9 somewhat intuitive kind of approach to this. When I
10 look at it, there's not a lot of concordance.
11 DR. BRAR: I see. First and foremost then,
12 I don't know if this may explain some of this
13 discordance. This is a subset population of the WHO
14 Group 1 idiopathic familial pulmonary hypertension
15 patients. When I look at the actual label where we're
16 looking at a change in six-minute walk distance or the
17 change in PVRI over placebo, we could see that they're
18 all in actually accordance, where they won on six-
19 minute walk distance, they also would win on PVRI. So
20 for this, this is a subset analysis.
21 In addition, I have also made the circles
22 into different dose groups. And I did not stipulate

1 which ones of those dose groups are actually approved.
2 But this can show you, one, that there is some sort of
3 dose response; two, that we do see, on average -- and
4 this is what I can gather from this -- that we see
5 improvement in PVRI, we see improvement in six-minute
6 walk distance over placebo. But the actual decision-
7 making for approvability based on this information --
8 and it may be confounded, because we looked at a very
9 --
10 DR. NEATON: That's a fair comment. So kind
11 of my approach, simplistic, it has some problems with
12 it, and one of them is potentially power, and that's
13 kind of what you're reaching to. It seems like that
14 needs to be very carefully considered along with the
15 type of validation that we looked at before, before
16 you can make any kind of meaningful statement about
17 substituting this endpoint. And so that's my main
18 point.
19 But the other is I guess I'm not getting one
20 point. And that is, we're being asked to consider
21 kind of whether or not the changes in PVRI are
22 reasonable substitutes for six-minute walk. And I can

1 think about that within adults, and there's ways of
2 approaching it. But I heard this morning that the six-
3 minute walk in kids is not really interpretable, and
4 it's not only because you can't do it, it's because
5 some kids walk a long distance even though their PVRIs
6 are bad.
7 So help me with that logic. Why am I trying
8 to consider this endpoint related to six-minute walk
9 when it can't be measured reliably in kids?
10 DR. BRAR: Because I think there is also
11 supporting evidence besides doing this relationship
12 between PVRI and six-minute walk distance. One, it's
13 diagnostic of the disease. And first and foremost,
14 this diagnostic that you have, PAH, is the evaluation
15 of pulmonary hemodynamics, and it's the same
16 diagnostic criteria that's used between pediatrics and
17 adults. That's one.
18 DR. NEATON: I accept all that. But you
19 heard earlier, I thought very well presented by a
20 member of the panel here, there were criteria for
21 surrogacy and you need a lot more than that. And
22 you're kind of beginning to get there, but it just

1 seems like, from looking at this graph, unless there's
2 more behind it, you're a long ways from it.
3 DR. BRAR: And what would you suggest, if
4 you don't mind me asking what the next procedure would
5 be then? And I think that's one of the AC questions,
6 actually, that could be hopefully addressed.
7 DR. KAUL: Why don't we get to that in the
8 afternoon?
9 Dr. D'Agostino?
10 DR. D'AGOSTINO: Just a comment here.
11 When the FDA presentation was being made, I
12 was taking it that part of their development was that
13 they were going to look at what happens with adults
14 and somehow or other infer that to children. And
15 you're saying what if you just looked at children, it
16 wouldn't work. But there is a big jump that I think
17 that underlies a lot of this that somehow or other, if
18 you find your relationship in adults, that it should
19 hold for children. Did I read that correctly or did I
20 hear that correctly from the FDA?
21 DR. TEMPLE: Yes. That's sort of the
22 fundamental question. We're reasonably persuaded

1 that -- correct me if this is wrong -- but we're
2 reasonably persuaded that the relationship exists for
3 adults. The little kids can't exercise. Do we know
4 enough to say this is a reasonable substitute for the
5 test you can't do?
6 DR. KAUL: The problem here is that you're
7 using two different indices of exercise capacity in
8 adults versus children.
9 DR. TEMPLE: Mostly six-minute walk.
10 DR. KAUL: But not in children.
11 DR. TEMPLE: Well, that's true.
12 DR. KAUL: So in adults, we're using
13 six-minute walk and we are using VO2 peak in children.
14 And so there is a missing link. Is there any
15 relationship between six-minute walk test and VO2 in
16 the adult population? Because that's the only
17 population where you can do the six-minute walk test.
18 If there was reasonable evidence of a
19 coherent relationship in the adults between these two
20 indices, then I would feel a little bit more
21 comfortable extrapolating it to the pediatric
22 population, because I'm somewhat reassured by the

1 consistency of the relationship across the age group,
2 including the lower end of the age group.
3 DR. TEMPLE: So you're saying in addition to
4 the six-minute walk in adults, you'd have VO2 in older
5 kids and that would show it, and then you'd feel
6 comfortable, more comfortable maybe.
7 DR. KAUL: Exactly, because this is the
8 missing link. This is a leap of faith that we are
9 asked to make.
10 Dr. Rich?
11 DR. RICH: So one of the fundamental
12 questions I guess we'll talk about this afternoon is
13 whether it's the same disease in children as adults,
14 because isn't that one of the bases for being able to
15 extrapolate and consider this? And my answer is it's
16 not, and let me point out why.
17 Histologically, under a microscope, the
18 pulmonary vessels look the same. But the disease as a
19 syndrome, if you will, is dictated by the right
20 ventricle. And all of the studies have shown that all
21 of the outcome measures and survival relate to RV
22 function, not to PA pressure. If you look at the PVRI

1 equation, it’s all driven by the changing cardiac
2 output and not by really the change in PA pressure.
3 In the adult trials, about 40, 50 percent of
4 the patients were idiopathic, another 40 percent were
5 connective tissue disease, and very few, less than
6 10 percent, are congenital heart disease. And the
7 kids typically are born with more muscular right
8 ventricles and do much better with pressure low like
9 with pulmonic stenosis than the adults do.
10 If you look at the pediatric trial as
11 described in the booklet I got from the sponsor, there
12 was about a third -- a third, a third. A third were
13 idiopathic. Two-thirds were congenital, of which half
14 of those were uncorrected congenitals. We excluded
15 uncorrected congenitals from all of the adult trials
16 because of the concern that their exercise physiology
17 is so different. They shunt right to left.
18 So in addition to their pulmonary
19 resistance, the amount of shunting, which very much
20 dictates how far they can walk, is related to their
21 blood pressure. Kids with higher blood pressure will
22 shunt less than kids with lower blood pressure. Their

1 hemoglobin, which is their compensatory response to
2 the hypoxemia -- and it was such a confounder that we
3 all agreed, for adult trials, we would take people
4 with repaired congenital heart disease, but never with
5 unoperated congenital heart disease.
6 Yet a third of the patients, I believe --
7 correct me if I'm wrong -- in the pediatric trial here
8 had uncorrected congenital heart disease. I haven't
9 seen any subset data. Maybe that explains some of the
10 ambiguity from the response here, but again, I need to
11 remind everybody that there are important differences
12 between children with pulmonary hypertension and
13 congenital heart disease versus adults.
14 DR. KAUL: Let me see if I can extend your
15 logic further. You're saying that RV function is not
16 only a modifier of survival but also of exercise
17 capacity. And if you use six-minute walk distance as
18 your index of exercise capacity, because RV function
19 is relatively better maintained in children than in
20 adults, that's why six-minute walk test is not as
21 reliable as an indicator of exercise capacity.
22 DR. RICH: Perhaps it may be too insensitive

1 to detect the changes where you see it in the
2 hemodynamics.
3 DR. KAUL: So are there any data where you
4 adjust for the RV systolic function in children and
5 demonstrate that this exercise capacity index becomes
6 a stronger predictor?
7 DR. RICH: The only thing I can say is that
8 the document that we got from the agency analysis
9 showed an equation that incorporated right atrial
10 pressure, and that was wonderful, because of all of
11 the hemodynamics that predict outcome, right atrial
12 pressure is the singly most powerful one.
13 In the NIH registry, before there are drugs
14 in every drug treatment trial, in every outcome, in
15 very survival analysis, single center, multi-center,
16 right atrial pressure stands out as the single most
17 important hemodynamic variable, because it's the one
18 that best represents the right ventricular function.
19 Since your equation that incorporated right
20 atrial pressure seemed to be appropriate, my request
21 is, please, if we adopt a hemodynamic biomarker --
22 and I'm not saying I'm against it -- in pulmonary

1 hypertension trials, please take the best hemodynamic
2 biomarkers we have and please include the right atrial
3 pressure.
4 An argument was made that in children, the
5 right atrial pressure is often not elevated, but that
6 was a single center study and that may be a stage
7 issue, because in the baseline data from Pfizer, the
8 right atrial pressure in the adults and children were
9 identical at the time of enrollment.
10 As Robyn showed in her graph, when the
11 patients were dying, the right atrial pressure was
12 going up and up and up as well.
13 DR. KAUL: So, Dr. Brar, you sort of
14 sacrificed your best model for pragmatic reasons.
15 DR. BRAR: Correct.
16 DR. KAUL: And that's understandable, but I
17 think we ought to at least see some data. I'm not an
18 expert in pulmonary hypertension. My guess is that
19 there are individuals in the pediatric age where the
20 RA pressures are elevated.
21 DR. BRAR: It was my understanding -- and to
22 clarify for everyone -- that our final model included

1 right atrial pressure and pulmonary vascular
2 resistance index in the adult population. It was my
3 understanding, as Dr. Rich eloquently stated, that
4 right atrial pressure -- and, also, Dr. Barst stated -
5 - that right atrial pressure isn't affected as much in
6 the pediatrics as it is in the adults. And that's the
7 primary reason why we took that out of the equation.
8 That is correct.
9 DR. KAUL: What happens if you compare data
10 from the two models?
11 DR. BRAR: What happens? First and
12 foremost, I did also a univariate measure looking at
13 PVRI and six-minute walk distance, also looking at RAP
14 as a function of six-minute walk distance. We also
15 see the same consistency.
16 As far as the comparison of the models
17 between PVRI versus PVRI plus RAP, both PVRI plus RAP
18 was able to explain the double delta a little bit
19 better than it does for the delta PVRI alone. That is
20 correct. But the main reason why we took it out was
21 because we thought, from the opinions that I've
22 received, that the right atrial pressure was not

1 affected much in the pediatric. And I may be
2 incorrect in doing so.
3 DR. KAUL: Dr. Black, you get the last
4 question before lunch break.
5 DR. BLACK: This may be a hard question. I
6 want to follow-up what Stu said. He said that he
7 wanted a clinically meaningful finding. Do you have
8 any to suggest or does anyone? I don't see patients
9 like this, and I wonder what you would use.
10 DR. KAUL: We will address that in the
11 afternoon, if you don't mind.
12 So at this point, we will break for lunch.
13 We will reconvene again in this room in one hour from
14 now at about 1:00 p.m. Please take any personal
15 belongings you may want with you at this time. And
16 for committee members, please remember that there
17 should be no discussion of the meeting during lunch
18 amongst yourselves, with the press or with any member
19 of the audience. Thank you.
20 (Whereupon, at 12:01 p.m., a lunch recess
21 was taken.)
22

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

2 (1:17 p.m.)

3 DR. KAUL: Welcome back. We will begin with

4 the open public hearing session. Both the Food and

5 Drug Administration and the public believe in a

6 transparent process for information gathering and

7 decision-making. To ensure such transparency at the

8 open public hearing session of the advisory committee

9 meeting, the FDA believes that it is important to

10 understand the context of an individual's

11 presentation.

12 For this reason, the FDA encourages you, the

13 open public hearing speaker, at the beginning of your

14 written or oral statement, to advise the committee of

15 any financial relationship that you may have with the

16 sponsor or its product and, if known, its direct

17 competitors. For example, this financial information

18 may include the sponsor's payment of your travel,

19 lodging or other expenses in connection with your

20 attendance at the meeting.

21 Likewise, the FDA encourages you at the

22 beginning of your statement to advise the committee if

1 you do not have any such financial relationships. If
2 you choose not to address this issue of financial
3 relationships at the beginning of your statement, it
4 will not preclude you from speaking.
5 The FDA and this committee place great
6 importance on the open public hearing process. The
7 insights and comments provided can help the agency and
8 this committee in their consideration of the issues
9 before them. That said, in many instances and for
10 many topics, there will be a variety of opinions. One
11 of our goals today is for this open public hearing to
12 be conducted in a fair and open way, where every
13 participant is listened to carefully and treated with
14 dignity, courtesy and respect. Therefore, please
15 speak only when recognized by the Chair. Thank you
16 for your cooperation.
17 We have two speakers. Speaker number 1,
18 Dr. Beardsworth.
19 DR. BEARDSWORTH: Good afternoon,
20 Mr. Chairman and advisory committee. As you just
21 said, my name is Dr. Anthony Beardsworth. I'm here
22 representing Eli Lilly and company and, as such, could

1 be seen as a competitor to the sponsor. I have no
2 financial interactions with the sponsor.
3 What I'd like to do is perhaps start off by
4 thanking the FDA for convening this advisory committee
5 in open forum. This is a very interesting and complex
6 scientific issue that has significant clinical impact
7 even today. So I thank the FDA for convening this
8 meeting.
9 I would also like to commend the sponsor and
10 the FDA and the advisory committee on the level of the
11 debate that has occurred already, and I look forward
12 to the rest of it this afternoon.
13 I don't envy the advisory committee, the
14 challenge that has been set them by the FDA. And as
15 they deliberate on those questions through this
16 afternoon, what I would ask is that when the
17 scientific complexity of the challenge that they've
18 been given seems overwhelming, that they grasp their
19 left thumb in their right hand, they take a few deep
20 breaths and they try and remember the three things
21 that I'm going to tell you in the next eight minutes.
22 Those three things, I think, are key aspects

1 that will impact your deliberations. The first --
2 and I don't think there's going to be anyone who
3 disagrees with this -- is keep in mind the patient.
4 The second thing that I'd like you to keep in mind is
5 the clinical reality of trying to conduct studies in
6 this patient population. And the last thing that I
7 would like you to keep in mind, and I think it will
8 become evident in your discussions, is the critical
9 need that we have, or need, for a single primary
10 efficacy endpoint that spans the entire age range of
11 this pediatric patient population.
12 So those are the three things that you're
13 going to need to think about when it's all getting too
14 much for you: the patient, the clinical reality of
15 conducting these studies, and the need for a single
16 efficacy endpoint to span the entire age range.
17 So let's talk about a little bit about the
18 patient. And as I said, I think we are all here to
19 try and improve the outcome, the care and the
20 management of the patient. No one will disagree with
21 that. And I'm not qualified to represent the
22 patients' views, but what I do know is that the

1 current situation of products that are licensed for
2 adults with PAH being used in children in the absence
3 of data is a situation that we must improve on. We
4 are crying out for robust, scientifically valid and
5 clinically relevant data that can guide the safe and
6 effective prescribing in this very vulnerable patient
7 population.
8 Now, Dr. Barst alluded to the fact of how
9 devastating, life-changing and ultimately life-
10 threatening this diagnosis is. And we've also heard
11 that, in fact, this condition is very rare. And it's
12 that rarity that moves me to my second point, which is
13 the issue around the clinical reality of trying to
14 conduct studies in this patient population.
15 The sponsor commented and alluded to the
16 difficulties and challenges that they have faced in
17 conducting this very impressive clinical trial. Five
18 or six years to recruit 250 patients, and I think I
19 heard -- and I may have got the number wrong -- only
20 25 patients in the North Americas over five years.
21 The challenges that the sponsor faced then
22 have escalated and have increased. I think what lies

1 behind that is obvious, but I'm going to comment on
2 them a little bit anyway. Clearly, the patient
3 population is rare. There are considerable concerns
4 raised by the patients, their parents, their carers,
5 their investigators, and ethical boards around the
6 conduct of these trials in this patient population.
7 That is made worse by the fact that there is
8 a belief that there are treatments out there already
9 that have significant efficacy for this patient
10 population. And so we're in a spiral of having an
11 inability to recruit for these studies, because
12 increasingly, drugs are being used in the absence of
13 data, a spiral we must break.
14 The problems that the sponsor faced were
15 made even more difficult by the fact that they didn't
16 have a single unifying endpoint that crossed the
17 entire age range. This resulted in only 50 percent of
18 the patients that they recruited into this study being
19 eligible for the primary efficacy endpoint. That is a
20 terribly inefficient use of these patients who have
21 volunteered their services for this clinical trial.
22 We must have a single unified efficacy

1 endpoint that spans this patient population. And, in
2 fact, we've had some debate about it already, and
3 there is already agreement that there are some
4 endpoints that do span the entire age range. And
5 those are the functional endpoints, obviously, of
6 mortality but also of clinical worsening.
7 The problem we have is returning to the
8 clinical reality of trying to conduct these studies.
9 I have no doubt that we could perform a clinical
10 worsening study if we were able to enrich the patient
11 population with a group of patients who are
12 sufficiently sick for us to have those events. The
13 problem we have is actually recruiting those patients
14 is very difficult because of the belief that there are
15 already existing therapies that will provide benefit
16 for them.
17 That's why I'm so excited about this
18 meeting, because I think the revelation of the data
19 that the FDA has put together, which I'm very excited
20 about, gives us a unique opportunity to gather you
21 people in this room to really look at these data and
22 try and understand whether we really believe that we

1 can move from the scientific ideal to the clinical
2 reality and allowing in drugs that have already proven
3 efficacy in adults and safety in adults, that we can
4 make that leap and use hemodynamics or PVRI, in
5 particular, as that unifying endpoint that spans the
6 entire age range.
7 I think this is a unique chance, and if we
8 don't take it now, we really need to understand what
9 we need to do to get to the point where we can have a
10 single unifying endpoint. Otherwise, we're going to
11 be having the same discussion in 20 years' time, and
12 we will not truly have served the patient.
13 So when it all gets too much, hold your
14 thumb, deep breaths and remember the three things.
15 We're here for the patient. There is a clinical
16 reality around recruiting studies in this patient
17 population. A significant answer to that problem, I
18 think, is a single unifying endpoint that spans that
19 entire age range in the patient population. Thank you
20 very much.
21 DR. KAUL: Thank you, Dr. Beardsworth, and
22 keeping on time.

1 Our next speaker is Linda Carr.

2 MS. CARR: As he said, I'm Linda Carr, and

3 thank you for holding this meeting. It's very

4 important. It's helping our children with pulmonary

5 hypertension.

6 I am not a medical professional. I am the

7 mother of a patient with pulmonary hypertension, and

8 I'd like to briefly tell you my daughter's story

9 today, put a face to all of this discussion. Hannah

10 is now 23 years old. She was diagnosed in 1993 with

11 idiopathic pulmonary hypertension at age 5. She had a

12 history of dizziness and fainting with exertion, which

13 brought us to the pediatrician and then the

14 cardiologist. They couldn't find anything for a long

15 time, several years.

16 Finally, the cardiologist did an echo which

17 diagnosed her pulmonary hypertension, and at that

18 point, he announced she had one to two years to live.

19 After some research, we found Dr. Barst in

20 New York and traveled there for her first visit with

21 Robyn. At age 6, Hannah had her first right heart

22 catheterization, which determined she was a responder.

1 She started calcium channel blocker therapy, which was
2 expected to be an effective treatment for her for
3 quite some time. And in addition, her symptoms
4 disappeared, the fainting with exertion, and she was
5 able to participate in all of her activities without
6 any restrictions. She was not limited in any way with
7 her exercise.
8 Surprisingly, at her next cardiac
9 catheterization after, I believe, one year, it showed
10 her PVR was not improved and her resting pressures had
11 not improved. The difficult decision was made based
12 on that catheterization to start her on Flolan, the IV
13 therapy. It wasn't even yet approved.
14 At the next cath, her pressure had returned
15 to basically normal after a period of time on the
16 Flolan. It was fantastic news. Even with the
17 cumbersome therapy, it was fantastic news. Hannah
18 remained on Flolan for 10 years, with a cath every few
19 years. I'm sorry I don't recall the exact intervals.
20 She transitioned to oral meds her senior year in high
21 school, and she has remained well on a variety of oral
22 and inhaled medications.

1 Hannah did try to take the exercise tests,
2 as was customary in New York from, the first visit at
3 age 6 and did the bike test that she could, and it's
4 obviously not effective with a 6-year-old. It's a
5 learning experience. And they were not effective for
6 several years. But eventually, the exercise testing
7 was very successful, and those tests and periodic
8 catheterizations along the way were used and still are
9 used to monitor her progress.
10 To conclude, in 2009, this little girl who
11 was not supposed to live beyond age 8, graduated
12 college, married her high school sweetheart and
13 adopted a baby girl.
14 These youngest pulmonary hypertension
15 patients, our children, my friends' children, deserve
16 effective medications to help them live longer and
17 healthier lives. I thank you for your time today and
18 your efforts on behalf of all of these very special
19 children. Thank you.
20 DR. KAUL: Thank you, Ms. Carr.
21 This concludes the open public hearing
22 portion of this meeting, and we will no longer take

1 comments from the audience. The committee will now
2 turn its attention to address the task at hand, the
3 careful consideration of the data before the
4 committee, as well as the public comments.
5 Now, we are scheduled to start with the
6 committee discussions and questions to the committee
7 at about 2:00 p.m. We have 45 minutes left. This is
8 what I propose to do for these 45 minutes. The FDA
9 will get about three minutes for some clarifying
10 information, some additional data that will help
11 inform the discussion.
12 The sponsor will get about two minutes to
13 make some clarifying statements, and Dr. Barst will
14 get about seven minutes to help focus the discussion
15 when we stopped about the relationship between
16 exercise capacity indices and hemodynamics and
17 outcomes.
18 So we'll start off with the FDA.
19 DR. BRAR: Satjit Brar, FDA. It was
20 mentioned by Dr. Rich earlier that we had initially
21 had the factor of RAP in our model, where, in essence,
22 we see on the left-hand side, again, the forest plot

1 looking at delta six-minute walk distance versus delta
2 PVRI, and on the right-hand side, the similar forest
3 plot looking at delta six-minute walk distance over
4 delta RAP.
5 As you can see, again, with the conclusions
6 I had earlier about pulmonary vascular resistance
7 index, it shows that qualitatively, it’s all going the
8 same direction.
9 We also see this qualitatively with right
10 atrial pressure across the trials. Where we see an
11 improvement in right atrial pressure, we also see the
12 improvement of six-minute walk distance. And in
13 essence, what we do see -- and this is one of the
14 reasons, as well, why we want to pinpoint more PVRI
15 rather than RAP, because we see, on average, that it’s
16 more consistent for PVRI versus RAP. That’s one of
17 the reasons, that across trials that we see that PVRI
18 is more a significant relationship compared to RAP.
19 In addition, this other information about
20 RAP not being affected much in the pediatric
21 population that we thought held true essentially is
22 one of the reasons why we took RAP out of the

1 equation. So in essence, RAP in adults does show a
2 consistent relationship for some trials. It does not
3 show a significant relationship, and this could be a
4 sample size issue. But for the most part, we took RAP
5 out of the equation essentially because that RAP, we
6 thought, was not going to be useful in the pediatric
7 population.
8 DR. KAUL: Would it also be fair to say that
9 it's less precise?
10 DR. BRAR: Yes. It is fair to say that RAP
11 itself is less precise than PVRI, correct.
12 DR. KAUL: Okay. Do you have any additional
13 comments?
14 DR. BRAR: That's the only thing I just
15 wanted to share with Dr. Rich.
16 DR. KAUL: Okay. Does anyone on the
17 committee have any follow-up comment or question
18 regarding this?
19 Dr. Rich?
20 DR. RICH: Just a brief comment. I think
21 one of the reasons is because the elevation in RAP is
22 typically seen late. And as trials enroll less and

1 less sick people, which they have, you're not going to
2 see much of a change in it. But if we're talking
3 about adopting a biomarker of hemodynamics that will
4 kind of be as encompassing of the disease process at
5 all, I see no reason why not to include rather than
6 one or the other. I don't see that it's a tradeoff.
7 We can include them together in a formula.
8 DR. KAUL: Dr. D'Agostino?
9 DR. D'AGOSTINO: I may be misreading this.
10 But is the confidence interval affected by the scale
11 of the variable? This is the confidence interval on
12 the independent variable.
13 DR. BRAR: It very well may be because --
14 DR. D'AGOSTINO: So wouldn't you want some
15 kind of standardized --
16 DR. BRAR: I would try to figure out then I
17 guess trying to standardize PVRI versus RAP. Is that
18 what you're suggesting?
19 DR. D'AGOSTINO: Well, standardized by the
20 standard deviation or something like that. I may be
21 wrong, but the variability, I think, is affected by
22 this scale of the independent variable.

1 DR. KAUL: Point well taken.
2 Dr. Veltri?
3 DR. VELTRI: Just a question, since the
4 treatment of this disease apparently is going towards
5 polypharmacy, since there's three different types, I
6 understand your analysis was based on the double-blind
7 placebo-control, but there could have been background
8 therapy. Do you have any information on these
9 indices, where there was combination therapy as
10 opposed to, let's say, monotherapy? Because
11 obviously, the pendulum is swinging, and there's a lot
12 more room to go, as Dr. Rich noted, with the deltas
13 and the PVRI as opposed to the exercise.
14 DR. BRAR: You are correct. Some of the
15 trials that we evaluated did have background therapy
16 that was, quote-unquote, "stabilized background
17 therapy," but the patients still were not doing well.
18 As far as differentiating between the relationship of
19 patients that were on background therapy versus just
20 pure placebo, I do not have that information here to
21 show you.
22 DR. KAUL: Thank you.

1 At this point, I'm going to call on the
2 sponsor. Please keep on time. We'd like to start
3 with the questions at about 10 minutes.
4 MS. MCKAY: So I really just wanted to make
5 a brief statement, if I could. Listening to the
6 discussions this morning has been really helpful to
7 us, and we just wanted to remind you that regardless
8 of the debate around surrogacy, Dr. Stockbridge
9 mentioned this morning the possibility of changes to a
10 written request even at this stage of development.
11 For sildenafil, we still believe that
12 hemodynamics is an important measure and important
13 toward informing a change to our written request,
14 besides the discussion on surrogacy. Thank you.
15 DR. KAUL: Thank you.
16 Dr. Barst?
17 DR. BARST: You'll be pleasantly surprised,
18 I'll speak less than seven minutes. I wanted to
19 clarify several points that were raised prior to
20 lunch, and one is -- if I could have backup slide RB-
21 11.
22 This is just an example of one study which

1 demonstrated a correlation and a relationship between,
2 in adult patients with PAH, distance walked in six
3 minutes versus the peak VO2. There also is data that
4 is published that demonstrates this same correlation
5 exists with children, however, only when the children
6 walk less than 300 meters, which precludes patients
7 such as those that were concerned about enrolling in a
8 placebo-controlled trial. But once the child walks
9 more than 300 meters, they still have a tight
10 correlation between peak VO2 and their pulmonary
11 vascular resistance.
12 The second point I wanted to make was
13 slide 42, and this is just to reiterate that the data
14 seen in the pediatric study, shown in mustard color,
15 and the data shown in the adults, in light blue, is
16 consistent with the treatment effect when we look at
17 percent change in exercise, whether we're looking at
18 percent change with six-minute walk of approximately
19 10 percent or the percent change in peak VO2 in the
20 children of approximately 10 percent. And they both
21 appear to correlate with what we've seen with the
22 plasma concentration.

1 The last point I'd like to make, as a
2 clinical investigator, is to reiterate what's been
3 said today, and that's that we rely extremely heavily
4 on hemodynamics. Whether it's a young child who
5 cannot exercise or an adult, they are very, very
6 critical to us in assessing how we should be treating
7 children. Thank you very much for the time.
8 DR. KAUL: Thank you, Dr. Barst.
9 We have the option of continuing asking
10 questions of the FDA and the sponsor and of each other
11 for the next 30 minutes or we can get down to the
12 business of asking the questions that are provided to
13 us. So can I see a show of hands? Does anybody have
14 additional clarifying questions?
15 Okay. So nobody has any questions, other
16 than Dr. Rich, who wants to probably respond. Dr.
17 Neaton has one. Okay. Well, let's deal with those.
18 And Dr. Black. Okay. Let's start with Dr. Rich
19 first.
20 DR. RICH: I apologize for stealing the
21 microphone so much today, but I'm an invited guest and
22 I may never be on this panel again, so I figure it's

1 an opportunity just to kind of point out some issues
2 in this disease, which have been absolutely correctly
3 characterized as devastating, fatal, progressive,
4 because there's a lot of, I use the term, mythology
5 about what we're doing here.
6 The treatment algorithm that's been endorsed
7 by the experts in the field require a right heart
8 catheterization at baseline followed by acute
9 vasodilator testing to see if they're vasoreactive.
10 This arose from the perception back in the 1960s that
11 it's a disease of vasoconstriction, and there was an
12 early paper with acetylcholine showing vasodilatation.
13 If the patient is vasoreactive, they almost
14 always will get calcium channel blockers, because as a
15 vasodilator, it works. It's about 10 percent, so it's
16 a very small subset of the whole picture. And the
17 single center data, there's two, long-term 20-year
18 single center data suggests that their survival is
19 straight across. And so that's been reassuring.
20 Interestingly, if they do not have the
21 ability to vasodilate, they now are treated with a
22 vasodilator. And so it should be no surprise that you

1 can’t lower the PA pressure very effectively with
2 these drugs, because if you could, they wouldn’t even
3 be here. They would be on the calcium channel
4 blockers. So there’s kind of a misperception about
5 that.
6 The average change in mean PA pressure in
7 these people across all trials is about a 2 to 3
8 millimeters of mercury. So when you consider that the
9 PA pressure is elevated 400 percent and you lower it 5
10 percent, that is unlikely the mechanism by which these
11 drugs make these people better.
12 I think the data that they make them better
13 is clear. The real question is mechanism of action,
14 something that is really not the charge of the FDA to
15 elucidate. And there’s been a lot of debate about how
16 these drugs clearly work. I can say, though, that
17 when the patients die, they die of right heart
18 failure. The PA pressure doesn’t continue to go up.
19 The RV fails, the RA pressure goes up. They have
20 worsening exercise tolerance, and then they die.
21 So if you go back and look at the mechanism
22 of action of these drugs, a lot of them have

1 cardiovascular actions, as well as others.
2 Prostacyclin clearly raises cardiac output in a dose-
3 response relationship. You can basically increase the
4 dose of intravenous epoprostenol and get the cardiac
5 output to go up along with it. Sildenafil recently
6 has been shown also to have pretty pronounced effects
7 on the RV, because you get selective increase in PDE5
8 in the right ventricle, in the filling right
9 ventricle. And my bias is it probably works on the
10 right ventricle in these people. Bosentan does not,
11 and that may be a distinguishing characteristic.
12 Epoprostenol also converts a failing RV from
13 glycolytic metabolism to aerobic metabolism.
14 So there are lots of mechanisms of action
15 here, but what they don't do effectively is bring the
16 PA pressure back to normal. It's an issue for this
17 committee, I think, in the next generation of drugs
18 that are being developed, which are really looking at
19 the disease, tyrosine kinase inhibitors, trying to
20 change the proliferation of the pulmonary vasculature
21 directly as opposed to changing the hemodynamics or
22 exercise tolerance, and you may see totally different

1 results there.

2 But I will tell you that there has never

3 been a study showing that these drugs do anything to

4 the disease. They don't halt progression. They don't

5 cause regression. The data actually suggests the

6 opposite, that they have no effect on the pulmonary

7 vasculature itself. And so it's something to keep in

8 mind when we're talking about our endpoints and

9 biomarkers and surrogates and all of that, because I

10 think there's so much confusion about the pathobiology

11 of the disease and the natural history that the

12 clarification is necessary. Thank you.

13 DR. KAUL: Thank you, Dr. Rich.

14 I'm going to call upon Dr. Rosenthal. He's

15 the card-carrying pediatric cardiologist, and I'd like

16 him to share his perspectives about what was just

17 commented upon.

18 DR. ROSENTHAL: Does that mean I can't ask

19 my question?

20 DR. KAUL: You can ask your question, as

21 well.

22 DR. ROSENTHAL: Well, I've been taking this

1 all in, and I think there are -- I'm not sure that I'm
2 seeing the rub. I mean, it seems like we started off
3 many years ago embarking on a path using the six-
4 minute walk test as something that was supposed to be
5 important. And I'm not sure that now we're not trying
6 to find a more relevant and uniformly applicable
7 endpoint. And I think there is some importance to
8 that.
9 One of the questions that I have regarding
10 endpoints in kids that we haven't really discussed is
11 that many of these kids end up coming to transplant.
12 And there are decision trees that are used. There are
13 decision processes that are used in trying to figure
14 out when is the best time to pull the trigger. And it
15 occurs to me that maybe some of the information that's
16 used in trying to arrive at the best timing for that
17 would also be relevant in this discussion of relevant
18 endpoints. We try and not transplant people for
19 anything before it's time.
20 I haven't yet heard, but I'd like to ask the
21 experts around the table and on both sides of the
22 aisle to reflect on how these different clinical

1 endpoints and hemodynamic measurements are used to
2 make these decisions in kids.
3 DR. KAUL: Dr. Newman or Dr. Kawut?
4 DR. NEWMAN: I can’t respond to that
5 question. As an adult pulmonogist, in the adult
6 pulmonary world, transplantation is the very last
7 thing that we want for a patient, and I don’t think
8 that we have fixed endpoints beyond advanced Class 3
9 to Class 4 disease without remission, without diuretic
10 effect, without drug effect, because transplantation
11 is the acquisition of a second disease, as we all
12 know. It’s not a cure. It may cure something, but it
13 creates another illness.
14 So I can’t really respond to your question
15 about pediatric transplantation, which is probably a
16 little more successful than adult transplantation.
17 But I would like to respond. I think that
18 Stuart Rich makes excellent points. It doesn’t
19 actually get us to the answer, though, which is that
20 the six-minute is an integrated function of the body
21 that includes hematology and the ability and
22 availability to disburse blood and fitness of the

1 muscles and ventilatory drives and the patient's
2 emotional state and their degree of -- and so it's a
3 very good integrated measure of something, but it's
4 not a very good measure of pulmonary vascular
5 function. And yet when pulmonary vascular function is
6 severely compromised, the six-minute walk is
7 compromised. And when pulmonary vascular function is
8 markedly improved, which, unfortunately, is rare, it
9 improves to a certain degree.
10 But the reason that I think we've all been
11 dissatisfied with that test is just for those reasons.
12 It has never been proven to correlate well with final
13 outcome. So I'm sort of worried about this issue of
14 substituting hemodynamics, which I think has been
15 beautifully and adequately shown today to associate
16 and correlate with the six-minute walk in a general
17 way, which is that you take one test that associates
18 with a test of soft specificity and sensitivity and
19 the risk then is that you're going to use it as a
20 substitute. So you take one test of uncertain
21 specificity and sensitivity with regard to outcomes
22 and use it to substitute for another test that we

1 don’t like.

2 If we were to decide to allow this to be

3 used in the pediatric age group below the age of 7 as

4 a substitute for the six-minute walk, I would hope

5 that the FDA would view this as a rigid exception to

6 the current practice, which is unsatisfactory, but for

7 which we have no solution.

8 Stuart Rich is a brilliant guy. He doesn’t

9 have a solution to this problem nor does anyone at

10 this table, unless somebody is going to speak up.

11 Steve’s a pretty smart guy, too.

12 So my big concern has to do with the

13 implications of any decision we make downstream, which

14 is do we open Pandora’s box; does all of a sudden

15 everybody want to use hemodynamics as a measure of

16 efficacy? If you did that, you could get Lasix and

17 Zaroxolyn approved by the FDA for the treatment of

18 primary pulmonary hypertension, because they can

19 change RA pressure and cardiac output in an instant.

20 In fact, they’re the most powerful drugs we have.

21 So we can’t be fooled into thinking that

22 we’re very close to the truth with any of these tests,

1 and we, therefore, have to be careful about getting
2 rigid in over-interpreting the information we get from
3 them.
4 So that's my sort of general view of where
5 we are right now, and I'm not sure that anybody here
6 is going to be able to improve on our understanding of
7 what's going on with these patients.
8 DR. KAUL: Thank you, Dr. Newman. You have
9 very eloquently articulated one of my major concerns.
10 If we act in a given manner, are we running the risk
11 of opening up the Pandora's box for other disease
12 conditions?
13 Dr. Rosenthal?
14 DR. ROSENTHAL: I just want to clarify. I
15 don't think transplant is a good idea, either. But I
16 think it's sort of a -- transplant is an outcome like
17 death. It's the end of the game. And so if there are
18 other combinations of clinically available data points
19 that can be used to help to predict the end of the
20 game, then I think that those should be considered in
21 a way that they're currently considered in the
22 clinical realm. That's my point.

1 DR. KAUL: Dr. Black?

2 DR. BLACK: I had asked before we had lunch

3 about whether there were clinical things you'd like.

4 And I just would like to take my thumb in my hand now

5 and ask the question. Yes, it'd be great to have a

6 single efficacy endpoint, but is this it or is

7 anything we've heard today good enough to do that?

8 And I'm not persuaded just yet.

9 The other thing that's a little bit puzzling

10 to me is we heard about the grim prognosis, and yet we

11 also hear about an 80 percent survival and how someone

12 who is 5 years old is now married at 23. Those don't

13 exactly compute, and it seems like the situation has

14 been getting better without having a single efficacy

15 endpoint. So also, we heard that an echo seemed to

16 make this diagnosis. That's a little easier, I think,

17 than a cath. So I need some help from people who see

18 this disease to explain those things that I think are

19 a little discrepant to me.

20 DR. KAUL: Dr. Barst, you mentioned that the

21 five-year median survival was 80 percent. But can you

22 sort of reinterpret that data for us and tell us about

1 the natural history? What is the median age of
2 demise?
3 DR. BARST: Yes. From natural history data,
4 the median length of survival after diagnosis to death
5 was less than one year. Looking at a number of
6 studies from around the world, including registry data
7 from 2007 when therapies were not available, there was
8 still a five-year survival of less than 30 percent.
9 The data that I reported of 80 percent 10-
10 year survival and similar studies of -- I think
11 there's a 90 percent five-year survival from another
12 center -- are based on using very aggressive
13 therapies, such as intravenous epoprostenol. There
14 are also registry data from other centers where the
15 five-year survival is not in the 90s, but it is 55 to
16 60.
17 It's my belief that the reason some of the
18 centers have had better survival is we've had to learn
19 along the way what's the best dose to use to treat
20 children with and we had to this without having hard
21 data that would help us immensely. So I believe that
22 having controlled data, for me, as a treating

1 clinician, is extremely important, because we cannot
2 say that children are just small adults and just use
3 the drugs off label without knowing what the safety is
4 or the right dosing.
5 DR. BLACK: I agree with you that it would
6 be great to have that, but you also told us how hard
7 it is to recruit people for these comparative trials.
8 So how does that work?
9 DR. BARST: If I could make one comment with
10 regard to the pediatric sildenafil trial, I was the
11 principal investigator for the study. And yes, it did
12 take us five years to enroll. Part of the reason it
13 took us five years to enroll is there was the
14 agreement that a certain number of children had to be
15 enrolled who could perform the cardiopulmonary
16 exercise testing.
17 If we had enrolled 200-plus children for
18 hemodynamics and then also performed cardiopulmonary
19 exercise testing in the children who would be able to
20 do it appropriately, that were developmentally able,
21 they did have exercise intolerance and they had no
22 history of syncope, we would have been able to perform

1 the study in a much shorter period of time, and we
2 would have been able to learn and get data about the
3 right dosing.
4 As the data was shown to you by Dr. Ewen, if
5 we had just assumed that using the low dose that we
6 saw was effective in adults and went ahead and did
7 that with children, we would have no evidence of
8 efficacy, and we really would have been not giving
9 these children the treatment that they should have.
10 DR. BLACK: Were you thinking about planning
11 a study where you compared several agents to each
12 other or pony doses or combinations of things that we
13 hear people are using?
14 DR. BARST: This was brought up by one of
15 the committee members. It has been the pulmonary
16 hypertension consensus and in the guidelines that I've
17 participated in writing that in the future,
18 placebo-controlled trials in treatment-naïve patients
19 are no longer considered ethical.
20 So all of our studies ongoing and designing
21 them will be add-on to standard of care background.
22 That would not preclude us from using hemodynamics as

1 a primary endpoint, as well as looking at exercise
2 capacity in the children who can do it. I fully
3 support that our adult studies need to continue to
4 have a primary endpoint that equates to feel better
5 and that we do hemodynamics as supportive data.
6 DR. BLACK: Thank you.
7 DR. KAUL: Thank you, Dr. Barst.
8 Dr. Neaton?
9 DR. NEATON: Can I just ask, before I ask my
10 question to the FDA, to what extent does the longer
11 survival relate to improved, more timely diagnosis?
12 We've heard a couple examples where it may take some
13 time to kind of get the diagnosis right. It doesn't
14 relate.
15 DR. BARST: That's something I wish I could
16 say has happened, because my colleagues and I have
17 spent an inordinate amount of time trying to increase
18 awareness and education to make the diagnosis earlier.
19 Unfortunately, we have been fairly unsuccessful with
20 this. From our early studies of the natural history
21 in the 1980s, the average time from onset of first
22 symptoms to diagnosis was 24 months.

1 Currently, the average time from onset of
2 symptoms to diagnosis is better than that, but it's 18
3 to 20 months. If we look at the hemodynamics and the
4 functional class at the time of diagnosis amongst the
5 pediatric and adult cohorts, we are not diagnosing
6 them particularly earlier in the course of the
7 disease.
8 DR. KAUL: Do you have your question,
9 Dr. Neaton?
10 DR. NEATON: My question is to Dr. Brar.
11 There was a question this morning that I just wanted
12 to make certain I understood the answer to, because I
13 think it's important. For the trials that you
14 included in your overview, how were those trials
15 selected and what's the universe of trials from which
16 they were selected from?
17 DR. BRAR: The trials that we selected were,
18 one, patient population had to be WHO Class 1 and
19 incorporate idiopathic or familial PAH patients. In
20 addition, they were to have six-minute walk data at
21 baseline, and the six-minute walk distance is
22 generally taken over a few weeks, every few weeks

1 until the end of trial. But also, hemodynamic
2 measures had to be measured both at baseline and end
3 of trial. A lot of the other trials that we looked at
4 only did a baseline measurement.
5 DR. NEATON: That's fine. But I thought I
6 heard that -- this may be just my imagination -- that
7 these were trials which led to approval and there were
8 trials that did not lead to approval that were out
9 there that you didn't have.
10 DR. BRAR: Currently, what I know of the
11 trials that we have in the database, those are
12 primarily all approved drugs.
13 DR. NEATON: So we have a selection of
14 essentially trials for which overall in these studies
15 the six-minute walk difference differed significantly
16 between the treatment groups.
17 DR. BRAR: I do have a trial in our double
18 delta analysis where actually you'll see a single
19 point back actually in the low left-hand quadrant.
20 This was a trial that was performed that failed both
21 on PVRI and six-minute walk distance. Primarily, it
22 was a drug that's already approved, but it was a very

1 low dose. So they didn't meet the criteria for either
2 PVRI or six-minute walk distance, so that was a failed
3 trial, actually.
4 DR. NEATON: Do you have an estimate of how
5 many trials are out there that --
6 DR. BRAR: Right now, in the FDA, we have a
7 total of 42 trials. But there are trials that are
8 involving CTEF patients, which is more of a
9 thromboembolic issue. There's also trials that
10 include connective tissue disease. We excluded those
11 trials because we didn't think those are
12 representative of what is in the pediatric population.
13 So it's prespecified. We specified that we want WHO
14 Group 1 that had idiopathic and familial hypertension
15 and that had complete efficacy data, meaning six-
16 minute walk distance at baseline and end of therapy,
17 in addition to hemodynamic information that was at
18 baseline and end of trial.
19 DR. KAUL: Thank you.
20 Dr. McGuire?
21 DR. MCGUIRE: I just wanted to come back to
22 one of the very clarifying moments was the

1 presentation by Dr. Durmowicz, which we haven't, at
2 this committee, thought much about this pediatric
3 extension, and I think all of us are struggling with
4 trying to accept this as a surrogate.
5 But it's not really a surrogate. It's an
6 extension of the adult data into a population and
7 seeing the experience to date using PK and PD data
8 with loratadine and anti-retrovirals and argatroban
9 and other drugs.
10 These have all been unilaterally decided and
11 taken and accepted, even as little as PK data. And so
12 we're not trying to reprove the concept in a different
13 population. We're just trying to have acceptably
14 interpretable -- I think that's the terminology that
15 Dr. Stockbridge used -- acceptably interpretable data
16 to make some conclusions based on the adult data.
17 So I think we're confusing ourselves a lot
18 trying to figure out the very best hemodynamic measure
19 or measures to serve as surrogacy for clinical
20 efficacy as opposed to saying it's acceptably
21 interpretable that we can, with some confidence, say
22 that the same effects should be expected in children

1 as adults. And so for me, that was very clarifying
2 for the historical precedent in this domain.
3 DR. KAUL: If I recall, the term that was
4 used was "sufficiently interpretable." Does the FDA
5 have a quantitative or a qualitative definition of
6 what is sufficient?
7 DR. TEMPLE: The people who know the
8 pediatric rules will know this better than I do, but
9 in a number of them, it talks about the possibility
10 that data in adults would convince you that a drug
11 works in children. And sometimes you might just be
12 convinced without any further data, but one of the
13 things you might also do -- and it says this -- is
14 note that the pharmacologic effect seen in adults is
15 present in children and that the dose response or the
16 PK/PD relationships are similar.
17 So it doesn't talk in those things about
18 surrogates particularly, but it is using those
19 measurements for a drug you already know works
20 somewhere to extend it. And these are all related
21 matters, and I don't think we care what you call it.
22 We're just asking you about whether we should do this.

1 DR. KAUL: Anybody else? Dr. Halperin?
2 DR. HALPERIN: Thank you. I'd just like to
3 follow up on a piece of Dr. Black's query that was not
4 addressed, and maybe just disabuse me in the absence
5 of a patient representative on our panel today.
6 Why not echocardiographic parameters, which
7 can give us some information about the right atrium,
8 right ventricle and estimates of pulmonary pressure?
9 And I'd perhaps just direct these to our experts on
10 the panel, Dr. Rich and Dr. Kawut.
11 DR. RICH: I'll be happy to. Good point.
12 Let me clarify, number one, the Doppler estimate of RV
13 systolic pressure is fraught with inaccuracy. We just
14 did a trial which will be published soon. It's plus
15 or minus 35 millimeters of mercury, and since you're
16 talking about an RV systolic pressure that starts
17 about 50, it's just way too inaccurate.
18 But RV function you can measure on echo or
19 other imaging modalities, and I think that that's
20 something that should be looked at. There are some
21 echocardiographic studies done in clinical trials
22 where they went back and analyzed it, and there was

1 some consistency with changes in right ventricular
2 function by a variety of Doppler measures other than
3 the pressure, something that certainly should be
4 looked at.
5 I think going forward, if a recommendation
6 is let's go prospectively and look at some biomarkers,
7 that should be one of them for sure, because I think
8 the data supports it. It certainly does predict long-
9 term outcome.
10 DR. KAUL: Dr. Coukell?
11 DR. COUKELL: I'd just like to ask for
12 clarification on one thing. We heard this morning
13 that at least in some centers, the mortality risk of
14 cardiac catheterization could be as high as 3 percent.
15 So if this measure were used either in the clinical
16 trial setting or in practice, would it result in any
17 increase in procedures in these children over what's
18 being done now?
19 DR. RICH: Three percent is totally
20 unacceptable. Let me just make a couple of comments.
21 These are sick kids, sick adults. It needs to be done
22 by experts, just like any invasive procedure. And so

1 in the wrong hands, anything is risky. But in the
2 right hands, I would say that whatever Robyn quoted is
3 probably where it's at. It should be once in five
4 years. In our experience in almost 10,000, we've not
5 had a single death.
6 So I think that's part of the issue, but
7 again, this committee has to understand that when you
8 approve something, that's going to be done in the
9 general practice, not only in specialty centers. So
10 that is a concern.
11 The guidelines and the current adopted
12 practice should be that every patient, adult or
13 pediatric, gets a baseline right heart cath to confirm
14 the diagnosis. You need to measure wedge pressure.
15 You need to measure these other measurements. How
16 often or how frequent physicians use follow-up cath
17 data is highly variable. I think the big volume
18 centers do it more frequently than the small volume
19 centers for reasons of comfort and experience and
20 things like that.
21 DR. KAUL: Dr. Rosenthal?
22 DR. ROSENTHAL: I just would point out that

1 I don't think that the risk estimate of zero is
2 realistic. I mean, there are anesthetic risks and
3 other risks that kids with pulmonary hypertension have
4 to a greater extent than kids without it. And I think
5 it's not a trivial point.
6 I think the answer to your question is that,
7 yes, the number of caths will go up if this is the way
8 we're monitoring our response to therapy, and there
9 might be a price to pay for that. Now, maybe it's
10 worth it to have good data and for all the reasons
11 that Dr. Barst pointed out earlier.
12 But I do think that even if the risk is
13 1 percent, that if, over a five-year period, people
14 are getting cathed eight times, the cumulative
15 increase in risk is something that is worth paying
16 attention to in this discussion.
17 DR. KAUL: Steve?
18 DR. KAWUT: I guess I would be careful about
19 the decision we're making here compared to clinical
20 practice. I think the decision here is would it be
21 reasonable to base approval for children on
22 hemodynamics for drugs which have been approved in

1 adults. And we're talking about an exquisitely small
2 number of children in a very small number of studies.
3 So I hate to extrapolate that, if, depending
4 on the decision here, clinical practice will be
5 changed and we could increase morbidity and mortality
6 in the general population of kids with this condition.
7 So I guess I'd be a little careful about slating those
8 two.
9 DR. KAUL: Dr. Rosenthal?
10 DR. ROSENTHAL: I think that's a good point.
11 So I'm not trying to suggest that clinical practice --
12 that we should be making decisions regarding how best
13 to design studies to explore this issue based on the
14 potential impact on clinical practice. But I do think
15 it will impact clinical practice.
16 DR. KAUL: Any more questions or comments?
17 If not, we will proceed with the business at
18 hand. The advisory committee is asked to opine on the
19 appropriateness of amending the pediatric written
20 request for sildenafil to treat children with
21 pulmonary arterial hypertension, also known as PAH.
22 Sildenafil currently has a written request

1 calling for a single study of the effect of sildenafil
2 on some unspecified clinical endpoint to support
3 extension of its indication from adults to children.
4 The study of exercise in young children has proven
5 difficult. FDA has pooled data from 13 studies on
6 hemodynamics and exercise in adults with PAH, and it's
7 considering making pulmonary vascular resistance index
8 an adequate basis for extending the indication to
9 children with PAH.
10 So the first question to the committee is --
11 as Dr. Marciniak said yesterday, the committee is
12 still having a platonic affair with --
13 DR. STOCKBRIDGE: You could start with those
14 questions again, if you were unhappy with those
15 answers.
16 DR. KAUL: Does the FDA analysis show PVRI
17 to be a reliable predictor of effects of vasodilator
18 therapy on exercise capacity in adults with PAH? Just
19 answer the question that is being asked.
20 Dr. D'Agostino?
21 DR. D'AGOSTINO: I'd be happy to start with
22 my view on it. I think that the data that they have

1 presented does indicate that there's a relationship.
2 I don't think that we have enough data to know what
3 the relationship really is. I think the point that
4 Dr. Neaton has raised about not having some of the
5 negative studies, we may very well find in the
6 negative studies that we see the PVRI moving up, but
7 not the exercise, the six-minute walk test.
8 So I think we're stuck with some problems in
9 terms of saying do we have a full relationship
10 established.
11 Some of the points that are interesting here
12 and useful here is that we don't have the validation,
13 the calibration that was raised at the very beginning.
14 I don't have a sense of the goodness of the R-square,
15 the standard error of estimate, the question about how
16 well this would perform in terms of discrimination. I
17 don't think that we would want to necessarily say we
18 believe the relationship if we didn't see something
19 like a receiver-operated characteristic curve or some
20 kind of cuts on when the six-minute walk test is
21 really telling us that we have seen a clinical
22 benefit.

1 The sort of idea that putting these all
2 together in what I'm used to seeing developing a model
3 versus what we have here, I think the presentation was
4 interesting, but not adequate for us to put a yes on
5 this question.
6 DR. KAUL: So let me reinterpret your
7 answer. The answer to this question is no. But if the
8 question were asked differently, was there an
9 association established, how would you answer that
10 question?
11 DR. D'AGOSTINO: Well, I think they'd have
12 an association established. Pinning it down in terms
13 of adequacy or being able to use it for prediction of
14 effect size and things of that nature, I don't think
15 we have it yet.
16 DR. KAUL: Dr. Neaton?
17 DR. STOCKBRIDGE: One thing. There's at
18 least one unapproved drug in the set of 13 studies.
19 And there are at least two other failed studies in
20 that set of 13. So Dr. Brar didn't select out the
21 successful drugs or the successful trials in that set.
22 DR. TEMPLE: Also, for anyone submitting an

1 application to us, they have to tell us about all the
2 studies. So there aren't any missing studies there.
3 There could be things where they just never bothered.
4 We might not know much about it then.
5 DR. KAUL: I think I heard Dr. Brar say he
6 had 42 trials and then --
7 DR. STOCKBRIDGE: Not with hemodynamic data
8 and exercise data. There have been 42 studies, but
9 not all of them have post-baseline hemodynamics.
10 DR. KAUL: Fair point.
11 Dr. Brar?
12 DR. BRAR: That's one of the main points.
13 In addition, I want to clarify, and I apologize,
14 there's actually a drug that's involved with the
15 double delta plot that is not an approved drug and
16 where we have, in total amongst those trials, there's
17 two of them that have actually failed.
18 DR. KAUL: Dr. D'Agostino, does that
19 reassure you a little bit more?
20 DR. D'AGOSTINO: Again, it's good to hear
21 that. That's not what I thought was said earlier. I
22 thought it was just approved studies. But it would be

1 very interesting -- and don't want to do it now -- but
2 to see where those dots fit on the curves and how well
3 you actually would be able to predict what goes in
4 those by some kind of cross-validation.
5 DR. KAUL: Did you see any deviation in the
6 relationship in those studies that were not approved?
7 DR. BRAR: Within the individual studies, I
8 saw the relationship still holds within those
9 individual studies. But if you're talking about
10 deviation from the ultimate complete patient
11 population -- is that the question, for clarification?
12 DR. KAUL: Yes.
13 DR. BRAR: Yes. So in essence, we did see,
14 because we're looking at a subset population of the
15 WHO Group 1 idiopathic familial patients, so there is
16 a little bit of deviation from what we found in terms
17 of the analysis seen on the double delta plot versus
18 what's seen in the label.
19 DR. KAUL: Dr. Neaton?
20 DR. NEATON: This is an important point, in
21 my mind, because you showed a very nice picture, your
22 slide 8, of the quadrants, kind of where there's

1 agreement and where there's misclassification. And I
2 agree with Darren. Whether you're talking about this
3 being a surrogate or just a substitute, you'd like to
4 have some degree of confidence that there's
5 concordance in the decision you'd make on the exercise
6 endpoint and the hemodynamic endpoint.
7 If everything is above the top two boxes and
8 almost nothing is down below, you're missing some very
9 important information. You're missing all the trials
10 that showed something negative on an exercise outcome,
11 but something positive on a hemodynamic one.
12 DR. TEMPLE: Why do you think anything is
13 missing? There just weren't any of those. Why
14 wouldn't those -- for example, if a trial had a
15 favorable effect on exercise, we get it. The company
16 wouldn't care. That was the end of it.
17 DR. NEATON: I'm not worried about the
18 trials that were done that don't have favorable
19 effects on exercise, Bob.
20 DR. TEMPLE: Okay. But you only know half
21 of what you want to know. But what you know that is
22 among the trials that had a favorable effect on

1 exercise, they also had the hemodynamic effect. Now,
2 could there be something that had a wonderful
3 hemodynamic effect and no effect on exercise?
4 DR. NEATON: That's what we don't know.
5 DR. TEMPLE: And that's what we don't have.
6 DR. NEATON: But actually, even for the
7 first part of what you said, I'm not confident about
8 that. From the graph that was put up, that's clearly
9 not the case. On that colored graph, there are trials
10 that had seemingly large --
11 DR. TEMPLE: Yes.
12 DR. NEATON: -- but that's potentially a
13 power issue because of the selection that you chose
14 that needs to be figured out.
15 DR. TEMPLE: Actually, I wanted to ask both
16 you and Ralph. Is this a question about where to draw
17 the line that tells you enough? For example, up on
18 the left-hand side of the line, where there's an
19 effect on both of them, that sort of is comforting.
20 But down over on the right side of the line, there are
21 some pretty small effects and not much. I mean, if
22 you believe there's a relationship shown, that still

1 leaves open the question of where you draw the line,
2 where you say I have enough effect.
3 DR. D'AGOSTINO: Let me take a crack at it
4 first. My concern is that there is the bottom
5 quadrant which we don't have any data. But some of
6 the failed trials may show an effect on the
7 hemodynamic parameters, but not on the walk test. And
8 I would really want to have some comfort that we have
9 trials -- well, we don't have any trials, that just
10 doesn't exist, as opposed to maybe they're out there
11 and we just don't have them in the pool.
12 DR. TEMPLE: Just remember, they can't be
13 out there for the drugs that we've looked at, because
14 somebody would have had to tell us. This would be a
15 drug that's been studied and never showed exercise, so
16 nobody submitted it.
17 DR. D'AGOSTINO: Exactly, exactly.
18 DR. KAUL: Dr. McGuire?
19 DR. MCGUIRE: Yes. Along those lines, my
20 concern is the opposite, as you mentioned, Dr. Temple,
21 is that studies where the PVRI improved, but not the
22 functional capacity. And, for example, anything that

1 lowers mean arterial pressure, raises left atrial
2 pressure, increases cardiac output or increases weight
3 is going to improve the PVRI, but may or may not
4 effect the six-minute walk test. And so this is a
5 very complex integrated parameter that we're talking
6 about, the PVRI, as Stu was talking about earlier,
7 too. It may be all cardiac output. It may be all
8 left atrial pressure changes, and we just don't know
9 in this disease state.
10 So if people had missed the functional
11 endpoint, I'm not so sure the FDA would have gotten
12 those data. Maybe they have. But that's my concern
13 that we may be missing something.
14 DR. TEMPLE: No, you're quite right. If
15 they didn't think they had a basis for a claim, we
16 might not have seen those in any detail anyway.
17 DR. KAUL: Dr. Veltri?
18 DR. VELTRI: Just to clarify. In the
19 universe of trials that the FDA has seen, there's 42,
20 are there any trials missing from the 13 where you had
21 both paired baseline and completer? Is this the
22 universe of data in all those trials where you had the

1 paired exercise and hemodynamics? So there's no
2 trials, at least that the FDA has seen, that are not
3 included.
4 DR. GOBBURU: That's correct.
5 DR. KAUL: Dr. Gobburu?
6 DR. GOBBURU: Yes. I would also like to
7 make two points to Dr. D'Agostino's comment. That is,
8 in the double delta plot that Dr. Brar showed, PVRI
9 versus six-minute walk, there are 18 bubbles in that
10 graph. Four of those bubbles represent doses or drugs
11 not approved, which are towards the lower quadrant or
12 lower portion of the changes, first point.
13 The second point is that it is true that
14 that sponsors will not submit submissions unless they
15 believe that there is some kind of indication, an
16 effect for us to consider market access approval.
17 Having said that, unless we think that a drug can be
18 inferior to placebo, you cannot have any other
19 relationship other than that was shown by Dr. Brar,
20 because the placebo data were included and we have
21 separated acting versus placebo arms, and it is still
22 the same relationship that holds good. So I don't

1 understand what failed trials will add to that data.
2 DR. D'AGOSTINO: Well, I think it would add,
3 because it's possible for you, as Dr. McGuire was
4 saying, to raise one parameter, PVRI, without
5 necessarily improving the walk test.
6 DR. KAUL: I think it would be helpful,
7 Elaine, if we can have that slide back up, Dr. Brar's
8 slide. Do you remember what the number of it was?
9 Number 9, thank you.
10 DR. KRANTZ: Can I ask a question while we
11 wait, Sanjay?
12 DR. KAUL: Go ahead.
13 DR. KRANTZ: Just to clarify, there is no
14 secondary pulmonary hypertension studies where we have
15 measurements whatsoever, collagen vascular disease, et
16 cetera?
17 DR. BRAR: We do have studies that show
18 secondary pulmonary hypertension trials that did
19 measure some hemodynamic measures, but they did it
20 primarily at baseline and not end of trial.
21 So I was trying to get, ideally and first
22 and foremost, I wanted to get a time course. Does the

1 time course of the PVRI relate to the time course of
2 the six-minute walk distance? Unfortunately, the
3 hemodynamic measures that are collected in these
4 trials are seen only at baseline and end of trial. So
5 I specified in my analysis that I looked at the trials
6 that had both baseline and an additional hemodynamic
7 measure, which is primarily at end of trial.
8 DR. KAUL: Done concomitantly, same day?
9 DR. BRAR: Same day, so same visit.
10 DR. KAUL: Dr. Neaton?
11 DR. NEATON: So going back to this chart,
12 which I think was a very informative analysis, so that
13 the big orange circle, the two green ones, the medium-
14 sized blue one, those are all trials that had a failed
15 six-minute walk, but there were no differences between
16 treatment and control.
17 DR. BRAR: A failed six-minute walk so --
18 DR. NEATON: So basically, they're sitting
19 on zero.
20 DR. BRAR: Yes, you are correct. So those
21 had a failed six-minute walk distance, and those are
22 the doses essentially that were the --

1 DR. NEATON: A big change in hemodynamic and
2 nothing in --
3 DR. BRAR: Correct.
4 DR. KAUL: Dr. Neaton, the answer to the
5 question is?
6 DR. NEATON: Well, I think I'd go back to
7 the question I had this morning that I think -- and
8 maybe it's kind of like what Ralph said -- that we
9 have an extremely informative interim analysis here,
10 and so we should continue this work. But we're not
11 there to stop the trial yet. And so I'd like to know
12 kind of two things.
13 Am I going to make the same decision on
14 what's been used in previous studies in adults kind of
15 if I was to use the hemodynamic measurement? And this
16 suggests that I might not. I might make a very
17 different decision in some of those trials. And that
18 might be good. That might be bad. That's something
19 to talk about. I'd like to kind of have that
20 quantified.
21 Then we also need to know, as Ralph kind of
22 started out this morning, if you took the Pfizer study

1 and pulled this out of here, how well would you
2 predict it based on this graph right here, this
3 relationship. And actually, that's something you
4 could do for each of these trials, which would be very
5 informative, is to understand kind of how well you
6 predict, based on this model, what the result would be
7 versus what you actually observed.
8 So that's a very key step, in my mind, that
9 kind of goes back to the comments that were made
10 earlier about establishing surrogacy, and I see
11 Darren's point about surrogacy. So let's just say
12 establishing that this is a reasonable substitute.
13 DR. D'AGOSTINO: I don't find that there's
14 anything with what has been done. I just think, what
15 Jim was just saying, I don't think it's complete. I
16 don't think we have enough comfort. Taking that
17 orange blob out of there and fitting the remaining
18 ones and then trying to predict that, it's not going
19 to predict that well. So it's that type of issue that
20 I think we need to go through.
21 It's not to say that, again, what we've been
22 presented is wrong. It's just that there are still

1 questions that remain; to make a judgment that is all
2 there is, I think, impossible for me.
3 DR. KAUL: We have two expert statisticians
4 who are used to looking at these data. If I'm
5 interpreting them correctly, they're not convinced
6 whether the model helps reliably predict. I happen to
7 concur with both of them. I think the model needs to
8 be developed better and more optimally characterized,
9 and some of the things that were brought up have
10 already been discussed.
11 Is there anybody on the committee that feels
12 otherwise?
13 Dr. Black?
14 DR. BLACK: I just wanted to say that the
15 word that I'm hung up on is "reliable," which you
16 brought up. And I think, as you say, it doesn't seem
17 reliable to me just yet.
18 DR. KAUL: Anybody that has another
19 perspective on this? Otherwise, we'd like to proceed.
20 Dr. Temple?
21 DR. TEMPLE: Well, I just want to ask the
22 question. See, I don't know which those orange balls

1 are, and I don't know whether they were erroneous
2 maybe. The next one showed that it really did work
3 and the study was just wrong in its exercise
4 assessment, and I can't tell from that.
5 But does that permit one to look at a double
6 delta PVRI, say, greater than 500 and say I know
7 something or is that too little data? That's what I
8 was asking before. Down at the lower ends, there's
9 obviously some scatter and noise and some things where
10 there's a disparity in results, all the ones along the
11 line. I just wondered if that also applies to the
12 larger values.
13 DR. KAUL: Have you done those analyses?
14 DR. GOBBURU: Well, before we can comment on
15 that, I want to make a comment just to be clear what
16 the question we're asking is. The question is, to
17 me -- and somebody can correct me if I'm wrong -- if
18 we made a decision to approve a drug based upon double
19 delta, mean change in double delta six-minute walk
20 distance, would we put a placebo on the market for
21 pediatrics? Given if it is approved in adults, it's a
22 yes or no question. We don't differentiate on the Y

1 axis the orange ball, which is 5 meters. We approved
2 a drug with 5 meters. We also approved a purple ball
3 with 50 meters. FDA does not require that they are
4 distinguished between 5 versus 50 in terms of making a
5 determination of whether the drug works or not.
6 So it's a binary outcome, I think, that it
7 makes sense for you to deliberate on, saying would we
8 make a yes or no mistake in a drug approved in adults
9 to be considered for approval in pediatrics based on
10 the hemodynamics. That's the first question.
11 The second question is, yes, now since we
12 have shown quantitative data, now we can start
13 interpreting maybe what type of double delta would
14 lead to double delta six-minute walk. Those are two
15 different questions.
16 DR. KAUL: For the purposes of record,
17 please identify yourself.
18 DR. GOBBURU: My name is Joga Gobburu. I'm
19 the Director of Division of Pharmacometrics at the
20 FDA.
21 DR. KAUL: Dr. Neaton, and then Dr. Temple.
22 DR. NEATON: The first question, I think

1 that is an important thing to address, that binary
2 question. And so I would not say, in and of itself,
3 it's all you want to do. I would have started exactly
4 like you did here, which is kind of a very nice
5 analysis in terms of the overall association. But
6 it's the next step in that summary which I think is
7 missing.
8 DR. KAUL: Dr. Temple?
9 DR. TEMPLE: Well, what I thought Jim and
10 Ralph were saying is that judging from these data,
11 some of the time, namely, those ones along the line,
12 the two orange and maybe the two are too small to
13 worry about. But at least some of the them, you would
14 actually declare it effective based on the double
15 delta PVRI, and you'd have been wrong, because there
16 really was no change in six-minute walking distance.
17 And that's the answer to Joga's question, I think.
18 That is, in fact, what you're worried about. It
19 obviously wouldn't happen often, but it might happen
20 sometimes, and that's what you're saying these data
21 might tell you.
22 I think it will help us to see a little more

1 what studies those actually are, but we --
2 DR. KAUL: I think all three of us are
3 pretty much articulating that.
4 DR. TEMPLE: But that's what you're saying.
5 DR. KAUL: The model that has been developed
6 is in the right direction. It has not been optimally
7 characterized. The information that we would have
8 sought was discrimination, calibration, and, more
9 importantly, just what you mentioned,
10 reclassification. Are we reclassifying these patients
11 correctly or incorrectly?
12 Dr. Krantz?
13 DR. KRANTZ: One word of caution. What are
14 we reclassifying for? There is no gold standard.
15 That person on the line may be having a lower
16 mortality. We just don't know. So I think, again,
17 we're taking two independent things and creating an
18 association and it's not really biological prediction.
19 DR. TEMPLE: Our proposal here is that it
20 might or should or it's supposed to tell you what
21 would happen had they been able to exercise. This
22 just might have wonderful things to do with survival.

1 We don't know that. But I'm just trying to be sure I
2 understand the reservations, and that's my
3 understanding of it, that at least at the lower
4 levels, but maybe not the higher levels of delta delta
5 PVRI, you're saying there's sometimes a disparity
6 between the effect that was seen on the hemodynamic
7 measure and the effect that you're proposing to
8 conclude would be there on the exercise measure.
9 DR. KAUL: Dr. Stockbridge, and then the FDA
10 staff.
11 DR. STOCKBRIDGE: Dr. Barst thinks she can
12 give you some perspective on the big orange dot close
13 to zero.
14 DR. KAUL: Thank you.
15 Dr. Barst?
16 DR. BARST: As an investigator in that
17 study, that was a post-registration study, and the
18 purpose of the study was to assess could we get a
19 significant improvement in hemodynamics in patients
20 who had very little exercise intolerance to start
21 with, and that was the purpose. So we did not
22 anticipate a clinically significant improvement in

1 six-minute walk. That was not the primary endpoint.
2 DR. JADHAV: Actually, I can supplement
3 that. My name is Pravin Jadhav with the Division of
4 Pharmacometrics. Just to supplement that, that most
5 of the PDE5 or the prostacyclin doses that are used
6 clinically or approved labels are having double delta
7 six-minute walk distance improvement about 20. So
8 really, if you look at that plot, PVRI improvement of
9 400 is almost meaningless from where we look at drugs,
10 at least most of the approved drugs. So if you are to
11 draw the line, I think at least I started looking at
12 it from the middle of that plot and then coming down.
13 So these data do show 200, 300 changes in PVRI have no
14 meaning in six-minute walk distance, because those
15 doses are not used clinically.
16 I just wanted to make the clarification,
17 because that's relevant to the question Dr. Neaton was
18 asking, would I make a different decision using PVRI
19 and six-minute walk distance, because you already can
20 see that most doses are up there.
21 DR. KAUL: Before Dr. Neaton and
22 Dr. D'Agostino respond to that, Dr. McGuire?

1 DR. MCGUIRE: Another point I don't think
2 we've discussed today is the difference between the
3 classes and even between the individual agents in the
4 classes. I know we saw a qualitative forest plot that
5 they're qualitatively similar, but there are important
6 numeric differences.
7 Especially here, if you just visually
8 regress through those different colored dots, you get
9 extremely different relationships. And so one could
10 query whether this should be a class-specific or even
11 a data-derived drug-specific consideration.
12 DR. KAUL: Dr. D'Agostino?
13 DR. D'AGOSTINO: If I heard correctly about
14 that study, then why in the world was it included?
15 It's these types of things that are really bothersome
16 in terms of trying to give a blessing on this. And
17 the other question, if you threw out below the 400,
18 you'd get a straight line that would have no slope.
19 So you can say if I'm in that range, I feel very
20 comfortable about a change in the walk, but in terms
21 of trying to get a relationship on how the PVRI
22 changes with the walk, you wouldn't really have it

1 anymore.

2 DR. KAUL: Dr. Neaton, do you have anything

3 else to add?

4 DR. NEATON: I was going to say the same

5 thing.

6 DR. KAUL: Dr. Halperin, and after that,

7 Dr. Temple, and we'd like to move on. We've got to

8 tackle seven questions.

9 DR. HALPERIN: Clearly here, the issue has

10 just been elucidated. It's that we are looking for a

11 reliable surrogate for a fundamentally unreliable

12 index of disease severity. The same applies to

13 asymptomatic patients as would apply to adults who are

14 nonambulatory for some reason, that they will be at

15 the extremes of function, in perfect fit to the PVRI

16 curve, and I think we're seeing that exposed to some

17 extent in these data.

18 DR. KAUL: Thank you. Dr. Stockbridge and

19 Dr. Temple, does that help you with the answers to

20 this question? Not the answers you were looking for,

21 but does that help you?

22 DR. TEMPLE: Well, I still have one more

1 question for Ralph.

2 Just because you only consider effects on

3 delta delta PVRI of above, say, 400 to be

4 unequivocally related to a benefit doesn't mean you

5 shouldn't use the whole curve to draw the line. So I

6 don't think I buy that last --

7 DR. D'AGOSTINO: Well, except that if we

8 think the ones below are unreliable, then --

9 DR. TEMPLE: Unreliable in that given the

10 smaller effect, they're not as predictive as you'd

11 like them to be.

12 DR. D'AGOSTINO: But having a population

13 where you anticipate no ability to measure the six-

14 minute walk test, I mean --

15 DR. KAUL: Dr. Stockbridge, was that

16 helpful?

17 DR. STOCKBRIDGE: I think that was helpful.

18 DR. KAUL: We move on to the second

19 question. If a drug has been documented to improve

20 exercise in adults with PAH, can PVRI be used to

21 extend that indication to another subpopulation of

22 adults? I just want to make sure we understand this

1 question. Another subpopulation means other than the
2 WHO PAH, but still including PAH or exclusive of PAH?
3 DR. STOCKBRIDGE: The suggestion was to see
4 if you were ready to take the smallest possible step I
5 could imagine, which was you've got a drug approved,
6 you understand its relationship between hemodynamics
7 and exercise in some group of adult PAH patients. Can
8 you use it to get you into another group of adults?
9 DR. KAUL: With heart failure?
10 DR. STOCKBRIDGE: No. With PAH of a
11 different variety than you have previously studied.
12 DR. KAUL: Okay. So the question is
13 constrained to the population of PAH, but other than
14 WHO 1. Thank you for that clarification.
15 Dr. Rich?
16 DR. RICH: No. You're really going into
17 shark-infested waters here. Patients with lung
18 disease are generally limited more by their
19 ventilatory insufficiency and hypoxia than they are by
20 hemodynamics, number one.
21 Number two, these drugs often will worsen VQ
22 mismatch and worsen gas exchange in patients with lung

1 disease. In patients with left ventricular diastolic
2 heart failure, they will not uncommonly put them in
3 pulmonary edema and create an acute crisis. So I
4 would be really reluctant to go beyond this one
5 category.
6 DR. STOCKBRIDGE: None of that's PAH.
7 DR. RICH: All right. Well, within the
8 category of PAH, you've kind of covered it, so I can't
9 imagine what we're talking about. Clearly, if you
10 subset out the connective tissue diseases in PAH,
11 because they've been enrolled in trial, but not used
12 by themselves, they don't do well and, in fact,
13 studies that have looked at them by themselves
14 generally fail. And a lot of us think it's because of
15 lung involvement as opposed to pulmonary vascular
16 involvement that's coexistent with it. So I think you
17 have to be really, really careful at this point to be
18 able to take that leap of faith.
19 DR. KAUL: Dr. Newman?
20 DR. NEWMAN: I agree. This group includes
21 liver disease, scleroderma-like disease, congenital
22 heart disease, HIV. These patients all behave

1 differently. Scleroderma has a terrible outcome
2 compared to idiopathic PAH. It would be a mistake to
3 extrapolate, in my opinion.
4 DR. KAUL: Dr. Kawut?
5 DR. KAWUT: I have to agree. And also, in
6 that these patients all have underlying diseases,
7 which you may improve their pulmonary vascular
8 disease, but they may die and have limitation from
9 their underlying disease and so you've done no actual
10 benefit for the patient. So you'd really want to
11 prove that it improves some clinical outcome in these
12 other individuals.
13 DR. TEMPLE: No, that's not correct. You
14 may or may not save their lives. We don't save a
15 whole lot of lives in a lot of conditions. But we
16 might improve their comfort for a period of time, and
17 that is a sufficient basis for approval if you believe
18 that it's been shown.
19 DR. KAWUT: I totally agree, but by
20 improving their PVR, you may not improve their comfort
21 or their quality of life.
22 DR. TEMPLE: That's the question, not

1 whether we've saved their lives.

2 DR. KAUL: Dr. Rosenthal?

3 DR. ROSENTHAL: I didn't have a question.

4 DR. KAUL: The answer to the question, your

5 answer to the question.

6 DR. ROSENTHAL: I don't have an answer for

7 it.

8 DR. KAUL: Dr. McGuire?

9 DR. MCGUIRE: Yes. And I think that's

10 clarifying. This question was intended to take the

11 smallest possible step, but because of the disparity

12 in the pathobiology of the other types of PAH, I think

13 it's a much smaller step to extend it to the pediatric

14 population than to extend to across the adult

15 population.

16 DR. KAUL: Dr. Halperin?

17 DR. HALPERIN: I believe that it depends on

18 the definition of subpopulation. If it's a

19 subpopulation defined on the basis of the same

20 criteria for type or etiology of pulmonary

21 hypertension, than I think it could be applicable, but

22 if we switch to a different etiology, a different

1 pathogenesis and different pathophysiology, then I
2 would say the answer is no.
3 DR. KAUL: Dr. Venitz?
4 DR. VENITZ: I'm concerned primarily about
5 the congenital etiology, so I would say, no, you
6 cannot extend it.
7 DR. KAUL: Dr. Black?
8 DR. BLACK: I also think no. I think this
9 is a real collection of things, some of whom we may
10 help, some of whom we may hurt, and I think it's a
11 little early to do that.
12 DR. KAUL: Anybody on the committee that
13 answers yes?
14 Dr. Rich?
15 DR. RICH: I just want to remind the agency
16 that the characterization of Category 1, the original
17 category PAH, has undergone four changes since it
18 first came out. And so things go in and things go out
19 of it all the time. And so when we talk about
20 subpopulations, there's inconsistency amongst that, as
21 well.
22 DR. KAUL: Dr. Stockbridge, does that help?

1 DR. STOCKBRIDGE: Yes.

2 DR. KAUL: Moving to question number 3, is

3 PAH in children sufficiently similar to the disease in

4 adults to allow PVRI to be used to bridge the adult

5 indication to children? In particular, please comment

6 on whether there are important differences between

7 adults and children with PAH with respect to etiology

8 of disease, symptoms of PAH, clinical course of PAH

9 and hemodynamic effects of PAH.

10 I'm going to call upon the experts here on

11 the committee to weigh in. Dr. Rosenthal?

12 DR. ROSENTHAL: So for this one, I do think

13 that based on the information that's been provided,

14 that if we believe that PVRI is a reasonable outcome

15 in adults, that it should also be considered a

16 reasonable outcome in children.

17 DR. KAUL: Dr. Newman?

18 DR. NEWMAN: There are clearly differences,

19 but there's enough similarity that the association

20 appears to be true, the association of exercise and

21 PVRI. So clearly, in children, there's more

22 congenital heart disease. There are clear-cut

1 differences. The PVRs are slightly different, but the
2 general trends are similar with regard to responses.
3 So I would say yes, with the caveat that subgroups and
4 cohorts within those groups don't behave the same.
5 DR. KAUL: Dr. Rosenthal?
6 DR. ROSENTHAL: Well, I would just follow-up
7 that I agree with that point. I was referring
8 specifically to the case of primary pulmonary
9 hypertension and not pulmonary hypertension that's
10 secondary to congenital heart disease.
11 DR. KAUL: Dr. Temple?
12 DR. TEMPLE: Let me make sure, Norm, that I
13 understand, because there's confusion in the two
14 answers. This does not go to the question of whether
15 you believe the relationship is well enough
16 established to do it. It's if you did believe the
17 relationship was well enough established, are the
18 diseases similar enough to make the jump. So it's
19 really what you answered. You said yes, the diseases
20 are close enough if I believed it. Okay?
21 DR. KAUL: That's Dr. Rosenthal's answer,
22 right?

1 DR. TEMPLE: Yes, he answered, but it's not
2 a perfect question.
3 DR. KAUL: Dr. Rich?
4 DR. RICH: With etiology, there are big
5 differences. Remember, in pediatrics, it's mostly
6 congenital and some idiopathic. In adults, it's
7 rarely congenital, a lot of connective tissue disease.
8 Symptoms are similar. Clinical course, a little less
9 consistent because of some stage biases between kids
10 and adults and conditioning in the right ventricle.
11 Hemodynamics, we think, are very similar.
12 DR. KAUL: Thank you.
13 Dr. Kawut?
14 DR. KAWUT: I think we can quibble about the
15 details, actually nicely laid out, but in the end, I
16 think this is the same disease.
17 DR. KAUL: Anybody else have a different
18 opinion or any comment? If not, was that helpful?
19 DR. TEMPLE: What's been said, I think, is
20 that if you bought the whole relationship and
21 everything, that would be useable. The question is
22 whether you --

1 DR. KAUL: Question number 4. Please
2 comment on the following aspects of studying
3 hemodynamics in young children. Number one, is it
4 technically feasible; and, number two, do the risks of
5 collection of hemodynamic data in children raise
6 ethical concerns?
7 And I will again start off with
8 Dr. Rosenthal.
9 DR. ROSENTHAL: I think it's feasible. It's
10 done all the time, particularly in the study context.
11 I think it's feasible. I think the ethical questions
12 as to whether the information that's obtained is worth
13 the risk, the ethical questions that arise, it's
14 probably a more complicated issue than what we can
15 address here. And I'm certainly not a ethicist, so I
16 don't want to sort of weigh into all the different
17 ethical considerations.
18 My sense is that it will be; that if you see
19 the risks that go along with diagnostic
20 catheterization as part of the cost of identifying an
21 effective therapy for an otherwise horrible disease
22 with high lethality, that you would be able to justify

1 the risks based on the potential benefit. But I would
2 defer for more in-depth conversation of that topic
3 with Skip Nelson or some of the ethicists over on the
4 ped side.
5 DR. KAUL: Dr. Kawut?
6 DR. KAWUT: The first part, I would say,
7 obviously, yes, it is technically feasible. For the
8 second part, certainly, this entails risk, as does
9 being in a clinical trial, as does having this disease
10 without proven therapies. And so I think it's
11 reasonable to burden study subjects, children and
12 their parents, with potential risks of hemodynamic
13 measurements for really the same reason that they're
14 in this study, which is altruism, because we need to
15 know if these drugs work in children and the only way
16 to find that out is by doing it this way.
17 The other justification for collecting
18 hemodynamic data is that it would let you do the
19 smallest trial necessary. You most likely would not
20 have to do a 200-person trial in order to find these
21 hemodynamic findings, which you might have had to do
22 to get your exercise findings. So that decreases the

1 risk and even perhaps increases the justifiability of
2 using this technique, because you're going to put the
3 fewest number of individuals into your study.
4 DR. KAUL: So in your mind, you don't have
5 any concerns about ethical issues?
6 DR. KAWUT: Yes. I don't.
7 DR. KAUL: Dr. Newman?
8 DR. NEWMAN: Feasible, yes; ethical
9 concerns, no.
10 DR. KAUL: Dr. Rich?
11 DR. RICH: Agree, yes and no.
12 DR. KAUL: Dr. Black?
13 DR. BLACK: I agree. I think it clearly can
14 be done, and I think it's something we're going to
15 have to do if we're going to improve our therapy any.
16 DR. KAUL: Dr. Halperin?
17 DR. HALPERIN: I agree.
18 DR. KAUL: Dr. Krantz?
19 DR. KRANTZ: I totally agree. I think the
20 only thing I would point out as we know from the
21 critical care literature in heart failure that we
22 actually increase mortality and complications when we

1 use Swan-Ganz catheters. So I think, again, not a
2 relative comparison, but I would make a plea that
3 could we try to do more echocardiographic studies
4 along with it, because although you won't necessarily
5 have agreement, you have good correlation and perhaps
6 we can refine the way we track these patients in the
7 future.
8 DR. KAUL: Dr. Halperin?
9 DR. HALPERIN: I think it's important,
10 though, to distinguish the in-dwelling Swan-Ganz
11 catheter from the single measurement in an out right
12 heart catheterization, which is associated even in
13 patients with pulmonary hypertension with
14 substantially lower risk.
15 DR. KAUL: I concur. If you look at the
16 anesthesia literature, the Swan-Ganz catheterization
17 complications rates are the lowest, and they have the
18 best data out there compared to the ICU data, where
19 you have the Swan-Ganz catheter for a longer period of
20 time. So I completely concur.
21 So my answers to the Question 4, is it
22 technically feasible, yes; are there any ethical

1 concerns, no.

2 We have two more questions or, actually,

3 three more questions. Two of them are voting

4 questions. We can take the break right now for 15

5 minutes, or we can continue. I'll leave it up to the

6 committee. What would you like? Take a break for

7 about 15 minutes? Take a break? Yes?

8 DR. ROSENTHAL: I say we forge ahead.

9 DR. KAUL: Okay. Great. Is that okay?

10 Before I read question number 5, I am

11 required to give instructions for the voting

12 questions. We will be using the electronic voting

13 system for this meeting. Each of you have three

14 voting buttons on your microphone: yes, no, abstain.

15 Once we begin the vote, please press the button that

16 corresponds to your vote. After everyone has

17 completed their vote, the vote will be locked in.

18 The vote will then be displayed on the

19 screen. I will read the vote from the screen into the

20 record. Next, we'll go around the room and each

21 individual who voted will state their name and vote

22 into the record, as well as the reason why they voted

1 as they did.

2 So the question is: Does the committee

3 agree that for a product with an approved indication

4 in adults with PAH, a treatment effect on PVRI can be

5 used to demonstrate effectiveness and to derive dosing

6 information in the pediatric PAH population?

7 DR. VENITZ: Product, does it mean any

8 product or vasodilator?

9 DR. KAUL: Dr. Stockbridge?

10 DR. STOCKBRIDGE: I think you have to be

11 thinking about this being a vasodilator. You can

12 easily imagine that there are therapies that have

13 nothing at all to do with this as a mechanism of

14 action. It really wouldn't make any sense to talk

15 about that.

16 DR. KAUL: Another clarifying question,

17 Dr. Newman?

18 DR. NEWMAN: Is this the nonexercising

19 pediatric population 7 years and younger or is it all

20 pediatrics? It doesn't specify. Is this just in the

21 kids that can't exercise?

22 DR. KAUL: My understanding is that's the

1 intent. Is that correct, Dr. Stockbridge?
2 DR. STOCKBRIDGE: You could certainly say
3 I'm voting a certain way in a certain patient
4 population when you get a chance to clarify your vote.
5 DR. KAUL: Does that help, Dr. Newman?
6 DR. NEWMAN: I guess so.
7 DR. KAUL: Any further clarifying questions?
8 DR. TEMPLE: I would think this should be
9 taken as any population. You can restrict it
10 afterward, but there have been all these reservations
11 stated about what the data show. Do those mean that
12 you just can't use it, or is there some population to
13 be described in further things in which you think you
14 could? I just want to be sure Norm agrees.
15 DR. STOCKBRIDGE: Yes.
16 DR. KAUL: And can you define the age range
17 we're talking about here?
18 DR. TEMPLE: Other people do that better.
19 It's below the age they can exercise. That's why
20 we're doing this, because you can't get the exercise
21 test.
22 DR. KAUL: And what is that age, for

1 clarification?

2 DR. TEMPLE: Well, it includes 2, but I

3 don't know how it goes. People with experience know

4 the answer better than I do.

5 DR. ROSENTHAL: Well, in the data that was

6 shown, 7 seemed to be the magic number.

7 DR. KAUL: Seven, okay. So 7 it is.

8 Put in your vote three times when the

9 buttons are flashing.

10 [Voting.]

11 DR. KAUL: I'll read the results of the

12 voting into the record. Seven yeas, six nays, zero

13 abstentions. I will start off with Dr. Venitz.

14 Please identify yourself and how you voted and the

15 reason for the way you voted.

16 DR. VENITZ: I'm Jurgen Venitz, and I voted

17 yes. I think despite some of the limitations that

18 were brought up throughout the day, I think this is a,

19 whatever you want to call it, surrogate market,

20 substitute marker that allows you to draw upon adult

21 information and extrapolate it to pediatrics.

22 DR. NEWMAN: This is John Newman. I voted

1 yes. I believe the association is strong enough to
2 extend the data to children that cannot otherwise be
3 tested for drug efficacy. I would strongly state,
4 though, that this should be limited to that group and
5 that not just any PVRI can be correlated with effect.
6 So caveats, but my answer was yes.
7 DR. KAUL: Dr. Halperin?
8 DR. HALPERIN: Jon Halperin. I voted yes
9 for just the reasons stated. Despite the
10 imperfections and inadequacies at the extremes of
11 exercise capacity, for those who are unable to
12 exercise in the young pediatric age group, there is no
13 alternative and we need some objective measure.
14 DR. BLACK: This is Henry Black. I voted
15 no. I just wasn't persuaded that it was, in fact, a
16 reliable and useful test and potentially dangerous if
17 we do it too often.
18 DR. RICH: Stuart Rich. I voted no, not
19 because I'm not in favor. I actually am in favor of
20 it, but my bigger concern is it would give legitimacy
21 to a six-minute walk endpoint which we feel is highly
22 problematic and a hemodynamic assessment which could

1 be improved upon. And my plea is to look at time to
2 clinical worsening and a combination of right atrial
3 pressure PVRI, and that would be the way to go.
4 DR. NEATON: This is Jim Neaton. I voted
5 no, because I believe we need more work on the
6 validation of the proposed hemodynamic endpoint. I'm
7 very kind of cognizant of the problem and agree it
8 would be very nice to have an endpoint, a single
9 endpoint, that would be ascertainable in everybody.
10 So I think the work should be high priority. But I
11 think somehow in the interim, a worsening of disease,
12 even in younger kids, work on that should proceed.
13 DR. KAUL: Sanjay Kaul. I voted no for the
14 reasons that have already been elucidated, not that
15 the -- I think the model that is being developed is, I
16 think, the right model. I think the information that
17 we have is rather incomplete. I think the model needs
18 to be characterized further, and if it is able to
19 answer some of the concerns that were raised by some
20 of the expert statisticians on the committee, I can be
21 persuaded to answer my question yes. But that's
22 something that can be doable even after these

1 deliberations.

2 DR. KRANTZ: Mori Krantz. I voted yes. I

3 think what's going to be more interesting from this

4 whole discussion will be how we come up with feasible

5 endpoints and approaches in the future. But I think

6 for me, there was a lot of biological and

7 methodological limitations. But I think that the big

8 context is that this is not an orphan disease, yet a

9 disease where we really need to sort of expand access.

10 So I thought it was a very innovative analysis and

11 useful.

12 DR. COUKELL: Allan Coukell. I voted no. I

13 don't think we quite know what PVR means in kids. It

14 correlates with the six-minute walk test in adults,

15 but we're told that the walk test doesn't mean much in

16 kids. And so some of the key data is around the

17 correlation of VO2 peak and PVRI in a single study in

18 a relatively small number of kids, and listening to

19 the statisticians, I'm not clear that that's quite

20 been nailed yet. But it seems to me possible that if

21 that were built out further, PVRI would be more

22 convincing in the pediatric population.

1 You might then think well, this is a
2 pediatric population, so I take more comfort that the
3 disease is the same as younger kids and might then
4 look at extending it to the population. And the last
5 thing I would say is I'm still not completely
6 convinced that enough effort has been made to develop
7 a physical performance measure in kids.
8 DR. D'AGOSTINO: Ralph D'Agostino. I voted
9 no. My comments earlier this afternoon in terms of
10 the incompleteness or my view that the model was
11 incomplete, I think, have to be addressed. I agree
12 with Dr. Neaton that they should be done right away,
13 because you're very much close to probably having the
14 right model. I do, even after that, though, still not
15 have a very -- I'm still not comforted by what this
16 would be in terms of children. You may find the model
17 holds in the adults. There's still a question in my
18 mind about does it then have a validity in children.
19 DR. MCGUIRE: Darren McGuire. I voted yes.
20 I do agree completely that continued work to refine
21 this model needs to be done. And specifically, as Dr.
22 Rich pointed out, I'd like to see, although the power

1 may be limited as similar associations with clinical
2 endpoints, time to clinical worsening is probably the
3 most legitimate one.
4 I think given the precedent in pediatrics
5 for the extensions of previous drugs and drug classes,
6 I think the level of rigor required for the endpoint
7 is much less in this situation than given the backdrop
8 of safety and efficacy in adults, I am accepting a
9 less rigorous endpoint for pediatrics and support it
10 in that context.
11 I think it should be considered to be at
12 least class, if not drug, dependent. And I'm a little
13 concerned that applying a one-size-fits-all to this
14 disease state may not be the best way to go for these
15 medications.
16 Then finally, I think this probably should
17 be the primary endpoint for those both developmentally
18 able and not able, with secondary endpoints buttressed
19 by developmentally able exercise data. But limiting
20 this to patient populations less than 7 means you'd
21 have to do trials limited to the patients less than 7.
22 And if it's difficult to get 250 patients overall,

1 it's going to be impossible to get meaningful sized
2 trials with less than 7 years old populations.
3 DR. KAWUT: Steve Kawut. I voted yes. I
4 agree very much with what Dr. McGuire said. Based on
5 extensive epidemiologic, as well as the clinical trial
6 data that we've been shown, I think this is going to
7 be a good surrogate endpoint. And while probably not
8 ready for prime time in adults, certainly for
9 children, where we have maybe a lower threshold for
10 approval, that it's probably a useful way to approve
11 drugs effective in adults in children not using these
12 measures.
13 I think as part of this approval process,
14 companies should be required to do follow-up studies
15 of drugs approved in this manner to make sure there's
16 no rare or unexpected side effects.
17 DR. ROSENTHAL: Geoff Rosenthal. I voted
18 yes, but I have a couple of -- I'm reflecting on
19 what's been said around the table. And regarding the
20 lower threshold for approval in kids, I'd just like to
21 say that that's not a principle that we routinely
22 adhere to in pediatrics. The goal would be to use

1 criteria that are equally rigorous.

2 I voted yes. I think PVRI is not perfect.

3 I think it may end up being a better endpoint to study

4 than the six-minute walk test.

5 I agree with the comments that have been

6 said regarding the study design to include people not

7 just who are unable to exercise, but those who could,

8 and then using exercise as a secondary endpoint.

9 I also agree very strongly with the comments

10 that have been made regarding the development of

11 perhaps more useful endpoints and, certainly, the

12 endpoint of time to clinical worsening is an important

13 one. But I think there may be some others that are

14 worth exploring, too. And I haven't thought that

15 through. It's just my general sense from thinking

16 about the clinical information that a lot goes into

17 PVRI, into some of these other hemodynamic assessment

18 and that it may be that there are more fundamental

19 measures rather than these complex parameters that

20 would be more useful.

21 DR. KAUL: Thank you.

22 Dr. Temple?

1 DR. TEMPLE: Well, I'm interested in the
2 queries about whether we should be looking at a whole
3 new class of endpoints. Remember, as a general
4 matter, you're not going to see any studies in little
5 kids until the drug is already approved for adults.
6 So we're talking about a study in which you do a time
7 to clinical worsening in what is presumably a
8 placebo-controlled trial in children, where some of
9 them are denied for a long period of time an active
10 therapy.
11 You've got to think about it. I doubt
12 anybody is going to do those trials. We can't do
13 hypertension trials more than a week in kids, because
14 their blood pressure would be over 130.
15 This needs more discussion perhaps at
16 another meeting. I just don't see how anybody is
17 going to do it.
18 DR. KAUL: What about applying those
19 endpoints for the adult trials and extrapolating? I
20 would be a lot more comfortable extrapolating if I had
21 a clinically relevant endpoint in the adults.
22 DR. TEMPLE: I think you could do it for new

1 class of drugs. But, for example, right now, is
2 anybody going to let you leave an adult off one of
3 those known effective drugs until they die? It's very
4 unlikely. It's very hard to get those.
5 DR. KAUL: Death is not the only component
6 of that.
7 DR. TEMPLE: Worsen materially, other people
8 have looked at it. It's very hard to do those studies
9 when there's a known effective drug that's a member of
10 the same class, and all of these are members of the
11 same class. But for a novel compound, yes, I think
12 you could.
13 DR. KAUL: Dr. Rich?
14 DR. RICH: Well, Bob, I really disagree with
15 that, because right now, no one is doing a placebo
16 trial. Everyone is on approved therapy. It's just an
17 add-on to that, so you're not leaving them high and
18 dry, number one. Number two, no drug has yet to show
19 survival advantage. So you can't make the claim that
20 if you randomize them to conventional therapy, they're
21 going to die, because you can't show that anything
22 makes them live longer anyway.

1 If you select your time to clinical
2 worsening endpoints as realistic things,
3 hospitalizations and need to add therapy, et cetera, I
4 think it's very doable. I think all of this clinical
5 trial data to go on. You have that data of time to
6 clinical worsening after the 16-week data, which shows
7 you those endpoints are reachable if you design your
8 trial right.
9 DR. TEMPLE: You can do an add-on study for
10 a new class. I think that's perfectly true. That's
11 correct. And you can do the study you're talking
12 about. But for a new Sentan (ph), where you're going
13 to compare this drug with placebo and they don't get
14 to use one of the marketed Sentans --
15 DR. RICH: Do we need a new Sentan?
16 DR. TEMPLE: Not particularly, but that's a
17 different question. I'm just trying to figure out who
18 you're going to do this study that we all would sort
19 of like to see in, and I'm finding it hard to think
20 where anybody is going to let you do it.
21 DR. KAUL: Thank you. There are two further
22 questions which partially address what you're asking

1 for, and I think some of the people who voted no have
2 already given you what they would require. I would
3 just add one more, what further validation would one
4 need for PVRI. I would like to see some concordant
5 data.
6 It doesn't matter whether we develop that in
7 adults, which is probably the only population we are
8 going to be able to develop that concordance data
9 between six-minute walk distance and VO2 peak. And if
10 that is reasonably concordant, then I don't have any
11 problem accepting the VO2 peak and PVRI relationship
12 in the pediatric population.
13 Anybody else have any further comments?
14 Okay. We'll quickly go through -- and this
15 is for those who voted yes, but others are free to
16 chime in, as well.
17 If you voted yes, would one need one study
18 or two? Can you please clarify what is being asked
19 here, Dr. Stockbridge?
20 DR. STOCKBRIDGE: Well, the question is how
21 compelling the proof of an effect on PVRI would need
22 to be.

1 DR. KAUL: So if you have one study with a
2 robust p-value, is that what you're asking, versus two
3 concurrent studies, each with a not so robust p-value?
4 DR. STOCKBRIDGE: No. I think the way to
5 frame this is in terms of trials powered for
6 conventional p-value, would you need one of those or
7 two of those? A substitute for two of those might be
8 a single study with a much lower p-value, but are we
9 looking at a one-trial away or a two-trial away kind
10 of scenario? That's the question.
11 DR. KAUL: Under the assumption that the
12 PVRI captures a clinically relevant or utile endpoint,
13 that's the clarifying.
14 DR. STOCKBRIDGE: That's correct. So if you
15 got here, that's what you thought.
16 DR. TEMPLE: This is a general discussion we
17 have on how much evidence do you need. We have a
18 whole guidance on when one study will do, and it's
19 built on studies on other populations. That might
20 mean one study is good enough. A really, really
21 strong study, a pharmacology that goes along, although
22 in this case the whole endpoint is pharmacology so

1 that's not really relevant.

2 Typically, in pediatrics we do expect that a

3 single study in the pediatric population will do, but

4 for what it's worth, in depression where studies have

5 failed repeatedly to show anything in children, we're

6 asking for two. So there's a judgment in it.

7 DR. KAUL: Okay. Well, why don't we start

8 with Dr. Rosenthal?

9 DR. ROSENTHAL: You need to stop calling on

10 me when I'm not ready.

11 DR. KAUL: Well, whoever is ready to answer

12 this. Dr. McGuire?

13 DR. MCGUIRE: I'll start. I think one would

14 be sufficient, and it's based on the fact that it is

15 the fundamental premise that it is sufficiently

16 similar in children as it is in adults, that we can

17 consider the adult data at least as one trial, if not

18 two antecedent trials.

19 DR. KAUL: Dr. D'Agostino?

20 DR. D'AGOSTINO: I agree with the comment.

21 If I understood correctly, we wouldn't go to the

22 pediatric population until after it was approved in

1 the adult population. Given that plus the need to
2 move things along, I think one trial would be
3 sufficient.
4 DR. KAUL: Dr. Coukell?
5 DR. COUKELL: Sorry, I didn't know I had to
6 weigh in on that one.
7 DR. KAUL: Okay. Dr. Krantz?
8 DR. KRANTZ: I would just add, I think one
9 study would be adequate, but again, to echo your
10 sentiments, Mr. Chairman, you need the other
11 endpoints, as well, even if it's not adequately
12 powered, whether it was a functional endpoint or other
13 hemodynamic data. I think we want a compendium of
14 information that we can evaluate on a individual study
15 basis.
16 DR. KAUL: But the question that is being
17 asked is PVRI, so the answer is one trial.
18 DR. KRANTZ: Yes, one trial.
19 DR. KAUL: Okay. I concur.
20 Dr. Neaton?
21 DR. NEATON: Agree with one.
22 DR. KAUL: Dr. Black?

1 DR. BLACK: I have nothing to add.
2 DR. HALPERIN: Jon Halperin, I agree as
3 well. One trial would be sufficient under these
4 circumstances.
5 DR. NEWMAN: One.
6 DR. VENITZ: Single trial is fine.
7 DR. KAUL: The other component of this
8 question is: Response to a single dose or after some
9 weeks of treatment. Who wants to take that first?
10 You're ready, Dr. Rosenthal?
11 DR. ROSENTHAL: No, but I'll answer it
12 anyway. So after some weeks would be my answer to
13 that, just because of the way that the disease seems
14 to behave.
15 DR. KAUL: Could you be a little bit more
16 specific, after some weeks, 12, 16, the conventional
17 time point that's being used or even earlier on?
18 DR. ROSENTHAL: Well, yes, 12 to 16 weeks
19 sounds good, some period longer than a measurement
20 that's obtained during the same time that the baseline
21 data are acquired.
22 DR. KAUL: Dr. Kawut?

1 DR. KAWUT: Agree, as long as possible.
2 DR. MCGUIRE: Agree, a longer study and I
3 think we could consider this situation a before-and-
4 after study without a parallel group if we have a good
5 feel for the placebo effect of the drug given the
6 orphan nature of the disease and the difficulty of
7 identifying the patients.
8 DR. KAUL: Let me ask, does anybody here
9 have any concerns if the time point was chosen at six
10 weeks?
11 DR. TEMPLE: Can I just ask the same
12 question I've been asking all along? If this is one
13 member of a class where the children would ordinarily
14 be treated with a member of the class, isn't there
15 going to be nervousness about leaving them off for six
16 weeks or eight weeks or 12 weeks or 16 weeks?
17 DR. MCGUIRE: That gets to my point about I
18 think because of the clinical penetrance of the drug
19 use off label, it's going to be awfully difficult to
20 maintain patients in a blinded placebo-controlled
21 trial. So I think we'd have to consider alternative
22 study designs.

1 DR. KAUL: Or early time points. Is there
2 any evidence to suggest that these hemodynamic
3 variables measured at four, six weeks are different
4 from what they measure at 16 or 12 weeks? In other
5 words, my understanding was that they're a highly
6 reliable predictor of what happens at 12 to 16 weeks
7 at four or six weeks. Is that correct, Dr. Rich?
8 DR. RICH: That's my understanding. I think
9 the only differences you've seen in the clinical
10 trials is when the dose has been escalated over time.
11 But once they're on the full dose, four weeks later,
12 you had the same effect you had 12 weeks later.
13 DR. KAUL: Dr. Barst, I see you. Are you
14 nodding in agreement or disagreement? Could you
15 please come to the microphone and share your rationale
16 for your disagreement?
17 DR. BARST: Some of our adult randomized
18 trials have shown that we see the dose effect not
19 until 12 weeks, for example, at 16 weeks. That's one
20 of our recent drugs that's been approved, and we have
21 seen that similarly with some of the prostacyclins.
22 So I would be uncomfortable saying that we should be

1 doing this at four, six weeks, because we may not
2 demonstrate a robust treatment effect that we could
3 see if we treated the child longer. So I would really
4 disagree with that.
5 DR. STOCKBRIDGE: The exercise effect takes
6 many weeks to manifest. I've always assumed that had
7 to do with after you've fixed the hemodynamic problem,
8 now you've got to train in order to get real exercise
9 response. But what evidence is there that it takes a
10 long time for the hemodynamic effects to fully
11 manifest?
12 DR. BARST: Certainly, the two studies for
13 the approval of IV epoprostenol showed minimal acute
14 effects, because they were all tested, and significant
15 hemodynamic effects at either eight or 12 weeks.
16 We did do an industry-sponsored prospective
17 study, which was very small, in children with Bosentan
18 because of concerns about safety. Even though we'd
19 already demonstrated safety and efficacy, we did do
20 acute effects for those children over 24 hours and did
21 not see favorable acute effects in hemodynamics.
22 However, when we looked at the data at 12 weeks, we

1 had significant hemodynamic improvement in the
2 treatment-naïve children, as well as add-on to
3 epoprostenol.
4 DR. KAUL: Does that help, Dr. Stockbridge?
5 Assessment of PVRI at peak or trough, the general
6 protocol is doing it at trough. Does anybody here on
7 the committee disagree with that?
8 So that's the answer, trough.
9 DR. STOCKBRIDGE: Okay. Well, if you really
10 thought it took many, many weeks to develop
11 hemodynamic effects, it would be a surprise to me that
12 you could tell peak from trough.
13 DR. KAUL: I kind of anticipated the
14 response. I leave it to the expert. My superficial
15 knowledge of the trial design and what I have seen is
16 that hemodynamics at early time points is quite a
17 reliable predictor, but I would submit to the
18 expertise of Dr. Barst and others here. But your
19 point is well taken.
20 Do I hear anybody else on the committee have
21 a differing opinion? Dr. Newman?
22 DR. NEWMAN: I wasn't going to speak to peak

1 or trough, but I agree with Dr. Barst about the
2 timing. Clearly, in the old days when vasodilators
3 were used, many of them had acute effects and had no
4 durability. In fact, tachyphylaxis would occur.
5 Biological responses would occur that rendered them
6 useless. So at the early end, you can't do it. And
7 clearly, when even Flolan came out, there were
8 patients that didn't have acute responses who, over
9 six to 12 weeks, got massively better due to some
10 compensations, perhaps myocardial function, so that
11 their exercise capacity and their hemodynamics
12 improved.
13 So I think it would be wrong to assume that
14 we're just looking at a pharmacologic effect on a
15 frog's leg. We're looking at an integrated response,
16 full human response, which we don't understand. And
17 so I think probably eight to 12 weeks would be the
18 minimum I think a study should go.
19 DR. KAUL: Is it a fair statement to make
20 that there is a lag between the hemodynamic
21 improvement and the measure of exercise capacity and
22 that hemodynamic improvement precedes the improvement

1 in exercise capacity, Dr. Barst?

2 DR. BARST: All we know is that limited data

3 where we did acute testing with the drugs, whether it

4 was Bosentan or epoprostenol or sildenafil, that we

5 saw far less of an effect, if any effect, acutely

6 compared to what we saw chronically.

7 One of the difficulties is that we feel,

8 based on risk-benefit assessment, we shouldn't do

9 serial cardiac catheterizations at four, eight, 12 and

10 16 weeks, even though in some of the studies we do

11 demonstrate the beginning of improvement exercise

12 prior to the end of the study. We've used our

13 experience to come up with what we think is the best

14 time to assess when we would expect to see a

15 hemodynamic improvement, if we were going to be able

16 to demonstrate one.

17 DR. KAUL: So the answer is -- you're

18 hearing quite a spread here from four weeks up to 16

19 weeks, and I think you'll have to reconcile what is

20 required to be captured with the real-world

21 pragmatism. Can we really keep these patients of

22 these medications for whatever time that you can

1 decide? I think that should really weigh in into this
2 question.
3 Yes, Dr. Black?
4 DR. BLACK: Just a point of clarification
5 for me.
6 Can you give the same answer for every drug
7 in every drug class? It sounds like that's a big
8 leap, and maybe you may have to have a different
9 answer for each drug in each class in each dose even.
10 DR. KAUL: I think Dr. Newman's -- that was
11 going to be my response, that what you told me had
12 more to do with the nature of the drugs that were
13 being given in the '70s and '80s, where you couldn't
14 really reliably predict, at least in part.
15 DR. NEWMAN: We don't know.
16 DR. KAUL: The tachyphylaxis and all that
17 stuff. Dr. Rich?
18 DR. RICH: There is a big difference between
19 intravenous prostacyclins and the oral agents. The
20 acute side effects of the IV prostacyclin prevent us
21 from giving what we call a therapeutic dose, unless we
22 do it gently over many periods of time, whereas

1 sildenafil, you can give the full dose at day 1. And
2 so that's a big issue here, and it's really a side
3 effect profile that we waited to abate before we up-
4 titrated the dose.
5 Once you get to whatever your target dose is
6 -- and maybe we all practice a little differently --
7 once you get there, your hemodynamics should reflect
8 it. I don't know of any hidden mechanism that
9 undergoes the pulmonary circulation or the right
10 ventricle that has a lag phase to it. 'm not saying
11 it can't be, but we certainly don't know about that.
12 DR. KAUL: Okay. Would one also need
13 exercise as a secondary endpoint in older children
14 able to perform the test? And by of clarification,
15 the age cutoff here is over 7; is that correct? Okay.
16 Dr. Kawut?
17 DR. KAWUT: It would be nice to have
18 functional status in exercise as a supportive
19 endpoint, as well as a patient- or parent-reported
20 outcome. And I know there's some work going on in
21 that in children, but that would be nice as something
22 to support hemodynamic changes and to also kind of

1 relate it to the effects seen in adults.

2 DR. KAUL: Dr. McGuire?

3 DR. MCGUIRE: As I said in the justification

4 for my vote, I think that would be an important

5 buttressing. I don't know that an age cutoff is so

6 appropriate as a developmental ability, as we know

7 that age over 7 Down syndrome kids, for example, can't

8 effectively do this walk testing.

9 DR. KAUL: Dr. Coukell, I think you made a

10 compelling argument for having other performance

11 measures.

12 DR. COUKELL: Right, so I vote yes.

13 DR. KAUL: Dr. Krantz?

14 DR. KRANTZ: Yes.

15 DR. KAUL: Dr. Venitz?

16 DR. VENITZ: I was going to say that was

17 part of my yes vote overall was to actually do the

18 exercise test.

19 DR. KAUL: Dr. Newman?

20 DR. NEWMAN: Yes.

21 DR. KAUL: Anybody with a no? Okay.

22 The final component of this question: Does

1 the PVRI exercise relationship for the adult data
2 offer a way to set the size of the required study? In
3 particular, if one wanted to resolve an effect
4 corresponding to a 10 percent exercise improvement in
5 adults, can one define the corresponding change in
6 PVRI? And I will add, in pediatric population.
7 Dr. Neaton, clarifying question or --
8 DR. NEATON: Can I ask? The way I'm
9 interpreting this is that you'd like some guidance.
10 You not only want to beat placebo, say, on PVRI, you
11 want to beat it by a certain amount.
12 DR. STOCKBRIDGE: No. It's good to clarify
13 that. Although it's possible you could have looked at
14 these data and said you shouldn't really even think
15 about doing this, the relationship's not reliable
16 until you get to a certain --
17 DR. NEATON: That was my original thought.
18 DR. STOCKBRIDGE: And that's fine. But this
19 gets at a different issue, which is trying to ensure
20 that the variance that is achieved in the trial, which
21 is purely a function of sample size, is small enough
22 that had the true effect been zero, you would have

1 reliably excluded a minimally interesting treatment
2 effect.
3 So it has to be somewhat independent of what
4 the apparent effect is. That can't figure into here,
5 because let's say if somebody had a drug where the
6 nominal effect, the true effect of the drug was
7 80 percent of the minimally interesting effect, they'd
8 never be able to exclude a minimally interesting
9 effect, no matter how many people they put in the
10 trail.
11 This is all about trying to get the
12 variability observed in the trial lower enough so that
13 if it fails, you can say I'm pretty sure the drug's
14 not useful.
15 DR. TEMPLE: This goes to one of the
16 problems associated with BPCA, which is you don't have
17 to win. You just have to do. And we want to be sure
18 the trial has a reasonable shot at showing what would
19 be considered a meaningful effect. So in blood
20 pressure, we ask people to have enough power to rule
21 out, I don't know, 3 millimeter mercury or something
22 like that. We also ask for people to recalculate the

1 variance toward the end to see if they've undermined
2 their power calculation. And that's really what this
3 is. How big should it be? What size effect should
4 you power it to show? And then we would probably also
5 ask people to recheck the variance late to see if they
6 should upsize.
7 DR. KAUL: If we accept a 10 percent
8 exercise improvement in adults to be an indicator of a
9 minimal clinically important benefit in adults, I
10 don't have a major problem in extrapolating the six-
11 minute walk data to the VO2 peak. I think it's likely
12 going to be concordant, but I would be less uncertain
13 or, should I say, more confident if there was any
14 data, body of data, to provide support for that
15 assumption. And then you can draw upon that and say,
16 yes, a 10 percent improvement in VO2 peak is the bar
17 that we should be powering the study for. So I think
18 that those are interrelated.
19 So anybody else have a -- Dr. D'Agostino?
20 DR. D'AGOSTINO: If you give that they want
21 and do a 10 percent exercise improvement, the
22 mathematics that was displayed this morning is, I

1 think, appropriate for ultimately sizing the study.
2 So the question we have, again, is that the model that
3 we've seen we're uncomfortable with it, but
4 technically or theoretically, that mathematical
5 procedure should work.
6 You have the variability in the study that
7 you're going to look at. You also have the
8 variability in the model. So you do have an added
9 problem in terms of how well you can use the model and
10 how well you're going to get the results. But I think
11 theoretically, the model could be used to do what you
12 were asking.
13 DR. KAUL: Dr. Venitz?
14 DR. VENITZ: I agree the answer to the
15 question that you raise is yes, but in addition to
16 this linear scale that I think we've been talking
17 about, part of I think my discomfort with question
18 number 1, accepting the model as is, had to do with
19 maybe trying to use a binary classification on the
20 data that Dr. Brar shared with us. And I think it
21 goes back to one of the questions you raised, where
22 you want to know can you win either way and how many

1 times do you win both ways and is there concordance
2 and discordance.
3 I think part of the cross-validation
4 exercise might be to try to look at different changes
5 in percentages or whatever units you want to use on
6 your pulmonary vascular resistance and see how many of
7 those studies then would end up winning on the
8 clinical endpoint of interest.
9 So you could actually use that as a way of
10 coming up with a number that would be clinically
11 meaningful if you're willing to accept that there is
12 an extrapolation to pediatrics.
13 DR. KAUL: Dr. Rich? Oh, I'm sorry.
14 Dr. Kawut?
15 DR. KAWUT: I would say no, just because we
16 really don't know what the minimally clinically
17 important difference in six-minute walk is and
18 especially as -- much less peak VO2. And as we go
19 into more studies where it's going to be add-on
20 treatment, so we're doing placebo-control trials in
21 people who are already treated, these effect estimates
22 are going to be much smaller, as they have been

1 already in adults. And so to try to size your study
2 based on an estimate that we don't have, I think, is
3 fraught with problems.
4 DR. STOCKBRIDGE: Okay. But I still have to
5 tell somebody how big a trial I want them to do. So
6 what's your solution to this problem?
7 DR. KAWUT: I guess I would look at the
8 effect of the drug in its previous adult studies, look
9 at the effect estimate in terms of pulmonary vascular
10 resistance there and knowing your variability in your
11 kids, try to hit that difference that you saw in your
12 adult studies.
13 DR. KAUL: Dr. Stockbridge, you're reluctant
14 to accept that answer.
15 DR. STOCKBRIDGE: Well, having a big effect
16 is not a problem. And in fact, developers, sponsors
17 frequently ignore our requirements for sizing a trial
18 in pediatrics and rely upon the fact that if they
19 ignore us and win big, we'll amend the written request
20 to say we thought you were going to need 80 subjects
21 per group, you won with 20, so the trial was
22 successful.

1 That's not the problem here. The problem is
2 trying to make sure that if they run the trial with 20
3 and say didn't work out, they should still get paid.
4 DR. KAWUT: That's a bigger question than
5 what's written down.
6 DR. KAUL: Dr. Gobburu?
7 DR. GOBBURU: We are here to seek your
8 opinion, but something has flashed based on the
9 discussion that's going on, so I'll just share it for
10 your consideration. I think what we're asking is a
11 way to design the pediatric trials using the
12 hemodynamic endpoint to minimize false negatives.
13 That's what we're asking.
14 So there are two ways to do it. One is as
15 the gentleman before alluded to. The other could be
16 we can take the previously approved database of drugs,
17 and we could come up with the lowest double delta PVRI
18 that we have put on the market and say we can work off
19 that. Just something for you to consider.
20 DR. KAUL: Dr. Newman?
21 DR. NEWMAN: There is no easy answer. It's
22 slide 56 from this morning that shows delta delta PVRI

1 versus the delta delta exercise, with the mean and the
2 range, that suggested that 20 percent reduction of PVR
3 was highly associated with a significant increase in
4 six-minute walk.
5 Obviously, you can't just take a statistical
6 difference in PVR going from baseline to some change
7 and call that a real effect. You're not going to be
8 able to do that. You're going to have to take some
9 threshold delta PVR that you feel associates reliably,
10 if you could exercise the patient, to an exercise
11 effect and pick it.
12 I think that you're always going to have the
13 problem of having false negatives. You may miss a few
14 patients that those little changes in PVR might
15 actually benefit them, but you got to make a cut
16 somewhere. We know that at the flat part of the line,
17 that you can get big changes in PVR, negative changes,
18 with no effect on six-minute walk, which is the
19 current gold standard, even though it's fool's gold.
20 So I think you're going to have to use your own data
21 to power the study to figure out what statistical
22 significance is. I mean, am I missing something? Did

1 I not get it?

2 DR. KAUL: Is that what, Dr. Temple, you

3 were trying to use 400 or 500 PVRI as your cutoff and

4 see?

5 DR. TEMPLE: Yes. That could help you

6 decide what the minimum effect size is. You have to

7 design to show effectiveness, but we have to look more

8 closely at that.

9 DR. NEWMAN: Can you go to slide 56?

10 DR. KAUL: Slide 56 off the sponsor, I

11 believe?

12 DR. NEWMAN: Yes, the sponsor.

13 DR. KAUL: Yes. Dr. Newman, did you have

14 any comment?

15 DR. NEWMAN: Yes. I just wanted to be able

16 to see that. That’s the way I think about it, right

17 or wrong.

18 DR. TEMPLE: That would be to say size the

19 trial to show an effect size of at least X, which

20 corresponds to what you think is a reasonably likely

21 chance to have been able to show a difference in PVRI

22 that corresponded to an observable, detectable

1 difference in exercise.

2 DR. KAUL: So the obesity drug development

3 program has one of those weight thresholds. You'd be

4 required to have a 10 percent or whatever the number

5 is, but you also have to have a minimum difference,

6 which is probably viewed as clinically important. Is

7 that what you're trying to ask the committee? Not

8 only do you have to cross the threshold, but you also

9 have to have a minimum change that is within that

10 bound.

11 Dr. Gobburu, did you have a comment?

12 DR. GOBBURU: No. I don't think that we are

13 asking that. What we're asking is that -- for

14 example, the sponsor might come in and say that my

15 best guess of the double delta PVRI is minus 60 on

16 this plot, and they can say I only need 10 patients to

17 do that. And then you do the trial, and then that's

18 not what you observed. So what we're asking is what

19 would be a reasonable target double delta to, say,

20 exclude from the confidence interval to interpret the

21 trial as not false negative.

22 So if we agree, let's say, on the plot --

1 just throwing numbers -- minus 20 is a meaningful
2 change in PVRI, we would say that you have to power
3 the study to exclude minus 20 from the double delta
4 confidence interval.
5 DR. TEMPLE: But the reason is different
6 from the weight loss. The weight loss, that's about
7 what's clinically meaningful. Here, it's what kind of
8 difference in double delta PVRI is big enough to
9 believe that it would correspond to a documentable
10 change in exercise.
11 DR. STOCKBRIDGE: Except for the fact that
12 the current written request has a 10 meter or 10
13 percent or something change in exercise as a minimally
14 important difference. So there really was something
15 to it. The goal wasn't to ensure the drug would beat
16 placebo.
17 DR. TEMPLE: You could do that, too, but I'm
18 going to the kinds of questions Ralph and Jim were
19 raising before. There were all these ones down on the
20 right side of the curve that didn't really show
21 anything. So maybe there's a minimum effect on double
22 delta PVRI given the drawing we had there that would

1 provide reasonable assurance to you that this would
2 have corresponded to an actual effect on exercise.
3 I'm not necessarily saying it has to be an
4 effect of a certain validity or value, just that it
5 would be detectable, that it would be real, that it
6 really would have been there. So it's slightly
7 different reasoning, although obviously not unrelated.
8 DR. KAUL: Dr. McGuire?
9 DR. MCGUIRE: If this is all I'd seen, I'd
10 think this looks beautiful, but that color-coded delta
11 delta by class really doesn't affect -- I mean, I'll
12 go back to my comments, and people are hinting around
13 this. I think this is going to be class dependent, if
14 not drug dependent, and I think we're going to be
15 basing this registration design on existing adult
16 data. And I think you take the drug that you're going
17 to test and analyze the data and plot out what delta
18 PVRI corresponds to the six-minute walk test.
19 The six-minute walk test is not perfect, but
20 that's the whole premise of our assumption that this
21 will apply to pediatrics. And so I think that's the
22 best way to do it.

1 DR. KAUL: Dr. D'Agostino?

2 DR. D'AGOSTINO: I'm saying the same. If

3 you try to go back to the company's data, they may not

4 have it. So you have to go to somehow or other this

5 collection of data, the best you can come up with.

6 And in terms of individual classes and what have you,

7 if you really think that's going to be a problem,

8 you'd have to be generating a model per class. So

9 you're going to have to bite the bullet somehow or

10 other and say I have enough data where I feel I have a

11 valid model. Then if you do, then the types of steps

12 that we would -- in terms of excluding 10 percent

13 increases and so forth can, in fact, be worked out.

14 DR. STOCKBRIDGE: If you really thought you

15 needed to do this at the individual drug level, you

16 didn't have any confidence in doing it by drug class,

17 we have the ability under the written request to

18 require the appropriate studies in adults that would

19 define the relationship that you would use to set the

20 margins for children. We could do that under a

21 written request.

22 DR. KAUL: Dr. Venitz.

1 DR. VENITZ: Can we go back to Dr. Brar's
2 slide number 9? I think that's the bubble slide that
3 we talked about, because I think what you want us to
4 do is basically draw a line parallel to the Y axis
5 somewhere between, I don't know, minus 200 and minus
6 400 and anything to the left of that would be
7 clinically significant, anything to the right of that
8 would not be clinically significant. Is my
9 interpretation correct?
10 DR. TEMPLE: You could say that, but I
11 didn't think of it as clinically significant. What I
12 meant was actually detectable.
13 DR. VENITZ: Well, I'm saying you have the
14 data right here. What I'm proposing is that you treat
15 both the X and Y axis as binary variables and then
16 play games and see how many times you show up.
17 DR. TEMPLE: That's fine, whichever you call
18 it.
19 DR. KAUL: Dr. Neaton?
20 DR. NEATON: This is a tough one, and maybe
21 some of the historical data that you showed would be
22 helpful. But if I were doing this, I'd want to base

1 it on the trials that I did in the adult population
2 with the drug. You've got to have a large body of
3 data there with the specific drug, with the
4 relationships done kind of in your labs and the sites,
5 and that's kind of what I want to base it on.
6 I guess one consideration that I think maybe
7 should be thought through, given the earlier
8 discussion, if you go this route and require in older
9 kids that you do the exercise testing, I might
10 consider some power situations around that endpoint,
11 as well, even though it's a secondary endpoint.
12 DR. KAUL: Dr. Kawut?
13 DR. KAWUT: I think your goal is worthy,
14 which is targeting some minimally clinically important
15 difference. The problem is it kind of holds this
16 trial up or a pediatric trial to a potentially higher
17 standard than an adult trial where you don't require a
18 minimally clinically important difference. And where
19 we could get a drug approved in an adult with
20 literally 1 meter difference in six-minute walk --
21 DR. STOCKBRIDGE: That's because people get
22 paid regardless of the outcome here, okay?

1 DR. TEMPLE: But also, that's why I'm not
2 calling it a clinically meaningful difference. One
3 way to read that -- I don't know if everybody is going
4 to read it that way -- is that if your value is below
5 400, you don't really know what you're going to get.
6 Some of them work; some of them don't work. But if
7 you're above 400, it looks pretty consistent. So
8 maybe above 400 or above minus 400, that's reliable
9 enough to use. I'm not sure we're convinced of that.
10 I sort of want to know more about those
11 bottom five balloons to see what's peculiar about
12 them. We already heard that the most impressive was an
13 oddity. So maybe that's a red herring. But there
14 still might be a cutoff before you'd say I know this
15 corresponds to exercise. It isn't so much how big the
16 exercise is. It's does it really correspond. So I
17 didn't think of it as a minimal effectiveness
18 standard.
19 DR. KAUL: So the disconnect between minimal
20 detectable difference versus minimal clinically
21 important difference, so what you're talking about
22 here is minimum detectable difference. And I think

1 the strategy that you just proposed seems to be quite
2 a reasonable strategy, unless Dr. D'Agostino and
3 Dr. Neaton disagree.
4 DR. NEATON: I think further work on this
5 along those lines makes sense, but like I said, I
6 would definitely consider the trials that were just
7 recently done in the adult population that led to
8 approval, as well.
9 DR. KAUL: Okay. I think we are going to
10 move to our question number 6. The committee is now
11 asked to consider the application of PVRI in the
12 pediatric development program for sildenafil. The
13 question is: What are the implications of the
14 unsuccessful study targeting exercise? Are the
15 exercise data supportive of use in children?
16 Let's tackle that first. Since this is a
17 nonvoting question, Dr. Veltri.
18 DR. VELTRI: Mr. Chairman, I just have a
19 point of order here. I'm putting on my hat as the
20 industry representative. We've seen data, but as I
21 understand it, the FDA hasn't reviewed it. The NDA is
22 in preparation. And certainly, I think the panel

1 members haven't had the opportunity to see in-depth
2 data, for instance, the long-term information.
3 So I just question whether, for instance,
4 having statements on support of use in children you
5 can argue it's being used off label already, but I
6 don't think the data has been appropriately reviewed.
7 So I have a concern there.
8 Secondly, I don't know about the precedent
9 of this. I understand the need for the written
10 request question about the amendment there, but
11 obviously, the data has now been unblinded. And I
12 think some of the questions here alluded to the fact
13 of changing something post hoc, so it's just a point
14 of order from an industry perspective, a sponsor
15 perspective overall.
16 DR. STOCKBRIDGE: And you've hit exactly the
17 right issue here. That's what we're talking about
18 here. I think one of my colleagues called it drawing
19 the bulls-eye around the arrow feel to it.
20 Nevertheless, the goal here was to try and get useful
21 information in children, and there is a trial. It's
22 done. It's in the can. We have not reviewed it. We

1 can’t tell you that we agree that the exercise data
2 are as good as the sponsor described it. You’ll have
3 to couch your answer with certain assumptions about
4 the validity of the data that they’ve acquired and go
5 from there.
6 DR. VELTRI: I just put it in the record
7 that these circumstances go beyond the usual. This is
8 the only randomized clinical trial in kids, a landmark
9 trial, perhaps. But this may not be setting the right
10 precedent.
11 DR. KAUL: Your comments are duly noted.
12 Does anybody else feel along the same way?
13 Dr. McGuire?
14 DR. MCGUIRE: I would just like a little
15 historical clarification as to when this uncommon
16 collaboration, I think you called it, began with the
17 agency and companies developing drugs in this domain.
18 Did that begin before the unblinding and the analysis
19 of this pediatric trial?
20 DR. STOCKBRIDGE: It absolutely did. We’ve
21 been pulling these data together for the last two
22 years or so with this thought in mind. We knew this

1 was going to be an issue and have been working
2 steadily at this. It's taken awhile to do what we've
3 done.
4 DR. MCGUIRE: And during that time period,
5 that has been in collaboration with at least some of
6 the industry sponsors or completely --
7 DR. STOCKBRIDGE: No, this was nothing to do
8 with any sponsor, including Pfizer. We've had the
9 data because people have sent in study reports with
10 applications for our consideration.
11 The recent cooperation came because we knew
12 that the Pfizer program was nearing an unsuccessful
13 completion and that happened to be about the same time
14 that we were putting together our analyses of the data
15 that we had homogenized and reviewed. So it was if
16 you agree on issues that question 6 raises, fortunate
17 timing for them. If you don't agree on things there,
18 then it was somewhat unfortunate timing for them. But
19 they've had no role whatsoever in the evolution of the
20 model, the selection of PVRI as a candidate. They've
21 had no role in that at all.
22 DR. KAUL: Dr. D'Agostino?

1 DR. D'AGOSTINO: I'm sorry if I'm not
2 remembering or so forth. But are we talking about
3 replacing the primary endpoint with -- is this what
4 the study is going to be judged on?
5 DR. STOCKBRIDGE: Well, in some sense, the
6 answer to that is yes. They had a different primary
7 endpoint that was negotiated with them at the time the
8 study was initiated. Those data exist, as well as
9 data that they collected that was not part of their
10 primary endpoint.
11 You're being invited to tell us how
12 concerned you are that the FDA basically is
13 contemplating allowing a change, inviting a change in
14 the primary endpoint to accommodate the view that PVRI
15 would have been an acceptable endpoint for them.
16 DR. D'AGOSTINO: So given the discussion
17 we've had where a number of us are not comfortable
18 with the establishing of the relationship, is it
19 possible that we could say yes on this and no
20 previously? I mean, is there a logic --
21 DR. STOCKBRIDGE: You could certainly say I
22 wasn't comfortable with the establishment of the

1 relationship, and perhaps you have enough information
2 on hand to address those concerns. But if I were
3 ready to adopt PVRI, I would or would not have trouble
4 allowing the Pfizer program to declare victory here.
5 DR. KAUL: I think that this question number
6 6 has to be taken independent of the answers to the
7 question number 5. This question number 6 assumes
8 that the relationship has been established. And if it
9 has been established, what is our thought process with
10 regards to the statistical analytical plan?
11 DR. PACKER: Milton Packer, I'm a consultant
12 to Pfizer today, being compensated for my time and
13 travel here. The sponsor, if I understand it,
14 prespecified the primary endpoint, which is exercise,
15 and on its primary prespecified analysis, achieved a
16 p-value of .056. One can spend a long time as to
17 whether that is consistent with a treatment effect or
18 not, especially given the totality of data within the
19 pediatric study and the positive data in the adult
20 study. It's a little bit hard to imagine calling the
21 pediatric study a clearly negative trial. It's just
22 not a fair characterization.

1 Having said that, I don't think the sponsor
2 is proposing in any way, shape or form changing the
3 primary endpoint. All the sponsor is asking for is
4 that the changes in PVRI be considered by the FDA in
5 the totality of the data in the pediatric study. And
6 that's a very different set of circumstances than are
7 implied in question number 6.
8 DR. KAUL: Dr. D'Agostino?
9 DR. D'AGOSTINO: This is where I was
10 heading, Milt, is that are we talking about a
11 supportive variable or variables whose analysis may be
12 supportive of the claim and so forth, and I had no
13 idea about the .056 or are we talking about sort of
14 redoing everything and saying now this is our primary.
15 And if I hear you correctly, now your point of view is
16 that this would just another variable supportive.
17 There's a lot of discussion that it looks like it's a
18 reasonable variable, but it's not replacing the --
19 it's not changing the whole analysis plan.
20 DR. PACKER: And that's the point. All
21 Pfizer wants is to say PVRI should be included in the
22 consideration of the totality of the data. It was a

1 prespecified secondary endpoint included in the total
2 assessment together with the fact that there's adult
3 data and together with the fact that the p-value on
4 the prespecified analysis on exercise is .056.
5 DR. KAUL: For clarification,
6 Dr. Stockbridge, has the FDA had a chance to look at
7 the sponsor's data for the pediatric population?
8 DR. STOCKBRIDGE: Absolutely not.
9 DR. KAUL: Okay. And so has it been
10 published?
11 DR. EWEN: It has been presented at ERS last
12 year, and it's been submitted for publication at the
13 moment.
14 DR. KAUL: So if the FDA hasn't had a chance
15 to look at the data and the p-value is .056, that, in
16 of itself, raises a flag for me. But the trouble I'm
17 having here is -- are we to sort of ignore that
18 completely and just answer the question that if we
19 assume that the relationship has been established, how
20 do we proceed ahead?
21 Dr. Temple, Dr. Stockbridge?
22 DR. TEMPLE: I guess I don't think you're

1 really ready to answer this question fully. What
2 Milton is proposing is do you think that a study with
3 a borderline result might be moved one way or the
4 other by an effect on something you knew about. If you
5 want to offer opinions on that, feel free. We've
6 accepted one-sided tests once in a while when we
7 thought it was the right thing to do. We like to say
8 we're not slaves to the p-value, although, of course,
9 we really are.
10 DR. PACKER: It's not a one-sided test.
11 It's a two-sided test, .056.
12 DR. TEMPLE: I understand. I'm giving an
13 illustration of flexibility.
14 DR. PACKER: Okay. No problem.
15 DR. TEMPLE: That's accepting .1, you know.
16 DR. KAUL: But regardless of whether the
17 p-value is .06 or .04, the issue is that -- is the FDA
18 asking the committee to weigh in on the data that was
19 presented to us or just assume that the relationship
20 has been established and independent of the data, what
21 would we advise?
22 DR. STOCKBRIDGE: I guess there are several

1 parts to that. One is you've got to assume that the
2 data are as they have described them. Upon review, we
3 may decide there are issues with them, but you've got
4 to assume that they've appropriately described their
5 study results.
6 It is a trial that's done, so there is a
7 nonprospective aspect to this that the question is
8 inviting you to consider. I certainly had been
9 thinking about this in terms of thinking about PVRI as
10 a primary endpoint, but I don't have any deep problem
11 if the committee wants to discuss the original primary
12 endpoint, plus I'm going to think about some other
13 results here. It's not the usual paradigm for making
14 a decision about whether or not an effect exists, but
15 that's okay.
16 DR. KAUL: Dr. Neaton?
17 DR. NEATON: I guess to me, it makes a lot
18 of sense what Milt Packer suggested. Whenever this is
19 reviewed formally, to consider the totality of the
20 data, that's kind of a no-brainer. Right now, we
21 don't have any safety data here, so we can't do that.
22 And your review, which is often insightful is not

1 here, as you mentioned, Norm.

2 So it just seems like it would be very easy

3 for me to say right now that when that review took

4 place, I would definitely capitalize on the work that

5 the FDA has initiated in interpreting the totality of

6 these data. Beyond that, it's a little hard.

7 DR. TEMPLE: That may be enough of a

8 response to question 6. If everybody thinks that's

9 reasonable, that's probably as far as you need to go.

10 DR. NEATON: Okay.

11 DR. KAUL: You mean all the other

12 components, too?

13 DR. TEMPLE: With what Jim said, yes.

14 DR. KAUL: Okay.

15 DR. TEMPLE: Because you don't have enough

16 data to go much further.

17 DR. KAUL: Dr. McGuire?

18 DR. MCGUIRE: Can I ask another

19 clarification, because it's two quite disparate

20 things, in my head, that we may be discussing here?

21 One, the matter is, is there some way that we can take

22 this trial that's done and analyze it and make it

1 somehow positive and, therefore, have something in the
2 product label at some point that says it's okay to use
3 in kids, or are we talking about has this trial
4 satisfied the written request?
5 If the answer to the second part is no,
6 that's a huge deal. If the second part, the trial is
7 done and whatever it showed, they've satisfied the
8 written request so they can get the six-month
9 exclusivity and all we're dickering about here is
10 whether or not it'll have a line or two in the product
11 label for kids, those are two completely different
12 issues.
13 So I just need to understand. Are we
14 talking about how we're going to interpret the data
15 from the trial or whether or not we've satisfied the
16 written request requirement?
17 DR. STOCKBRIDGE: The intent of the written
18 request is to reward companies for providing data that
19 are useful in labeling. The development program -- I
20 think it's fair to say, the development program --
21 unless we revise the written request, according to the
22 current written request, the sponsor's development

1 program does not meet its terms.

2 It's entirely possible to -- it's

3 conceivable to leave it in that state and reach a

4 totally independent decision about whether or not

5 something should go into labeling. That's not the

6 agency's policy about how to handle written requests,

7 which are generally provided, as I say, to reward

8 companies that do provide useful data.

9 DR. VENITZ: Then why don't we move forward

10 with the vote on number 7?

11 DR. KAUL: Yes. Dr. Rich, unless you have

12 something --

13 DR. RICH: I thought they did fulfill the

14 written request to do a study in children. You're

15 telling us no, they didn't fulfill it? How did they

16 miss?

17 DR. STOCKBRIDGE: There is a term in the

18 current written request that has to do with the sample

19 size that the existing program did not meet.

20 DR. MCGURE: And added to that is it was

21 designed, as I recollect, to have 75 percent with

22 primary endpoint data. There's 75 percent with

1 exercise testing data and only had 50 percent. So
2 it's a study that, as it was executed, it was we were
3 aware that it was going to be terribly underpowered
4 based on the primary assumptions.
5 DR. KAUL: Dr. D'Agostino?
6 DR. D'AGOSTINO: I was going to add
7 something on this effect that we're talking about if
8 we say yes to this, then they analyze it on all the
9 data, right, on all the subjects? Do they have the
10 data on all the subjects, this PVRI? I mean, they
11 don't have the exercise on all.
12 DR. STOCKBRIDGE: They certainly don't have
13 exercise on everybody. Does the company want to
14 comment on who has hemodynamic data?
15 DR. EWEN: Yes, we have hemodynamic on all
16 the age groups.
17 DR. D'AGOSTINO: On all the age groups.
18 DR. KAUL: Please identify yourself.
19 DR. EWEN: I'm Colin Ewen from Pfizer.
20 DR. KAUL: Yes, I think we should proceed to
21 question number 7, which is a voting question.
22 DR. NEWMAN: Can I ask a question first? If

1 we vote to amend the written request and the sponsor
2 then is allowed to reanalyze the data based on that
3 and the FDA hasn't specified a PVR change, then does
4 allow every company to go back retrospectively and
5 reanalyze their data in studies that might have been
6 denied where PVR was within the threshold, but the
7 exercise data wasn't, and then reapply for FDA
8 approval for that drug?
9 DR. STOCKBRIDGE: It's an interesting
10 question, but there isn't anybody in that state.
11 DR. KAUL: If the FDA acts on this, you can
12 be sure there will be many lining up.
13 DR. PACKER: Sanjay, if I understand it, the
14 written request only deals with whether the company
15 gets pediatric exclusivity or not. It has nothing to
16 do with whether there is an approval for the
17 indication, and the distinction is really quite
18 important.
19 DR. VENITZ: That's why I'm proposing that
20 we vote on number 7 and then go back to number 6.
21 DR. KAUL: I think I'll take the suggestion.
22 Dr. Kawut, unless you have really something

1 compelling, we'd like to go ahead.

2 DR. KAWUT: I guess I'm confused. The only

3 way to amend the written request is by changing the

4 primary endpoint; is that correct?

5 DR. STOCKBRIDGE: No. In principle, the

6 written request could say almost anything. It could

7 say as long as you have a trial in which you collected

8 X, Y and Z in as many as 26 patients, it can say

9 anything we wanted it to say.

10 DR. BLACK: Sanjay, I'm not sure I

11 understand this yet. So rather than abstain, I wish

12 we could get another run-through of exactly what the

13 differences are. If we vote yes, they can amend it,

14 what does that mean? And if we vote no, they can't,

15 what does that mean? And I guess I ought to ask Bob

16 and Norman to explain that.

17 DR. KAUL: Who wants to take that?

18 Dr. Temple?

19 DR. TEMPLE: I distracted Norman. Could you

20 repeat it, Henry?

21 DR. KAUL: Dr. Black, please repeat the

22 question.

1 DR. BLACK: Yes, I'm really still not sure
2 what the implications of the differences are if we
3 were to vote yes or no right now. So what is the
4 immediate and what is the long-term implication if
5 they're not allowed to amend it or if they are?
6 DR. TEMPLE: For them to get six months of
7 exclusivity, it has to be amended. As Milton said,
8 that was exactly right. It has nothing to do with
9 whether we would utilize the data to change the
10 labeling, although some people would say it's a little
11 unfair if we thought the study was good enough to use
12 for that purpose, that they not get their exclusivity.
13 But don't worry about that.
14 This was intended to be a question about the
15 data. Is what we've seen about the hemodynamics
16 persuasive enough to say that that could be
17 incorporated into considerations? But I have a little
18 piece of view that we sort of have to reach our
19 conclusion on that by ourselves after looking at the
20 data before we really decide that. So I'm a little
21 wondering whether we should even do this vote.
22 Where are you on that, Norm?

1 DR. KAUL: Actually, that is a good
2 suggestion.
3 Dr. Veltri?
4 DR. VELTRI: Would it be simple enough to
5 say to amend the written request but just to -- I
6 mean, they collected hemodynamic data, right? That
7 this would be an exploratory analysis, PVRI, because
8 the hemodynamic data was collected and that this would
9 be an exploratory analysis -- it has nothing to do
10 with changing endpoints or what have you -- which
11 would be analyzed. Wouldn't that suffice?
12 DR. TEMPLE: We would have to conclude that
13 those data made it okay not to have met the terms of
14 the written request. And we don't do that lightly.
15 We like to have our written request taken seriously
16 and everybody stick to them. That's the whole point.
17 DR. KAUL: I think the dilemma here is that
18 we really cannot seriously answer this question
19 without divorcing ourselves from the preceding
20 question.
21 DR. TEMPLE: The one thing you do know, I
22 mean, you voted seven-six, to think that the

1 hemodynamic data could actually, conceivably, by
2 itself, be a basis for granting -- this was a mixed
3 view, obviously -- that the hemodynamic data alone
4 could be the basis for approving a drug for 2-year-
5 olds. That could mean that the hemodynamic data are
6 very valuable and should help us interpret stuff. You
7 might also think, though, that before you apply that
8 to this study, which involves older people, maybe the
9 data should be looked. And I think we'll live with
10 whatever you want to do.
11 DR. KAUL: Let me make a proposal. The
12 numerical translation of the split vote may give the
13 appearance of a lack of consensus. But I don't see it
14 that way. I see there is a consensus. There is
15 information that is available. Some are more
16 enthusiastic that that information is actionable, and
17 others are less enthusiastic whether that information
18 is actionable. So my proposal to the FDA, with or
19 without the cooperation of the sponsor, is to work on
20 that information, refine it and see if it's
21 actionable. If it is actionable, I think you have the
22 answer to your vote 7.

1 I don’t see really a lack of consensus in
2 the vote. That’s what I don’t like about the votes.
3 I don’t like them, but we have to vote. But I think
4 it’s the deliberation around the vote.
5 DR. STOCKBRIDGE: Well, you don’t have to
6 vote. I suppose if I really had my choice, I’d never
7 ask you to vote. Well, look, because there are --
8 DR. KAUL: Was that specifically directed
9 towards me or --
10 [Laughter.]
11 DR. STOCKBRIDGE: No, it’s because there are
12 always issues that we don’t bring you that affect the
13 approval decision. We don’t ask you whether or not
14 you think the site where they’re manufacturing this is
15 sufficiently developed. There are always issues that
16 are outside of your view. And if we discuss a little
17 bit further sort of what it is people would like us to
18 have looked at before we made a decision about things,
19 that’d be just fine. So the vote matters, rarely
20 matters much and doesn’t matter much at all here,
21 certainly.
22 But again, having people clarify -- several

1 people have said useful things. I'd like to see the
2 effect on this endpoint by dropping studies one at a
3 time. Okay. Well, we can do that. People should try
4 to develop what other things might be useful to know
5 about the sponsor's data or about the endpoint that
6 you think would help us make a decision.
7 DR. BLACK: I just want to support what you
8 said about there probably being more consensus than
9 was obvious from a seven to six vote. My problem as a
10 no voter was that I just didn't think I had enough
11 assurance and that with further work which has been
12 suggested -- I think what was done is very good, but I
13 think further work, I would be much more able to make
14 a reliable yes or no vote.
15 DR. TEMPLE: I think we heard it that way.
16 I actually want to say that at least in a lot of
17 cases, the vote sort of forces people to cut on
18 certain issues and you get some of these nuanced
19 discussions at the time of a vote, whereas sort of
20 people duck it a little beforehand. So I'm not quite
21 as negative as Norman is about votes, but I agree.
22 Those votes were not nearly as different as yes and no

1 votes, absolutely.

2 DR. KAUL: Exactly. So with that, unless

3 anybody else has any specific comment or question, I

4 would like to adjourn the meeting. And I hope that

5 the FDA got the answers it was seeking. I'd like to

6 thank the sponsors for a very excellent and clear

7 presentations and the advisory committee members for

8 their very thoughtful deliberation.

9 Dr. Rosenthal, do you have a comment?

10 DR. ROSENTHAL: I'd just like to make one

11 comment on behalf of the -- sorry to stick in an extra

12 comment as we're adjourning, but I'd just like to let

13 everyone know that the Pediatric Advisory Committee

14 would love to participate in these discussions. And I

15 know that others were invited. I'm sorry that I was

16 the only token pediatric person on the panel, but I

17 think the extent to which the Pediatric Advisory

18 Committee and the Office of Pediatric Therapeutics can

19 be involved in these discussions around written

20 requests and approval in kids, it can only help the

21 process.

22 There's a rich resource there, and I would

1 encourage that it be taken advantage of to the fullest
2 extent. Thank you very much.
3 DR. KAUL: Thank you, Dr. Rosenthal.
4 The committee stands adjourned.
5 (Whereupon, at 4:12 p.m., the meeting was
6 adjourned.)
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