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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

ANESTHESIOLOGY AND RESPIRATORY  
THERAPY DEVICES PANEL

Monday, July 16, 2001

12:10 p.m.

Room 020B  
9200 Corporate Boulevard  
Rockville, Maryland

MILLER REPORTING COMPANY, INC.  
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P R O C E E D I N G S

## Call to Order

DR. PROUGH: The meeting of the Anesthesiology and Respiratory Therapy Devices Panel will now come to order.

We would like to begin by asking the panel members to introduce themselves. Why don't we begin with Dr. Hudson.

DR. HUDSON: I am Len Hudson from the University of Washington at Seattle.

DR. ROIZEN: I am Mike Roizen from SUNY Upstate in Syracuse.

DR. MUELLER: Robert Mueller from the University of North Carolina at Chapel Hill.

DR. SESSLER: Curt Sessler, Virginia Commonwealth University.

MR. AMATO: Michael T. Amato, Monaghan Medical Corporation.

DR. GARMAN: Tom Garman, InCharge Institute of America.

DR. BAZARAL: Michael Bazaral. I am a medical officer at the FDA and the Executive Secretary for this panel.

DR. PROUGH: Don Prough. I am from the University of Texas Medical Branch in Galveston.

1 DR. SCHROEDER: Becky Schroeder. I am  
2 from the Uniformed Services University of the  
3 Health Sciences.

4 DR. KIRTON: Orlando Kirton from the  
5 University of Connecticut, School of Medicine.

6 DR. DeMETS: David DeMets, University of  
7 Wisconsin at Madison.

8 DR. ZUCKERMAN: Bram Zuckerman, Deputy  
9 Director, DCRD.

10 DR. PROUGH: The next item on the agenda  
11 are some announcements. Dr. Bazaral.

12 **Announcements**

13 DR. BAZARAL: Yes. The first announcement  
14 are the appointments to temporary voting status.  
15 Dr. Feigel appointed several persons to this panel,  
16 and I will read his appointment memo.

17 "Appointment to temporary voting status.  
18 Pursuant to the authority granted under the Medical  
19 Devices Advisory Committee Charter dated October  
20 27th, 1990, as amended August 18, 1999 and November  
21 16, 1999, I appoint the following individuals as  
22 voting members of the Anesthesiology and  
23 Respiratory Therapy Devices Panel for the meeting  
24 on July 16, 2001: David DeMets, Ph.D., Leonard  
25 Hudson, M.D., Robert Mueller, Ph.D./M.D., Michael

1 Roizen, M.D., Curtis Sessler, M.D.

2 "In addition, I appoint Donald Prough,  
3 M.D. to act as temporary chair for the duration of  
4 this meeting.

5 "For the record, Dr. Sessler is a  
6 consultant to the Pulmonary Allergy Drugs Advisory  
7 Committee of the Center for Drug Evaluation and  
8 Research. Dr. Prough is a voting member of this  
9 panel, and the other individuals are consultants to  
10 this panel or other panels under the Medical  
11 Devices Advisory Committee.

12 "They are special government employees who  
13 have undergone the customary conflict of interest  
14 review and have reviewed the material to be  
15 considered at this meeting."

16 Signed David W. Feigel, Director, Center  
17 for Devices and Radiological Health, 6-28-01.

18 I will also read the Conflict of Interest  
19 Statement for the open session.

20 The Anesthesiology and Respiratory Therapy  
21 Devices Panel meeting of July 16, 2001, Conflict of  
22 Interest Statement.

23 The following announcement addresses  
24 conflict of interest issues associated with this  
25 meeting and is made as a part of the record to

1 preclude even the appearance of an impropriety.

2           To determine if any conflict existed, the  
3 Agency reviewed the submitted agenda and all  
4 financial interests reported by the committee  
5 participants. The conflict of interest statutes  
6 prohibit special government employees from  
7 participating in matters that could affect their or  
8 their employer's financial interests. However, the  
9 Agency has determined that participation of certain  
10 members and consultants, the need for whose  
11 services outweighs the potential conflict of  
12 interest involved is in the best interests of the  
13 government.

14           A waiver has been granted to Dr. Rebecca  
15 A. Schroeder for her financial interest in a firm  
16 at issue that could potentially be affected by the  
17 panel's deliberations. The waiver allows this  
18 individual to participate fully in today's  
19 deliberations.

20           Copies of this waiver may be obtained from  
21 the Agency's Freedom of Information Office, Room  
22 12A-15, of the Parklawn Building.

23           In the event that the discussions involve  
24 any other products or firms not already on the  
25 agenda, for which an FDA participant has financial

1 interest, the participant should excuse himself or  
2 herself from such involvement, and the exclusion  
3 will be noted for the record. With respect to all  
4 other participants, we ask in the interest of  
5 fairness that all persons making statements of  
6 presentations disclose any current or previous  
7 financial involvement with any firm whose products  
8 they may wish to comment upon.

9 I will elaborate briefly on that. Persons  
10 who are making a presentation should, at the  
11 beginning of the presentation, identify themselves  
12 and should state if they have a relationship to the  
13 manufacturer of the device under review or to the  
14 manufacturer of a potential competitor of this  
15 device. The relationship may be as an employee of  
16 a manufacturer, as having stockholding or other  
17 ownership interest, as a paid consultant, or as a  
18 person whose travel and lodging for this meeting  
19 was paid by the manufacturer.

20 That completes the announcements.

21 DR. PROUGH: Thank you. We will now begin  
22 the open public hearing.

23 **Open Public Hearing**

24 Prior to this meeting, there have been no  
25 requests from the public to be scheduled to make a

1 presentation. If there are members of the public  
2 who would like to make a presentation, please let  
3 me know now.

4 [No response.]

5 DR. PROUGH: Since there are no  
6 individuals who request to make a presentation, I  
7 would like to ask Mr. Stenzler to begin the  
8 sponsor's presentation of SensorMedics 3100B.

9 Sponsor Presentation

10 SensorMedics Corporation Device 3100B

11 High Frequency Oscillatory Ventilator

12 Alex Stenzler

13 MR. STENZLER: Thank you very much. My  
14 name is Alex Stenzler. I am Vice President of  
15 Advanced Technologies for SensorMedics Corporation.  
16 I am an employee. I have no ownership in the  
17 corporation.

18 I would like to thank the FDA for  
19 convening this panel today, particularly Dr.  
20 Bazaral and Mr. Noe for their assistance in the  
21 preparation of materials as far as what we had to  
22 prepare.

23 The outline of what we will be presenting  
24 today. I will be introducing the people presenting  
25 on behalf of SensorMedics and the 3100B, a little

1 bit of background on how high frequency in the  
2 3100B works, the controls, so you will have an  
3 understanding of those. Dr. Bazaral asked us to  
4 provide that.

5 A little bit about the difference between  
6 the 3100A and the 3100B, a little bit about past  
7 data and prior FDA approvals for sale.

8 Dr. Derdak will present the clinical trial  
9 data, the trial and the results.

10 Then, we will have a discussion of the  
11 study hypotheses, limits of effectiveness, and then  
12 I will present education and training programs,  
13 future research, and then obviously we will be  
14 available to answer questions.

15 [Slide.]

16 Representing SensorMedics and 3100B at  
17 this meeting is myself, Thomas Bachman, who is  
18 President of Econometrix, and he was the study  
19 monitor for the 3100B trial; Colonel Stephen  
20 Derdak, who is in Critical Care Medicine at  
21 Williford Hall Medical Center, Lackland Air Force  
22 Base in San Antonio, who was the study PI, and Dr.  
23 Thomas Stewart, who is in Critical Care Medicine at  
24 Mt. Sinai Hospital, Toronto, Canada, who was the  
25 site PI and the current trial PI for one of our

1 future trials.

2 [Slide.]

3 This is a picture of the 3100B just so you  
4 can see what the device looks like.

5 [Slide.]

6 The 3100B has an electrically-powered,  
7 electronically controlled piston diaphragm, so we  
8 have an electromagnetic piston. It can generate  
9 mean airway pressures between 3 and 55 cm of water,  
10 can produce pressure wave amplitudes for  
11 ventilation between 8 and approximately 140 cm of  
12 water, runs at a frequency of 3 to 15 hertz, which  
13 is the equivalent of 180 to 900 breaths a minute,  
14 and a variable inspiratory time 30 to 50 percent,  
15 and has flow rates of 0 to 60 liters per minute.

16 [Slide.]

17 This is what the piston looks like, the  
18 actual driver. Again, it is electrically powered.

19 [Slide.]

20 It is basically a large subwoofer. We  
21 have a voice coil just in a loudspeaker with a  
22 permanent magnet in the back and we entrain air up  
23 front which controls the mean airway pressure, and  
24 this piston slides back and forth just as though it  
25 were a loudspeaker to create a wave form.

1 [Slide.]

2 This is what the front panel looks like.

3 The mean airway pressure is controlled by the rate  
4 at which we let gas into the circuit or by how fast  
5 we let it escape with a control knob here. It is  
6 just like a CPAP device that you allow gas flow in,  
7 controls the pressure in the circuit, and how much  
8 you resist its exit is controlled here, and that  
9 gives you the mean airway pressure directly on the  
10 screen. So, we set mean airway pressure directly  
11 with this device.

12 [Slide.]

13 The mean airway pressure is used to  
14 inflate the lung--I am certain many of you have  
15 seen this slide of an excised lung--this is the  
16 inflation limb reflected in this pressure volume  
17 curve. This is the deflation limb.

18 As we increase surface area by increasing  
19 mean airway pressure, we go up the inflation limb,  
20 coming down the deflation limb we set at a much  
21 lower pressure, but a much higher volume,  
22 typically, this type of difference in lung  
23 inflation. So, lung inflation is directly related  
24 to oxygenation with this device.

25 [Slide.]

1           The oscillation wave form is a little bit  
2 different than in conventional ventilation. One of  
3 the proposed benefits of high frequency is that in  
4 conventional ventilation, the pressure measured at  
5 the airway opening, the fidelity of that is  
6 continued on, so at the carina, the pressure is  
7 done by Gestmann, published in the eighties. The  
8 pressure at the carina, as well the alveolar level,  
9 measured alveolar capsules, the pressures are quite  
10 high, similar to airway opening.

11           In high-frequency oscillation, because the  
12 respiratory frequency is so high, the time for  
13 inspiration is so short, there is a significant  
14 attenuation that these large pressure wave forms at  
15 the airway opening are attenuated at the carina and  
16 further attenuated down at the alveolar level.

17           In small animal models, such as this, this  
18 is done in adult rabbits, the attenuation drops  
19 down to about 5 to 10 percent of the pressure at  
20 the airway opening. Similar data, we have  
21 collected in larger animal models demonstrates  
22 somewhere between 5 and 20 percent because of the  
23 larger endotracheal tube, so we still see  
24 significant attenuation.

25           [Slide.]

1           That control, this is the ventilation  
2 control panel, and there are three knobs here. The  
3 primary control of the CO<sub>2</sub> is by the stroke volume,  
4 how big its pressure amplitude is, recorded here as  
5 amplitude, and that is controlled by this power  
6 knob. You basically control the amount of voltage  
7 going to the piston, which controls how fast it  
8 goes back and forth, and this amplitude is the  
9 primary control of CO<sub>2</sub>.

10           [Slide.]

11           High-frequency alveolar ventilation is a  
12 little different than conventional. Conventional  
13 alveolar ventilation is typically defined as  
14 frequency times tidal volume. In alveolar  
15 ventilation, it is typically you refer to as  
16 frequency times tidal volume squared. If it's not  
17 number of species dependent, it may go as high as  
18 over 2.5 to 3, and down to 1.5, but the main  
19 determinant is volume change. So, as you change  
20 volume, you have the greatest impact on  
21 ventilation.

22           [Slide.]

23           Inspiratory time also controls ventilation  
24 to a certain extent because it controls the  
25 duration of the piston moving to and fro within the

1 circuit. Increase in the inspiratory time will  
2 also affect lung recruitment as well as  
3 ventilation. The more time the piston is moving  
4 forward, the more time there is for gas to get  
5 across the endotracheal tube and into the lung for  
6 ventilation.

7 [Slide.]

8 The last parameter that controls  
9 ventilation is the frequency, and typical  
10 frequencies that we talk about for the ventilator  
11 is 3 to 15 hertz. In the adult population, it is  
12 typically 3 to 8 hertz. The lower the frequency,  
13 conversely, as you normally think about  
14 conventional ventilation, as you lower frequency,  
15 you decrease alveolar ventilation.

16 With high frequency, as you decrease the  
17 frequency, you actually increase alveolar  
18 ventilation, because as the frequency decreases,  
19 your inspiratory time gets longer, there is more  
20 time for gas to get across the endotracheal tube,  
21 and therefore, the tidal volume squared, the  
22 benefits of a lower frequency is the greater  
23 volume, therefore, ventilation goes up.

24 [Slide.]

25 The 3100A, remember this is a supplement

1 to the 3100A, it was approved in 1991 for  
2 ventilatory support of newborns. Then, in 1994, we  
3 came back with another randomized controlled trial,  
4 and it was approved for the support and treatment  
5 of selected pediatric patients who were failing  
6 conventional ventilation.

7 There was no upper weight limit defined  
8 for the 3100A. It was actually an age limit only  
9 at the time.

10 [Slide.]

11 Prior to that time and since that time,  
12 there have been 8 prospective, randomized,  
13 controlled trials in infants and children, a total  
14 of 1,100 newborns and children have been randomized  
15 to high frequency or control arm studies, and these  
16 are the 8 studies.

17 This last one was just finished in 2001,  
18 and was for 481 babies, so it was a very large  
19 trial.

20 [Slide.]

21 These trials have demonstrated many  
22 benefits of high frequency or proposed benefits.  
23 Not all the trials have found the same benefits,  
24 some have found selected pieces of them, but for  
25 the most part, high frequency has been found to be

1 a beneficial adjunct for treating respiratory  
2 failure in children and newborns.

3 [Slide.]

4 The key differences between the devices,  
5 the 3100A is presently approved, and the 3100B that  
6 we are here to present, the flow rate through the  
7 system goes from 40 to 60 liters per minute. Mean  
8 airway pressure has increased by 10 cm. Delta  
9 pressure, approximately 140. Frequency and I time  
10 are the same. We have automated the centering of  
11 the piston from a manual control to automatic  
12 control. Those are really the only differences  
13 between the devices.

14 [Slide.]

15 To date, there have been more than 1,900  
16 3100A's shipped worldwide. Based upon our sales of  
17 circuits, we estimate that 32,000 patients are  
18 treated annually with the 3100A. In the U.S., we  
19 estimate that 88 percent of all level 3 nurseries  
20 and 75 percent of all PICUs have 3100A's for  
21 treating their patients.

22 [Slide.]

23 The purpose of this presentation to the  
24 panel is to enable the panel to determine if we  
25 have demonstrated that the 3100B is a safe and

1 efficacious ventilator for treating patients with  
2 respiratory failure, and recommend that the FDA  
3 approve us to introduce the 3100B into commercial  
4 distribution in the U.S.

5 Now, Dr. Derdak will present the clinical  
6 data, the trial design and clinical data.

7 **Trial Design and Clinical Data**

8 **Stephen Derdak, D.O.**

9 [Slide.]

10 DR. DERDAK: The specific aim of the  
11 randomized, controlled trial was to demonstrate the  
12 safety and effectiveness of the 3100B for the  
13 treatment of ARDS in the adult population.

14 [Slide.]

15 The center was a multicenter with 13  
16 university-affiliated centers participating. A  
17 sample size of 148 patients was estimated based on  
18 pediatric trials, such that there be a 95 percent  
19 confidence interval that high frequency was  
20 comparable to, but at least not 10 percent worse  
21 than conventional ventilation, and that power to  
22 detect a 20 percent difference in key adverse  
23 outcomes, such as intractable hypotension and  
24 oxygenation or ventilation failure.

25 DR. PROUGH: Before you go on, could you

1 please let us know what relationship, if any, you  
2 have to the manufacturer?

3 DR. DERDAK: I am sorry. This is the  
4 first time I have done this, I am sorry.

5 I was the principal investigator for the  
6 multicenter study. SensorMedics provided the test  
7 oscillators to each center including our own  
8 center. We also received research funding for a  
9 research respiratory therapist, and SensorMedics  
10 provided funding for attendance at this meeting and  
11 for two principal investigator meetings.

12 I have no stock in the company, nor have I  
13 received honoraria from SensorMedics for  
14 presentation of this data. Is that sufficient?

15 DR. PROUGH: Thank you.

16 DR. DERDAK: The computer randomization  
17 occurred at each site and was structured such that  
18 a difference of not more than two patients could  
19 occur between study groups with a oxygenation index  
20 greater than 40, which in previous pilot studies  
21 has suggested a worse prognosis.

22 All patients were analyzed by intention-  
23 to-treat.

24 [Slide.]

25 Eligibility criteria for the study

1 included a diagnosis of ARDS with a P:F ratio less  
2 than 200, on PEEP greater than 10, so it is  
3 different than the European Consensus Conference  
4 because of the addition of PEEP. Bilateral  
5 infiltrates on chest x-ray and no clinical evidence  
6 of congestive heart failure, or if measured, a  
7 wedge pressure at less than 18. A wedge pressure  
8 measurement was not required for entry into the  
9 study.

10 Surrogate consent was obtained and 148  
11 patients were recruited over this time interval.

12 [Slide.]

13 Exclusion criteria included age less than  
14 16, weight less than 35 kilos. Again, this was the  
15 cutoff from the pediatric trial, so we included  
16 patients greater than 35 kilos. A diagnosis of  
17 severe asthma or severe obstructive lung disease,  
18 intractable shock, severe air leak score greater  
19 than 3, which generally was more than 3 chest tubes  
20 in our scoring system.

21 They could have bilateral pneumothorax  
22 with one chest tube on each side, but if they  
23 required more than two chest tubes, they put them  
24 into this category. If they had an FiO<sub>2</sub> more than  
25 80 percent for more than 48 hours, and if they had

1 a non-pulmonary terminal diagnosis, they were  
2 excluded.

3 [Slide.]

4 These are the demographics at baseline.  
5 Seventy-five patients were randomized to high  
6 frequency, 73 patients to conventional ventilation,  
7 and you can see that the patients were well matched  
8 in age, weight in kilos, Apache II scores, the  
9 percentage of patients with sepsis, which required  
10 a positive blood culture, pneumonia, trauma,  
11 impaired immunity, and the percentage of patients  
12 who had some evidence of air leak.

13 [Slide.]

14 The physiologic parameters at baseline  
15 also was well matched. The numbers indicate the  
16 mean, and the brackets are the standard deviation,  
17 75 and 73 patients. You can see that the peak  
18 inspiratory pressures at baseline prior to starting  
19 the study was 39 and 38, PEEP of 13, mean airway  
20 pressure at 22, tidal volume in actual body weight,  
21 mL per kilo, actual body weight, 8 mL per kilo and  
22 7.8.

23  $FiO_2$ ,  $PO_2$ , oxygenation index 24 and 27.

24 The oxygenation index is the mean airway pressure  
25 times the  $FiO_2$  divided by the  $PO_2$ . It is the

1 pressure cost of oxygenation or correction of P:F  
2 ratio for mean airway pressure.

3 The mean arterial blood pressure and the  
4 cardiac output, you can see were well matched.  
5 There were no significant differences in any of  
6 these variables at baseline.

7 [Slide.]

8 The number of days on conventional  
9 ventilation prior to starting the study, mean days  
10 was 2.7 and 4.4 in the high frequency and  
11 conventional groups. Median days were closer.  
12 There was an outlier in the conventional  
13 ventilation group, but median days was very close,  
14 1.8 and 2.0.

15 The percentage of patients on conventional  
16 ventilation more than 4 days prior to randomization  
17 of the study was 22 percent and 36 percent. These  
18 were not statistically significant differences.

19 [Slide.]

20 The goals of the ventilator strategies for  
21 both arms were similar, was to normalize lung  
22 volume and minimize peak ventilator pressures, but  
23 the physiologic targets were identical in both  
24 groups, saturation greater than or equal to 88  
25 percent.

1 Weaning would not occur until  $FiO_2$  was  
2 below 50 percent, and the pH goal was to maintain a  
3 pH greater than 7.15 with the expectation that  $PCO_2$   
4 would be in the range of 40 to 70 to achieve this  
5 goal. This was not a strict requirement, however.  
6 So, SAT 88, weaning did not occur until  $FiO_2$  was  
7 below 50 percent.

8 [Slide.]

9 The strategy of high-frequency ventilation  
10 is referred to as an open lung strategy whereby the  
11 mean airway pressure on conventional ventilation is  
12 used to set the mean airway pressure on high  
13 frequency plus 5 cm. So, we use a higher mean  
14 airway pressure by design when we start high-  
15 frequency ventilation.

16 If the patient is unable to improve their  
17 saturation, such that the  $FiO_2$  is more than 60  
18 percent, the mean airway pressure is then increased  
19 in 2 to 3 cm increments every 20 to 30 minutes  
20 until you achieve a maximum mean airway pressure of  
21 45 cm, again, the goal being to achieve a  
22 saturation greater than 88 percent.

23 The inspiratory time set on the ventilator  
24 was left at 33 percent.

25 [Slide.]

1           The ventilation strategy was to primarily  
2 adjust the delta P with the initial setting of  
3 delta P at starting high frequency to achieve chest  
4 wall vibration to the level of the mid-thigh, and  
5 then increasing in 10 cm increments by adjusting  
6 power if the CO<sub>2</sub> is rising to a maximum delta P of  
7 between 90 and 100.

8           The starting frequency was 5 hertz or 300  
9 breaths per minute, and this could be decreased to  
10 3 hertz if delta P had been maximized to achieve  
11 additional CO<sub>2</sub> elimination, followed by inducing an  
12 endotracheal cuff leak if the CO<sub>2</sub> continued to be  
13 high with the pH goal not being met assuming we  
14 have already maximized delta P and decreased the  
15 hertz. Again, these were our physiologic goals.

16           [Slide.]

17           The conventional ventilation arm used a  
18 pressure control strategy, and remember the study  
19 was designed really back in 1996, and at that point  
20 it was not clear if volume cycled to pressure  
21 cycled was a preferred mode, but we chose a  
22 pressure control mode with a tidal volume of 6 to  
23 mL per kilo of actual body weight adjusted based on  
24 patient's pH and ventilation, PEEP of 10 cm, which  
25 was required at baseline, could be increased to 18

1 cm, and the I:E ratio could be increased as far out  
2 as 2 to 1, but required a PEEP of 18 cm before that  
3 was done.

4           The same physiologic goals. Again, this  
5 was a guideline, not a strict goal, but the pH of  
6 7.15 was a goal. Weaning occurred when the  $FiO_2$   
7 was reduced to 40 percent and the PEEP was 5, the  
8 patient has pressure support trials.

9           Actual extubation was not protocolized as  
10 part of the study, and was left up to the  
11 discretion of the attending team.

12           [Slide.]

13           This shows some of the data from the  
14 ventilators. The mean airway pressure over the  
15 first 72 hours of treatment in the high-frequency  
16 arm versus the conventional arm, and you can see  
17 there is about a 6 cm difference here, and this is  
18 by design. The oscillator is deliberately set at a  
19 higher mean airway pressure, and you can see that  
20 over time, there was a gradual decrease, but at all  
21 time points conventional ventilation had a lower  
22 mean airway pressure than did high frequency, which  
23 was significant.

24           [Slide.]

25           The arterial blood gas data, the P:F ratio

1 over the first 72 hours of treatment. You can see  
2 that the high-frequency group, in black, had an  
3 early oxygenation improvement, again, during higher  
4 mean airway pressures, an early oxygenation  
5 improvement, which by 48 hours was similar to  
6 conventional ventilation. The significance was in  
7 the first 24 hours of an improved P:F ratio  
8 compared to conventional ventilation.

9 [Slide.]

10 This shows you the oxygenation index data.  
11 Again, the oxygenation index mean airway pressure  
12 times F:P ratio or pressure costs of oxygenation  
13 was essentially identical between the two forms of  
14 ventilation with no significant difference between  
15 high frequency and conventional ventilation.

16 Both groups showed a decrease in  
17 oxygenation index consistent with improvement, but  
18 no difference between high frequency or  
19 conventional.

20 [Slide.]

21 This shows the PCO<sub>2</sub> data over the first 72  
22 hours, and you can see that in the high-frequency  
23 group, PCO<sub>2</sub>'s averaged about 5 to 6 mm of mercury  
24 higher during high frequency, in the range of 45 to  
25 50, compared to the conventional ventilation group.

1 This was still well within the physiologic range  
2 that we had set out as a guideline.

3 [Slide.]

4 This shows our primary outcome data at 1  
5 month. In the high-frequency arm and the  
6 conventional arm, 75 and 73 patients, the  
7 percentage of patients alive, requiring no  
8 respiratory support or supplemental oxygen at 30  
9 days was 21 percent and 26 percent, and this was  
10 not statistically significantly different.

11 The patients alive with respiratory  
12 support, which could include any supplemental  
13 oxygen or any form of mechanical ventilation  
14 including noninvasive mechanical ventilation, was  
15 41 percent in the high-frequency group and 21  
16 percent in the conventional arm.

17 Mortality data in the high-frequency group  
18 showed 37 percent mortality at 30 days versus 52  
19 percent mortality in the conventional group and  
20 there is the p value of 0.098. The p value for  
21 this was 0.014.

22 [Slide.]

23 This shows 6-month outcome data showing  
24 that the percentage of patients alive on the high-  
25 frequency arm was 53 percent versus 38 percent in

1 the conventional group. This did not achieve a p  
2 value less than 0.05. The number of patients alive  
3 and still requiring respiratory support was zero in  
4 high frequency, whereas, some patients still  
5 required supplemental oxygen or ventilatory support  
6 in the conventional arm. The mortality in the  
7 high-frequency group was 47 percent at 6 months  
8 compared to 59 percent in the conventional group.  
9 Again, it did not achieve statistical significance  
10 because of the sample size.

11 [Slide.]

12 This shows the overall survival for all  
13 patients randomized to high-frequency versus  
14 conventional ventilation, and at the 30-day point,  
15 and at the 90-day point with the corresponding p  
16 values. Again, not less than 0.05.

17 [Slide.]

18 Secondary outcomes including adverse  
19 outcomes are displayed here. Intractable  
20 hypotension was defined as a mean pressure less  
21 than 60 for 4 hours or less than 50 mm for 1 hour.  
22 We did very well in high frequency in terms of  
23 hemodynamic stability. No significant differences  
24 here. The worsening or new air leak 9 percent, 12  
25 percent, no significant difference and comparable

1 to other recent ARDS trials.

2           The percentage of patients who had  
3 oxygenation failure, defined as an oxygenation  
4 index more than 42 at 48 hours, 5 percent and 8  
5 percent, no significant difference. Ventilation  
6 failure, no significant difference. Mucus plugging  
7 requiring the urgent change of an endotracheal tube  
8 was similar in both groups with 2 patients in both  
9 groups.

10           [Slide.]

11           Thirty-day mortality causes is listed  
12 here. The percentage of patients with multi-organ  
13 failure was similar in both groups, no statistical  
14 difference, as were hypoxemia, and the percentage  
15 of patients who had care withdrawn as part of their  
16 death was similar in both groups. There was no  
17 significant differences.

18           [Slide.]

19           Post-hoc analysis was done in order to  
20 look at possible pre-study indicators of response  
21 to high frequency, as well as post-treatment  
22 indicators, the oxygenation index, that would  
23 indicate survival or response to treatment.

24           [Slide.]

25           In terms of post-study or post-entry

1 criteria or predictors of outcome, the oxygenation  
2 index was the only predictor that showed a  
3 difference in outcome for survival, and this shows  
4 that the risk of death was increased about 2  
5 percent for every oxygenation index increase at 16  
6 hours.

7           Oxygenation index predicted mortality, but  
8 did not show a difference between the high  
9 frequency and the conventional ventilation group.

10           [Slide.]

11           In terms of pre-treatment variables that  
12 would indicate response or it might show a  
13 difference in mortality, for the high-frequency  
14 group, among parameters that were looked at  
15 including P:F ratio,  $FiO_2$ , Apache scores, days on  
16 mechanical ventilation, only the median peak  
17 inspiratory pressure showed a difference in  
18 mortality between high frequency versus  
19 conventional groups. 38 cm was the median peak  
20 airway pressure in our combined groups, and this  
21 shows a breakout of the patients randomized to high  
22 frequency versus conventional ventilation who had a  
23 median peak pressure less than 38.

24           It shows the peak pressure of the PEEPs,  
25 the tidal volumes, which were similar in both

1 groups, so the compliances presumably were similar,  
2 that is an assumption. P:F ratios, oxygenation  
3 index, Apache score similar, but the mortality was  
4 26 percent in the high-frequency group and 52  
5 percent in the conventional group. Again, this is  
6 a retrospective, post-hoc analysis of patients who  
7 had a peak airway pressure at less than 38, and  
8 there was a significant change in mortality here.

9 At 6 months, the mortality difference was  
10 preserved, as well.

11 [Slide.]

12 This shows the survival curves in patients  
13 who had peak pressures less than 38 at the time of  
14 entry into the study, again showing the improvement  
15 in mortality of high frequency versus conventional.

16 [Slide.]

17 Our conclusions are that high-frequency  
18 ventilation oscillatory ventilation is associated  
19 with a nonsignificant difference in 30-day survival  
20 with or without respiratory support. There was  
21 also a nonsignificant absolute reduction in the 1-  
22 month mortality. The percentage was a 15 percent  
23 reduction, and at 6 months, a reduction of 12  
24 percent, however, we did not achieve statistical  
25 significance.

1           There was no significant difference in the  
2 adverse outcomes of air leak, hypotension,  
3 oxygenation failure, ventilation failure, or  
4 plugging requiring an endotracheal tube. We feel  
5 the data supports the premise that high frequency  
6 is effective and that it is safe for the use in  
7 ARDS.

8           MR. STENZLER: Tom Bachman will now  
9 discuss hypotheses and limits of effectiveness.

10                   **Hypotheses and Limits of Effectiveness**

11                                   **Thomas Bachman**

12           MR. BACHMAN: My name is Tom Bachman. I  
13 am a consultant to SensorMedics. I don't have any  
14 stock in the company, and my expenses were paid for  
15 on this trip.

16           I am going to touch very briefly on three  
17 areas, the objective of the study specifically from  
18 the IDE relating to the hypotheses and questions  
19 about limits of effectiveness.

20                   [Slide.]

21           The objective of the study, as stated, was  
22 to demonstrate the safety and effectiveness of the  
23 3100 for ventilatory support and treatment of  
24 patients, large children and adults with ARDS.

25                   [Slide.]

1           The effectiveness hypothesis used an  
2 endpoint of death or respiratory support at 30 days  
3 as Dr. Derdak said. There was a definition of  
4 respiratory support that involved continued  
5 mechanical ventilation, noninvasive ventilation, or  
6 need for oxygen.

7           The criteria for that endpoint was that in  
8 a comparability study, was that the data would show  
9 that HFOV was not worse than 10 percentage points  
10 than the outcome with conventional ventilation.

11           As you can see in the Result Section, in  
12 fact, the incidence of death or respiratory support  
13 was very high in this study. The confidence limits  
14 are that high frequency could be 10 percent better,  
15 but it could be somewhere in between 10 percent  
16 better and 20 percent worse. We did not satisfy  
17 this hypothesis, the primary one for effectiveness.

18           [Slide.]

19           The safety hypotheses revolved around  
20 three prospectively defined parameters - death at  
21 30 days, intractable hypotension, which Dr. Derdak  
22 stated the definition of, and then development of a  
23 new air leak during the study. As you can see  
24 here, there is a slight trend towards a benefit in  
25 mortality of the high-frequency patient, the

1 incidence of intractable hypotension and new air  
2 leaks are very low and quite comparable.

3 [Slide.]

4 Finally, with regard to limits of  
5 effectiveness, we had a prospectively defined  
6 oxygenation failure and ventilation failure built  
7 into the study, and the incidence of both of those  
8 in both ventilators were low and low and  
9 comparable, so that we didn't identify any  
10 particular limit of effectiveness.

11 MR. STENZLER: One of the areas that Dr.  
12 Bazaral asked us to address was our training  
13 programs and support of customers that would have  
14 this device for treating patients.

15 [Slide.]

16 SensorMedics for both the 3100A for  
17 neonatal applications, 3100A for pediatric  
18 applications, has run training courses. The  
19 neonatal course, we run about 10 of them a year.  
20 It is a 2 1/2 day course. Our pediatric course  
21 runs about four times a year. It is a 2-day formal  
22 training program. Both of these are physician-  
23 provided and directed courses, and include animal  
24 laboratories where the physicians receiving  
25 training can get some hands-on experience with

1 physiologic models.

2 We have used this same training program,  
3 and we did provide an outline of what the program  
4 looks like to the panel, and we have used that same  
5 training program for the study investigators, as  
6 well.

7 We provide a significant amount of visual  
8 and printed training materials including videotapes  
9 and what we call critical care reviews, which  
10 discuss clinical applications. We have on-site  
11 clinical training specialists that go to the  
12 hospitals and do training specifically on the  
13 clinical applications and device applications, both  
14 patient and device management.

15 We have a 24-hour technical and clinical  
16 support hot line, and we have 85 depots across the  
17 U.S. where we have machines available for loaners,  
18 so if someone owns a unit and they have a problem  
19 with it, or they need a second patient, this is  
20 also a 24-hour-a-day, 7-day-a-week service.

21 [Slide.]

22 We have other ongoing research directed at  
23 the 3100B applications. We have several studies  
24 ongoing looking at various degrees of inflammatory  
25 response. We also have several human studies that

1 are either in process or planned. Johns Hopkins  
2 Hospital is looking at lung inflation by CT. The  
3 ARDSNet has a pilot study running at Duke. The  
4 Tools [?] trial, which is an open lung trial, Tom  
5 Stewart, who is here with us today, is the PI for  
6 that study. That is looking at other recruitment  
7 methods for using the 3100B.

8 We have a proposed study looking at post-  
9 op ARDS and inflammatory response from the Cornell  
10 North Shore in New York. We also do registries  
11 where we have an ongoing registry of patients who  
12 have been managed on 3100B.

13 I should point out the 3100B has been  
14 approved for export outside the U.S., and there are  
15 units outside the U.S., so in Canada, it is a  
16 device that can be sold, and they have a registry  
17 running there of patients treated outside the U.S.

18 We also have a European study which is  
19 presently closing down, but it is a randomized  
20 trial. We don't have any data on that. There is a  
21 high frequency with nitric oxide study proposed to  
22 the Drug and Device Division for nitric oxide.  
23 That is in preparation, combining high frequency  
24 with nitric oxide.

25 [Slide.]



1 FDA will also be interested in the panel's  
2 comments and recommendations on specific aspects of  
3 the Model 3100B or the clinical trial.

4 [Slide.]

5 The SensorMedics Model 3100B High-  
6 Frequency Oscillatory Ventilator is a modification  
7 of the Model 3100A, which has an approved PMA.

8 The Model 3100B can provide the larger  
9 pressures and volumes required to ventilate large  
10 children and adults with respiratory failure.

11 [Slide.]

12 A PMA supplement was filed to demonstrate  
13 the safety and effectiveness of the Model 3100B for  
14 ventilatory support and treatment of selected  
15 patients 35 kg and greater with acute respiratory  
16 failure.

17 The PMA supplement includes the results of  
18 the clinical trial under discussion today.

19 [Slide.]

20 In the next several minutes, I will do  
21 five things:

22 First, I will provide a brief regulatory  
23 history of the Model 3100B.

24 Second, I will briefly discuss the  
25 SensorMedics trial and its most important results.

1 Third, I will briefly discuss a recent  
2 clinical trial, the ARDS Network or ARDSNet trial.

3 Fourth, I will relate the results of the  
4 SensorMedics trial and the ARDSNet trial.

5 Finally, in the course of relating the two  
6 trials, I will present FDA's specific questions to  
7 the panel.

8 [Slide.]

9 First, the regulatory history of the Model  
10 3100B

11 [Slide.]

12 A PMA for the SensorMedics Model 3100  
13 high-frequency oscillatory ventilator was approved  
14 in 1991 for treatment of neonates and infants.

15 [Slide.]

16 A PMA supplement was approved for a  
17 modified device, the Model 3100A, in 1995. The  
18 Model 3100A could provide larger pressures and  
19 volumes, and could be used to treat children  
20 weighing up to 45 kg.

21 [Slide.]

22 An IDE proposing the clinical trial of the  
23 Model 3100B for treatment of large children and  
24 adults was approved in 1996, and the trial enrolled  
25 its final patient in December 2000. The data from

1 this trial are those under discussion today.

2 [Slide.]

3 The Model 3100B can provide pressures and  
4 volumes sufficient to ventilate large children and  
5 adults. With respect to the Model 3100A, the Model  
6 3100B has increased maximum mean airway pressure,  
7 increased maximum pressure oscillation amplitude,  
8 and a modified alarm system.

9 The engineering review of the Model 3100B  
10 has been completed, and FDA is satisfied that the  
11 device operates safely and as intended. Minor  
12 labeling changes are probably necessary. Whether  
13 the Model 3100B is safe and effective was beyond  
14 the scope of the engineering review and required  
15 clinical study.

16 [Slide.]

17 Now, I will briefly discuss the methods  
18 and results of the SensorMedics trial. Because Dr.  
19 Derdak has discussed the methods and results in  
20 detail, I will primarily discuss those results  
21 immediately relevant to the questions directed to  
22 the panel.

23 [Slide.]

24 The SensorMedics trial was a multicenter  
25 trial which enrolled 148 patients, randomized to

1 one of two groups. The control group, which  
2 consisted of 73 patients, was treated with  
3 conventional ventilation. The treatment group,  
4 which consisted of 75 patients, was treated with  
5 the Model 3100B high-frequency oscillatory  
6 ventilator.

7 [Slide.]

8 This slide lists the inclusion criteria,  
9 which Dr. Derdak has already discussed.

10 [Slide.]

11 Similarly, this slide lists the exclusion  
12 criteria for the SensorMedics trial.

13 [Slide.]

14 The physiological goals for the two groups  
15 were the same: First, to maintain an oxygen  
16 saturation greater than or equal to 88 percent, and  
17 to maintain pH greater than 7.15.

18 In each group, the treatment priority was  
19 the same.

20 [Slide.]

21 Control group patients were treated using  
22 a conventional ventilator which provided pressure-  
23 limited, volume-controlled ventilation.

24 Tidal volumes between 6 and 10 mL/kg of  
25 actual body weight.

1 As Dr. Derdak explained, PEEP and percent  
2 inspiratory time could be increased, within limits,  
3 to improve ventilation.

4 [Slide.]

5 Treatment group patients were treated  
6 using the Model 3100B high-frequency oscillatory  
7 ventilator. The mean pressure was initially set 5  
8 cm of water higher than the ventilator settings  
9 prior to entry into the trial, and pressure  
10 oscillations were initially provided at a rate of 5  
11 hertz.

12 As Dr. Derdak explained, the magnitude and  
13 frequency of pressure oscillations could be  
14 adjusted to improve ventilation. In some cases,  
15 the cuff of the patient's endotracheal tube was  
16 partially deflated to flush the airway and tube  
17 with fresh gas.

18 [Slide.]

19 Patient outcomes were determined after one  
20 month and six months. The possible outcomes were:  
21 death, survival with respiratory support, or  
22 survival without respiratory support.

23 Only survival without respiratory support  
24 was considered a successful outcome. Both death  
25 and survival with respiratory support were

1 considered unsuccessful outcomes.

2 [Slide.]

3 Respiratory support was defined to include  
4 mechanical ventilation, CPAP, or supplemental  
5 oxygen.

6 [Slide.]

7 The hypothesis to be tested in this trial  
8 can be stated as follows: The proportion of  
9 patients with an unsuccessful one-month outcome,  
10 that is, the proportion of patients who died or who  
11 were still receiving respiratory support after one  
12 month, would be no more than 10 percent greater in  
13 the high-frequency group than in the conventional  
14 group, with 95 percent confidence.

15 If this hypothesis were proven by the  
16 trial, one could conclude that the outcomes in the  
17 two groups are statistically equivalent.

18 [Slide.]

19 So, now I will review the outcomes from  
20 the SensorMedics trial.

21 [Slide.]

22 Comparing the one-month outcomes from the  
23 SensorMedics trial, one observes that in the high-  
24 frequency group, 78 percent of the patients had  
25 unsuccessful outcomes, that is, 78 percent of the

1 patients had died or were still receiving  
2 respiratory support after one month, compared to 73  
3 percent in the conventional group.

4 In addition, one observes that in the  
5 high-frequency group, 37 percent of the patients  
6 had died after one month, compared to 52 percent in  
7 the conventional group. Here, I would like to  
8 clarify that there was an inconsistency in the  
9 slides previously shown. These numbers are correct  
10 for the proportions of patients who died within the  
11 next first month of the trial, 37 percent and 52  
12 percent for the control group.

13 [Slide.]

14 Now, comparing the six-month outcomes, one  
15 observes that in the high-frequency group, 47  
16 percent of the patients had unsuccessful outcomes,  
17 compared to 62 percent in the conventional group.

18 In addition, one observes that in the  
19 high-frequency group, 47 percent of the patients  
20 had died compared to 59 percent in the conventional  
21 group.

22 [Slide.]

23 SensorMedics provided the statistical  
24 analysis presented in this table. This analysis  
25 was verified by John Dawson of FDA.

1 From the table, one can readily make  
2 several observations.

3 [Slide.]

4 The proportion of patients who had  
5 unsuccessful one-month outcomes, that is, the  
6 proportion of patients who died or were still  
7 receiving respiratory support after one month, was  
8 greater in the high-frequency group than in the  
9 conventional group.

10 Based on the 95 percent confidence  
11 interval computed, the treatment in the high-  
12 frequency group could fail as much as 20 percent  
13 more often.

14 [Slide.]

15 The proportion of patients who had died  
16 after one month was lesser in the high-frequency  
17 group than in the conventional group.

18 Based on the 95 percent confidence  
19 interval--this was retrospectively computed--  
20 mortality could be as much as 32 percent lower and  
21 as much as 3 percent higher in the high-frequency  
22 group than in the conventional group.

23 [Slide.]

24 When interpreting the results of the  
25 SensorMedics trial, it is important to note that

1 the conventional group in the trial was treated  
2 according to prevailing practice at the time the  
3 trial was designed. Average tidal volume was 10.2  
4 mL/kg of ideal body weight.

5 Since the beginning of this trial, there  
6 has been increasing appreciation that conventional  
7 ventilation with lower tidal volumes may improve  
8 patient outcomes.

9 [Slide.]

10 Most recently, the results of the ARDS  
11 Network or ARDSNet trial were published in the New  
12 England Journal of Medicine.

13 [Slide.]

14 The ARDSNet trial was a multicenter trial  
15 in which patients were randomized to one of two  
16 groups: a control group, in which patients were  
17 ventilated with "traditional" tidal volumes,  
18 between 10 and 15 mL/kg of ideal body weight; and a  
19 treatment group, in which patients were ventilated  
20 with "lower" tidal volumes, 6 mL/kg of ideal body  
21 weight.

22 [Slide.]

23 Enrollment was stopped after 861 patients.  
24 Mortality was 31 percent in the treatment group  
25 compared to 39.8 percent in the control group.

1 This difference was statistically significant with  
2 a p value of 0.007.

3 This result suggests that conventional  
4 ventilation using lower tidal volumes yields  
5 improved outcomes.

6 [Slide.]

7 Relating the SensorMedics and the ARDSNet  
8 trials.

9 [Slide.]

10 One observes that the mortality rate in  
11 the SensorMedics control group is high compared to  
12 both the control and treatment groups in the  
13 ARDSNet trial.

14 I would also like to point out that the  
15 SensorMedics control group was treated with tidal  
16 volumes similar to those in the control group of  
17 the ARDSNet trial.

18 [Slide.]

19 So, our first question: In light of  
20 current practice, please discuss whether the  
21 control group in the SensorMedics trial alone is  
22 appropriate and reasonable for evaluation of the  
23 Model 3100B High-Frequency Oscillatory ventilator.

24 [Slide.]

25 Recalling that the proportion of patients

1 who had unsuccessful one-month outcomes was greater  
2 in the high-frequency group, but that the one-month  
3 mortality was lower, our second question.

4 [Slide.]

5 Please discuss whether the information  
6 presented provides reasonable assurance that the  
7 Model 3100B is safe and effective.

8 [Slide.]

9 We have two additional questions for the  
10 panel.

11 [Slide.]

12 FDA's evaluation of devices includes  
13 review of the labeling, which must identify the  
14 patients that can be treated with the device,  
15 identify potential adverse effects, and explain how  
16 the product should be used to maximize benefits and  
17 minimize adverse effects.

18 [Slide.]

19 So, our third question. Please comment on  
20 the labeling provided for the Model 3100B.  
21 Specifically, please discuss whether Chapter 8 of  
22 the Operator's Manual, which instructs the user on  
23 treatment strategy, adequately reflects the  
24 protocol and data from the SensorMedics trial;  
25 whether the two-day training program described will

1 adequately prepare physicians to use the Model  
2 3100B, and whether any other specific changes  
3 should be made to the labeling of the device.

4 [Slide.]

5 Finally, please discuss whether additional  
6 clinical follow-up or postmarket studies are  
7 necessary for the Model 3100B.

8 Thank you.

9 DR. PROUGH: Thank you.

10 We are well ahead of schedule. Let's move  
11 directly into committee discussion and plan to take  
12 a break after the open committee discussion and  
13 before the open public hearing, which should be  
14 roughly an hour from now.

15 Dr. Sessler is the primary reviewer for  
16 the panel. He has a brief prepared presentation  
17 and will begin the discussion.

18 Dr. Sessler.

19 **Committee Discussion**

20 DR. SESSLER: Thank you.

21 The preceding presentations clearly have a  
22 wealth of information and what I really distilled  
23 down I think are selected issues that revolve  
24 around the questions posed by FDA, but I have  
25 changed the order a little bit as far as

1 conceptually how I think they might be best  
2 addressed.

3           The first of those is what really are the  
4 primary outcome measures that we should focus on,  
5 as well as addressing the issues of adequacy of  
6 conventional ventilation as a control group, and a  
7 question raised as to mortality in the conventional  
8 ventilation group.

9           [Slide.]

10           The primary efficacy outcome was 30-day  
11 survival without chronic lung disease. I think it  
12 bears perhaps a closer look at what the components  
13 of that definition include, and perhaps asking the  
14 sponsor to provide a little bit more information  
15 about how that broke down.

16           Specifically, we have, on the one hand,  
17 death, and on the other hand, markers of "chronic  
18 lung disease" or continued respiratory support.

19           I think it is obvious to all of us that  
20 supplemental oxygen requirements may be vastly  
21 different than the death of an ICU patient, and I  
22 have some questions about what CPAP actually  
23 represents in the nonventilated patient.

24           So, if I may, I would like to start out by  
25 asking the sponsor to perhaps give us a little bit

1 more information, if this data exists, about what  
2 percent of patients at 30 days met this endpoint  
3 merely through supplemental oxygen, through CPAP,  
4 and through mechanical ventilation.

5 DR. DERDAK: Steve Derdak, the principal  
6 investigator. The percentage of patients that were  
7 on mechanical ventilation versus noninvasive CPAP,  
8 noninvasive ventilation, face mask ventilation, I  
9 don't have that figure for you today, that  
10 breakdown of mechanical versus CPAP requirement.

11 Of the patients that were requiring any  
12 respiratory support, 61 percent required other than  
13 supplemental oxygen in the high-frequency group  
14 versus I think 71 percent or 73 percent--73 percent  
15 in the conventional group.

16 So, of the patients who required  
17 respiratory support, at 30 days, it was  
18 predominantly ventilatory support with roughly  
19 about a third of the patients just on oxygen, but  
20 the breakdown of the mechanical ventilation versus  
21 percent on noninvasive ventilation, I don't have  
22 that figure.

23 DR. SESSLER: One of the concerns I guess  
24 I have about the primary efficacy endpoint I  
25 suppose is mixing in a very hard endpoint of death

1 versus some very soft endpoints including  
2 supplemental oxygen.

3           The other question I have about mechanical  
4 ventilation is one of the potential, I suppose, for  
5 even having longer ventilation in the treatment  
6 arm, that is, the high-frequency arm, because of  
7 the lack of familiarity perhaps with the  
8 clinicians, in terms of that additional step of  
9 weaning the patient from high-frequency to  
10 conventional ventilation prior to where both arms  
11 would enter into the process of weaning from  
12 ventilatory support.

13           DR. DERDAK: I think we have a slide that  
14 shows that, but the mean days on mechanical  
15 ventilation for the high-frequency group was  
16 approximately 22 days, and for the conventional  
17 ventilation group, total days on mechanical  
18 ventilation, about 20 days.

19           In the high-frequency group, the patients  
20 that required the time they spent on high  
21 frequency, the mean value was approximately 6 days.  
22 So, there is additional days on mechanical  
23 ventilation after patients transition to  
24 conventional ventilation, but there was no real  
25 significant difference in total days on mechanical

1 ventilation in either arm of the study.

2 DR. STEWART: I am Tom Stewart. Just  
3 because I didn't say anything previously, I don't  
4 work for SensorMedics, and I have occasionally  
5 received honoraria from SensorMedics or their  
6 affiliate in Canada which supplies their devices.

7 Just to point out, as an investigator in  
8 this, I mean I share your concerns about the  
9 primary outcome, which some people could label as a  
10 failure, in fact, you know, I think as someone who  
11 manages a lot of patients with ARDS, to have oxygen  
12 need at 30 days, it is almost universal, and it is  
13 just no surprise, and my eye automatically goes to  
14 30-day survival and to 6-month survival. In fact,  
15 all the multicenter trials in ARDS on mechanical  
16 ventilation primarily look at that.

17 DR. SESSLER: Thank you. I think the  
18 reason why this moved this up is, first, I think it  
19 is a crucial question really is what is a proper  
20 primary outcome measure that we are interested in  
21 given the potential contamination of the one that  
22 was selected prospectively, and that is including  
23 supplemental oxygen and softer endpoints where the  
24 goal of efficacy was not actually met, but it was  
25 certainly met in terms of an equivalence level for

1 survival and even with a strong trend towards  
2 higher survival in the treatment arm.

3 I would welcome other comments and  
4 questions from the group.

5 DR. HUDSON: Len Hudson. I have the same  
6 question. I just don't think it is an appropriate  
7 primary outcome because I am not aware of any data  
8 actually that is published of the number of  
9 patients that require oxygen at 30 days. So, I  
10 don't think there is anything to compare it to. I  
11 understand from the written material, it probably  
12 came from dealing with neonatal patients, but I  
13 don't think it is really comparable.

14 So, to talk about chronic lung disease at  
15 30 days is inappropriate since we know that these  
16 patients, when they do survive, improve so much  
17 over the next six months that I am more impressed  
18 by the 30-day mortality.

19 I guess the other thing that I am pleased  
20 at is that you reported six-month mortality,  
21 because from the analysis of the ARDS Network study  
22 in a publication that actually has been prepared,  
23 but hasn't been submitted yet one of their  
24 recommendations out of that is going to be that we  
25 need a later endpoint for mortality since there is

1 considerable further death rate, about what was  
2 found in this study, about something like 20  
3 percent more additional deaths after 30 days. So,  
4 I think it is good to be looking at six months.

5 DR. ROIZEN: Mike, maybe you can clarify,  
6 the primary endpoint was one that the company and  
7 FDA staff agreed on beforehand, was it not?

8 DR. SESSLER: 1996.

9 DR. ROIZEN: I mean it wasn't forced on  
10 them.

11 DR. DERDAK: I think that that endpoint  
12 you could view as the best possible outcome, that  
13 is, not on ventilation and requiring no  
14 supplemental support whatsoever, the best possible  
15 outcome. Whether that is a feasible outcome in  
16 adult ARDS trials is arguable.

17 Other surrogates that are used like in the  
18 ARDS Network, ventilator-free days, for example,  
19 multi-organ failure scores, et cetera, but I think  
20 clearly that would be the best possible outcome.  
21 Whether it is a practical outcome to sort out  
22 subtle differences between interventions, I think  
23 is arguable.

24 DR. ROIZEN: To clarify what you said,  
25 what you answered to that prior question was 61

1 percent in the high-frequency group required--

2 DR. DERDAK: Some form of ventilator  
3 support.

4 DR. ROIZEN: Some form of ventilator  
5 support versus 70 percent.

6 DR. DERDAK: Of the conventional group, 73  
7 percent.

8 DR. ROIZEN: And you don't have the data.

9 DR. DERDAK: I don't have the breakout of  
10 that percentage, mechanical ventilation versus  
11 noninvasive ventilation. We may be able to get  
12 that.

13 DR. SESSLER: To make sure I have got this  
14 correct, the 61 percent is actually the percent of  
15 that large group, I think was 47 percent of  
16 patients who were alive and on some sort of  
17 respiratory support, is that correct?

18 DR. DERDAK: Correct.

19 DR. SESSLER: Roughly 21 percent of the  
20 conventional arm that was alive and on--

21 DR. DERDAK: That is correct.

22 DR. SESSLER: Those percentages are of  
23 those subsets, I guess.

24 DR. DERDAK: That is correct, of the  
25 patients alive and with respiratory support, that

1 was the percentage that required mechanical.

2 DR. SESSLER: Thirty-day and six-month  
3 survival seem like logical endpoints, in keeping  
4 with other ARDS trials.

5 DR. DERDAK: Actually, in the study, I  
6 don't believe we had deaths after 90 days, even at  
7 the three-month point, so that three months was  
8 really a very good cutoff, as well, and that might  
9 be looked at in future studies, as well, but 30  
10 days, three months, six months.

11 DR. SESSLER: One additional question I  
12 have that relates to the issue of mechanical  
13 ventilation I guess, we may need to consider  
14 revisiting when addressing what other information  
15 might be useful, and that is, given that clinicians  
16 may be dealing with a process that they are not  
17 terribly familiar with, how can we facilitate the  
18 ability to wean patients in a timely fashion.

19 In other words, one potential down side is  
20 that these folks are on the ventilator longer, and,  
21 in fact, that might be supported by the data that  
22 you showed. How can we optimize timely weaning  
23 from high-frequency to conventional ventilation, so  
24 that we don't actually have a longer or fewer  
25 ventilator-free days?

1 DR. DERDAK: The total time on mechanical  
2 ventilation was really quite similar, 20 days  
3 versus 22 days. The weaning algorithm other than  
4 reducing  $FiO_2$  to 40 percent and then PEEP to 5 to  
5 do spontaneous breathing trials wasn't carefully  
6 protocolized, in other words, the weaning was left  
7 up to the physician team, once they met criteria of  
8 40 percent and 5 at PEEP.

9 I think we still argue about which are the  
10 best ways to do final weaning to extubation,  
11 whether to do spontaneous breathing trials, et  
12 cetera. I think that with the experience we have  
13 had using the oscillator, that we I think have  
14 consensus, probably between Tom and I, that once  
15 you have achieved a low  $FiO_2$  and you have gradually  
16 worked the mean airway pressure down, as the mean  
17 airway pressure approaches 20, one can switch back  
18 over to conventional ventilation and easily  
19 achieve those kinds of mean airway pressures on  
20 conventional ventilation and maintain oxygenation.

21 How fast we can accelerate the weaning of  
22 mean airway pressure on high frequency once you  
23 have already lowered the  $FiO_2$ , I think is subject  
24 to debate. In other words, I think that practice  
25 styles may differ in terms of just like how quickly

1 we wean PEEP down in the patient who has achieved  
2 an  $\text{FiO}_2$  of 40 percent. Some will come more  
3 aggressively, quickly down on PEEP, others will  
4 more gradually come down on PEEP.

5 I don't think we have carefully  
6 protocolized yet how often one should--I mean that  
7 would impact probably on how many total days  
8 someone would have on mechanical ventilation., but  
9 irregardless, I think it is quite remarkable that  
10 in the two groups, we were that close in terms of  
11 total days on mechanical ventilation including the  
12 fact that the high-frequency groups spent six days  
13 on average on high frequency with the remainder of  
14 the days on conventional.

15 DR. STEWART: That is one of the things I  
16 am excited about is we perhaps achieve U.S.  
17 approval, that we will have more colleagues  
18 interact to fine-tune more some of the questions  
19 that are still remaining, for example, this is a  
20 good protocol, it works, and we know it is safe,  
21 but there is definitely fine-tuning available for  
22 us to investigate, the time to wean, how do we  
23 protocolize the weaning better, should we jump  
24 right to the ARDS Network PEEP table or should we  
25 use a more aggressive PEEP--lots of good questions

1 that still need to be answered.

2 DR. SESSLER: Next slide, please.

3 [Slide.]

4 DR. SESSLER: One of the other questions  
5 that I think was posed by the Agency was adequacy  
6 of conventional ventilation as a control arm in  
7 2001 versus 1996 or '97, and I believe I correctly  
8 summarized the parameters, but I do have a  
9 question. Was it pressure-controlled ventilation  
10 or, in fact, was it volume-controlled ventilation?

11 DR. DERDAK: It was pressure controlled.

12 DR. SESSLER: Next slide, please.

13 [Slide.]

14 So, I think one of the questions that has  
15 been alluded to by some of the written materials,  
16 as well as the materials presented, revolve around  
17 the question of how lung protective was the control  
18 arm if you might compare it to either previous  
19 studies or where we are now with the ARDS Network  
20 results.

21 I have summarized some of this, which is  
22 also in the printed material. It has been  
23 presented earlier with both the conventional  
24 ventilation arms and the "lung protective" arms. I  
25 think from my perspective many reviewers have

1 looked at this and argued that the first three  
2 trials where no difference was found represent  
3 really varying levels of lung protective strategies  
4 from perhaps mild lung protective strategies versus  
5 moderate or more complete until the ARDS Network  
6 design really focused on a comparison of two vastly  
7 different approaches.

8 I don't know, Dr. Hudson, if you would  
9 care to add any comments since you were one of the  
10 primary investigators.

11 DR. HUDSON: One of the problems with  
12 comparing these is they all have, as you can see,  
13 they all use different bases for the tidal volume  
14 in terms of the weight, and when Roy Brower has  
15 tried to do the analysis and convert them over,  
16 either to the actual body weight for the  
17 conventional ventilation group, or use the  
18 predicted body weight by height that the ARDS  
19 Network used, those values all come a lot closer  
20 together actually. There is not that big  
21 difference between 11.8 and 10, they are all more  
22 in the range of 10 to 10 1/2, or 10 to 11. Some of  
23 them actually go up, and the ARDS Network comes  
24 down.

25 DR. STEWART: Do you mind if I show a few

1 slides around this issue?

2 DR. SESSLER: That is fine.

3 DR. STEWART: I am Tom Stewart again. I  
4 did one of those trials together with a lot of  
5 other Canadians.

6 [Slide.]

7 Just to point out that there has been at  
8 least six trials if I lump the study we are talking  
9 about together, and they all had slightly different  
10 definitions for what they meant by ARDS. We took  
11 patients at the time of intubation at high risk of  
12 ARDS.

13 Roy Brower was within 24 hours of ARDS.  
14 The French, within 72 hours of ARDS. NIH took  
15 acute lung injury, which is the different P to F  
16 ratio cutoff, 300 as opposed to 200. The  
17 Brazilians, Marcello Amato [ph] took ARDS after one  
18 week, and MOAT had no time on it. That might be  
19 important.

20 [Slide.]

21 There is a study that is currently under  
22 review. This was the abstract presented at the ATS  
23 by Antonio Anzueto, 5,000 patients in 361 ICUs in  
24 20 countries, of which we participated in.

25 Basically, they looked a subset of those

1 mechanically ventilated patients with ARDS. Some  
2 of them had ARDS at the time of intubation, some of  
3 them developed it late, after 48 hours. The  
4 mortality rate across the world was 60 percent  
5 versus 71 percent.

6 So, late ARDS, like you could argue MOAT  
7 at least allowed, may have a worst prognosis.

8 [Slide.]

9 The other thing is how we define ARDS  
10 varied dramatically. The current AECC definition,  
11 which will still probably hold with the next  
12 definition, you can be on any PEEP. In the MOAT  
13 study, we said the PEEP had to be at least 10.  
14 This is a little bit of concern because  
15 investigators can get patients in and out of ARDS  
16 studies by taking away PEEP or applying PEEP. You  
17 can cure ARDS by having a higher mean airway  
18 pressure. A little bit of a concern.

19 So, you could argue that this study took  
20 sicker patients.

21 [Slide.]

22 As was brought up at the last AECC  
23 Consensus Conference, there are, at least in my  
24 mind, three concerns, and more with the current  
25 definition. So, we really don't know how to

1 compare different studies.

2 One is we can't agree on how best to read  
3 a chest x-ray, and that is a real concern. When it  
4 says diffuse--no, it doesn't even say diffuse--it  
5 says bilateral infiltrates. At Len's center, I  
6 know that means white chest x-ray, both sides. At  
7 some centers it means a little bit of clouding in  
8 the x-ray, because it just says bilateral  
9 infiltrates.

10 Outcome will depend on the use of PA  
11 catheter. If you have a PA catheter in, your wedge  
12 has to be less than 18. There are lots of patients  
13 that don't have a PA catheter in, that have wedges  
14 much higher than 18. When you put a PA catheter  
15 in, the group that has high wedges actually has a  
16 worse outcome, even though they meet other criteria  
17 for ARDS, a PA catheter is not needed. I will  
18 briefly show that.

19 Standard vent settings affects mortality,  
20 which we had standard vent settings.

21 [Slide.]

22 Just to point out, we published in the  
23 Blue Journal that, as Len Hudson's groups has  
24 published I think in Chest, that chest x-rays are  
25 poorly read, and training can help with that.

1 [Slide.]

2 Something that we have currently submitted  
3 is the results from our study looking at wedge  
4 pressures, and we found that in 120 patients  
5 randomized to our study, when we excluded people  
6 that had high wedges, if they had a PA catheter in,  
7 in the beginning--

8 [Slide.]

9 A lot of them, 59 percent had a PA  
10 catheter at some point during the study, a  
11 randomized trial looking at vent strategies.

12 [Slide.]

13 And 82 percent of them had at one time a  
14 wedge greater than 18. So, if a center is  
15 excluding people with a wedge pressure higher than  
16 18 at the beginning, and then putting in later--if  
17 they include people that don't have a PA catheter  
18 in, put them into the study, then, they put in  
19 later, in fact, a lot of them will have high wedges  
20 during the study. So, they would have been  
21 excluded in some trials if they had a PA catheter  
22 in.

23 [Slide.]

24 The average percentage of high readings is  
25 34 percent.

1 [Slide.]

2 I just want to point out if you ever have  
3 a wedge pressure greater than 18, your mortality in  
4 ARDS could be 66 percent versus never had a wedge  
5 pressure greater than 18, 23 percent.

6 So, what does that mean? If you are in a  
7 trial where they use lots of PA catheters, you are  
8 more apt to have a less severely ill cohort of  
9 patients as opposed to centers that don't use a lot  
10 of PA catheters. That is very important. We don't  
11 yet have a handle on how best to define ARDS, so  
12 comparing multiple trials is extremely difficult.

13 [Slide.]

14 Standard vent setting, something we used  
15 in this study, and this is some results that we  
16 have now from the Tools trial we are doing with  
17 high-frequency oscillation. We are screening  
18 patients for the current AECC definition of ARDS,  
19 and then we are putting them on standard ventilator  
20 settings and seeing if they still have ARDS, and  
21 then putting them into our study.

22 [Slide.]

23 The standard vent settings include a PEEP  
24 of 10, like we did in the MOAT study.

25 [Slide.]

1           What we found out, 34 patients actually  
2 had ARDS, 13 of them met some of our exclusion  
3 criteria, 12 of them were cured of ARDS by putting  
4 them on standard vent settings, a PEEP of 10, 9 of  
5 them were able to be enrolled, so the majority were  
6 cured.

7           [Slide.]

8           The reason they are excluded is because  
9 they are P to F improved.

10          [Slide.]

11          If you look at mortality, the group that  
12 isn't cured have a much worse mortality than that  
13 is.

14          What is the message? The message is if  
15 you use high PEEP standard vent settings, you are  
16 more apt to have a sicker population of patients.

17          I think I am done.

18          DR. PROUGH: Just to remind the panel, we  
19 are really not in a position to consider new  
20 information that was not provided previous to the  
21 meeting, but thank you for your comments.

22          Dr. Sessler.

23          [Slide.]

24          DR. SESSLER: So, the question I think  
25 remains, I suppose, as to the comparability of the

1 conventional arm to what is current practice now, I  
2 guess based on the ARDS Network results, and how it  
3 compares to the conventional tidal volume and lung  
4 protective strategies in previous publications.

5 I think it is well worth supporting what  
6 Dr. Stewart has just mentioned, that a comparison  
7 of these different trials with different enrollment  
8 criteria are extremely difficult, and I think Dr.  
9 Hudson's comments about the weight, as to how that  
10 is specifically addressed is actually quite  
11 important when one looks at tidal volumes  
12 themselves.

13 Do you all have other information as far  
14 as plateau pressures and anything that would be  
15 helpful in that regard as far as confidence that  
16 the plateau pressures remain in an acceptable level  
17 in the conventional arm?

18 MR. STENZLER: We didn't record plateau  
19 pressures when we designed the trial, but  
20 typically, you can expect plateau pressures to be 3  
21 to 5 cm lower than the peak, just from historic  
22 data comparing of the trials. So, there is no way  
23 to actually get at that plateau data.

24 DR. SESSLER: Dr. Hudson, do you have  
25 anything to add as far as the tidal volume issue

1 and the comparability?

2 DR. HUDSON: It goes to Mr. Noe's question  
3 about the comparability of the control group or the  
4 adequacy of the control group, but it is really  
5 unfair to take a recent study when this study was  
6 designed back in 1996, and to expect it to meet  
7 standards that weren't identified until later.

8 I actually think that it was a  
9 conventional strategy that was appropriate at that  
10 time, in fact, it was probably looking at the tidal  
11 volumes they used, it was better than what we found  
12 in the ARDS Network before the patients were  
13 entered into that protocol, they had a higher tidal  
14 volume than was used here.

15 So, it met at least conventional, maybe a  
16 good conventional arm, and I think the more  
17 important thing is the randomization and the fact  
18 that it was controlled. The other thing is it is  
19 very hard to compare the mortality because the  
20 mortality in this group was 52 percent in the  
21 control versus 40 percent in the ARDSNet. To me,  
22 that doesn't bother me because the patient  
23 population was different. The data would suggest  
24 it was a sicker population, and there is a whole  
25 lot of things that could be different, more

1 patients with sepsis with a higher mortality.

2           So, I think there is lots of things that  
3 could explain that, and that is why again the  
4 controlled nature of the study is more important to  
5 me than trying to compare it with other trials. It  
6 is interesting to do that and see if you can  
7 explain it, and, in fact, the differences, and, in  
8 fact, in this case I think they have presented data  
9 that to me is suggestive that there are  
10 explanations, that is, that they had a lower P to F  
11 because they included just ARDS, not acute lung  
12 injury, and there is a higher percentage of  
13 patients with sepsis.

14           DR. SESSLER: I agree. I put this  
15 together as a mildly lung protective strategy, and  
16 it seemed very reasonable at the time that the  
17 protocol was developed.

18           DR. DERDAK: We don't have the plateau  
19 pressures because we were more focused on tidal  
20 volume in mL per kilo and peak pressure, but we  
21 have our peak pressure data, and in comparison to  
22 the peak pressure data of the ARDS Network, we were  
23 on the average of 4 to 5 cm of water higher than  
24 the lung protective group and the ARDS Network, as  
25 I am looking at their paper, 32, 33 cm is their

1 peak pressure, ours in the range to 36 to 38, so it  
2 was slightly higher than the ARDSNet protective  
3 arm.

4 We were, on the other hand, lower than the  
5 ARDSNet high volume arm, so we were somewhere in  
6 between those two arms in terms of our peak airway  
7 pressures as a surrogate for compliance.

8 MR. STENZLER: One of the other things I  
9 think that we look at, tidal volume and then later  
10 management strategy, is the actual application of  
11 the strategy, so while the ARDSNet study suggests  
12 that 6 mL per kilo is the gold standard for  
13 ventilation, I think Gordon Rubenfeld from Dr.  
14 Hudson's facility at ATS presented some data on the  
15 four months prior to the publication of the paper,  
16 and the four months post-publication, and the  
17 application was about 5 to 6 percent before, and  
18 about 5 to 6 percent after.

19 I don't know if Dr. Hudson would care to  
20 comment or expound on that.

21 DR. HUDSON: Well, I think the point is  
22 just because you have prove in a study that  
23 something is better, the next step is to get it  
24 employed, and the impression is across the country,  
25 looking at this in different ways including more

1 since Gordon has looked at that, is that although  
2 it is starting to be used, there is a lot of  
3 patients where this still would be conventional, I  
4 mean that we aren't employing 6 mL per kilo tidal  
5 volume in a lot of patients, at least half.

6 DR. SESSLER: That ties in with the final  
7 issue that I thought might be discussed, and that  
8 is the question of mortality, and some comments  
9 have already been directed at that, and the  
10 question being is the 52 percent excessive.

11 I think the points that have been made  
12 about the severity of illness of the population are  
13 extremely relevant particularly the P:F ratio  
14 reflecting a tighter entry criteria of ARDS, not  
15 acute lung injury, as well as the addition of the  
16 PEEP requirement for enrollment.

17 In addition, the relatively high Apache II  
18 score, although there are not many other  
19 comparisons, some of the other studies published,  
20 they used Apache III scores, for example, and then  
21 the high rate that sepsis was a predisposition is  
22 certainly something that is generally viewed as a  
23 negative outcome predictor.

24 You can see some of the conventional  
25 ventilation group mortality rates, and these are

1 actually displayed in somewhat greater detail  
2 within Supplement 14, Amendment 4, page 32, if  
3 anybody cares to peruse that, but the message is  
4 the same, that it seems when one accounts for some  
5 of the differences in severity, that, in fact, the  
6 mortality does not appear to be excessive.

7 Those were the comments that I had, Dr.  
8 Prough.

9 DR. PROUGH: Thank you.

10 Dr. DeMets is also primary reviewer for  
11 the panel, and will briefly present his findings.

12 DR. DeMETS: Thank you. I am going to use  
13 a little lower tech approach here and go back to  
14 transparencies. The reasons for that are too long  
15 to explain, but at any rate, I appreciate the  
16 opportunity to comment.

17 For 10 years I was a statistician advising  
18 the Division of Lung Disease at the National Heart,  
19 Lung, and Blood Institute, but I haven't done that  
20 for 20 years, so I have had to re-familiarize  
21 myself with some of the terms for this study.

22 [Slide.]

23 What I thought I would do, I was asked to  
24 comment on this study from the point of view of a  
25 statistician, and my own interest over the past 30

1 years has been in the design and analysis of  
2 clinical trials.

3           There are many, many positives about this  
4 trial in terms of its clinical trial design and  
5 conduct, and I am not going to elaborate a great  
6 deal other than to say the one that I would be  
7 interested in some comment from the sponsor is the  
8 outcome. I call this disease-free survival,  
9 borrowing a term from Oncology, it is survival  
10 without the recurrence or existence of the disease  
11 as defined in the protocol. But that is, from my  
12 perspective, a nonblinded, and I am just curious as  
13 to what kind of care went into defining that,  
14 because obviously, if one carried a bias and  
15 tweaked the knobs in whatever way you needed to,  
16 one could create outcomes, so I would be curious  
17 about that.

18           With that exception, I think the design  
19 and the conduct meets many of the standards that I  
20 am interested in seeing in such a trial. I think I  
21 will just continue and then we can come back to  
22 that question later, if you don't mind.

23           The existence of a Safety Monitoring  
24 Committee, I think is a nice additional piece. I  
25 don't think it would have any direct bearing on the

1 discussions for today, but I was glad to see that.

2 [Slide.]

3 Although not stated in these terms, and  
4 probably in FDA circles, this term was not even  
5 used in 1996, but certainly is now, the idea of  
6 equivalence or, in fact, more correctly, non-  
7 inferiority. The hypothesis which my mind locked  
8 into was that the disease-free survival at 30 days  
9 should not be worse than the convention by 0.1.

10 That was a discussion and an agreement  
11 made between the sponsor, the investigators, and  
12 the Agency.

13 Well, first of all, you need adequate  
14 power to make sure you have a reasonable chance to  
15 detect differences of that size. I am not sure  
16 about the discussion in the documentation I read,  
17 but at any rate, that may be a second clarification  
18 the sponsor can make, but for sure, failure to  
19 achieve significance is not adequate.

20 In other words, if you had a very small  
21 study, you are guaranteed to see no difference, so  
22 just quoting a nonsignificant p value is not an  
23 adequate criteria to achieve this goal of  
24 equivalence or non-inferiority.

25 In fact, the FDA has recently written down

1 criteria they think are relevant for this goal of  
2 non-inferiority, it is not new. Some of us  
3 published these ideas 25 years ago, but they have  
4 finally been put into the form of guidelines.

5           There is two key criteria I would like to  
6 draw your attention to. The first one, which is  
7 the confidence interval, is that the upper  
8 confidence interval for the difference needs to be  
9 less than that criteria, that delta, that one set  
10 forth as your goal.

11           I would just like to jump ahead to the  
12 next transparency for a moment.

13           [Slide.]

14           Let me try to show you why this is  
15 important. I have depicted three scenarios here.  
16 The absolute difference in rates or relative risk,  
17 I haven't declared, but it doesn't matter, the  
18 principle is the same.

19           This is the line of no effect. There is  
20 no treatment effect. This is the delta that is  
21 agreed upon as the criteria. In this case, it is  
22 0.1. Now, scenario one is you get the estimate of  
23 your difference in the confidence interval, 95  
24 percent confidence interval, which goes above the  
25 delta, as well as way down here.

1           Scenario A is a trial which cannot claim a  
2 non-inferiority or even, for that matter,  
3 superiority. In fact, it is what we have in our  
4 primary outcome, we didn't quite make it, and I  
5 will come back to that point.

6           Scenario B is what I presume this trial  
7 would have liked to have hit for their declared  
8 disease-free survival outcome. This confidence  
9 interval, the upper limit is less than delta, less  
10 than the 0.01 in this case, so one would declare  
11 Trial B to have achieved non-inferiority, that it  
12 is not worse than this amount, whatever that amount  
13 happens to be

14           Trial C is our dream, that is, we would  
15 like to be able to rule out that it is worse than  
16 the standard therapy by a certain amount, and even  
17 better yet, it is better by some level.

18           So, these are the three areas that get  
19 sometimes confused, and we have to keep I think  
20 those straight in evaluating this trial, as I  
21 understand the hypothesis that was posed. So, that  
22 is Criteria 1. We need to understand, and I have  
23 oversimplified things here, there is a document  
24 that has much more detail, but at any rate, that is  
25 an oversimplification.

1           Let's go back to the previous slide, and I  
2 want to now focus on the second criteria.

3           [Slide.]

4           The second criteria is one that has been  
5 already discussed a bit. If you are going to claim  
6 that your new device or your new therapy is as good  
7 as or is not worse than the conventional therapy by  
8 some amount, one of the questions, the natural  
9 question is was your control group any good.

10           So, the second key criteria in the FDA's  
11 discussion, as well as in other circles, is that  
12 you would like to know how would this new therapy,  
13 this new device have done had a control arm best  
14 standard of care without the therapy being there.

15           Now, for ethical reasons and in clinical  
16 practice, one wouldn't do that trial, but the  
17 question is still there, why. Well, if you keep  
18 picking, if you did over time, weak sisters, weak  
19 control arms, over time you would have what we  
20 would call control group creep, that is, you get  
21 weaker and weaker and weaker standards, to the  
22 point that eventually you are comparing something  
23 effectively as a control arm that is no better than  
24 placebo.

25           So, all of us should worry about this

1 issue of control group creep, and that is why the  
2 questions do you have the right population, did you  
3 apply conventional therapy as best you could, and  
4 all those kinds of reasons. So, that is the  
5 concern.

6           What do you do about it? Well, it is not  
7 a nice answer. In fact, the answer is not, in my  
8 opinion, as easy as described in the document and  
9 in the literature. We wind up using historical  
10 controls to compare our standard of care arm in  
11 this trial with previous studies, and that is about  
12 as good as we can get.

13           If we believe that methodology too much  
14 though, we wouldn't bother with the randomized  
15 trials at all, we would just use historical  
16 controls. So, there is a catch-22 in this, and  
17 there is no way out of it as far as I can figure  
18 out, having thought about this for 20 years, but  
19 that is what we are left with.

20           So, the issue of the control group arm is,  
21 in fact, very important in trials where you are  
22 trying to establish that your therapy, your device  
23 is no worse than conventional by some amount.

24           So, at any rate, I would like to go then  
25 to the next transparency.

1 [Slide.]

2 In trials of this kind, which I have  
3 labeled as non-inferiority, is especially  
4 important, did you have a high quality trial. If  
5 you are trying to achieve a superiority, it is your  
6 natural incentive to do the best darn job you can  
7 to beat the competition. In non-inferiority, the  
8 incentive is actually the opposite. The lousier  
9 job you do, then, the easier it is to show  
10 equivalence.

11 So, you have to establish that you have  
12 the best possible trial done, at least from what I  
13 have read and what I have heard, I think that has  
14 probably been accomplished here, but that is a key  
15 issue, that if you are going to try to say that at  
16 my trial, my therapy is no worse than conventional,  
17 you want to be sure that you have actually given it  
18 a stiff test.

19 Not discussed today, but at least alluded  
20 to in the review, and some of the discussion I saw,  
21 was the issue whether these centers are poolable.  
22 My own bias, and here I am at odds, I suspect, with  
23 some of my FDA colleagues, I don't put too much  
24 emphasis on the issue of poolability.

25 I think if you have randomized within

1 center, which this trial was done, then, if you are  
2 really concerned about that, then stratify the  
3 analysis by center and move on, but certainly you  
4 don't want to eliminate centers because somehow  
5 they are different, and the next slide will I think  
6 indicate why I believe that strongly. It is not an  
7 issue, and I won't dwell on it too much.

8 [Slide.]

9 Here is a trial that is from the  
10 cardiology world, which is where I live a lot of my  
11 life, there is 32 centers. This is a trial done 20  
12 years ago. This is the odds ratio, a relative risk  
13 for the drug versus placebo. To the left is good,  
14 to the right is bad. In an overall trial, it was  
15 one of the more significant, and it is one of the  
16 standard trials that says beta blockers and heart  
17 failure are good, you still notice that for some  
18 centers, here is center 7, had some bad luck. It  
19 doesn't mean you throw out center 7, it is just an  
20 effect of small numbers of patients and small  
21 numbers of events.

22 So, for reasons like this, I would not  
23 want us to dwell too much on the issue of  
24 poolability. I think you randomize within the  
25 center, you take all patients, you take all

1 centers.

2 Let's move on.

3 [Slide.]

4 So, where are we with respect to this  
5 trial from my perspective? Well, I have summarized  
6 here, and I hope I got all the numbers correctly.  
7 I did this somewhat quickly. But to look at this  
8 from the framework that partly was presented and  
9 partly what I alluded to earlier, this was the  
10 outcome that we see as the hypothesis.

11 I have taken one disease-free survival,  
12 which is the failure rate, so we have actually it  
13 is certainly in the wrong direction, and has  
14 already been said, the confidence interval does not  
15 exclude point 1. So, you don't have either  
16 superiority or non-inferiority.

17 Interestingly enough, the other variables  
18 that are at least secondary, if not close primary  
19 events, in fact, have upper confidence intervals  
20 which exclude point 1. Now, I don't know what the  
21 right delta would be for those outcomes for  
22 mortality and failure to wean, I mean what delta  
23 would be appropriate clinically or from a  
24 regulatory point of view, but if you applied the  
25 same delta, 0.1, at least one might make an

1 argument that these, in fact, did meet those  
2 criteria of non-inferiority, and air leak came  
3 pretty close. But we clearly didn't make it as has  
4 been stated for disease-free survival, but I think  
5 there is something interesting here that we should  
6 keep in mind as we discuss this thing.

7 [Slide.]

8 I am not familiar with all the literature,  
9 but at least as an idea and a principle is that one  
10 should at least take into account the previous data  
11 or perhaps the ongoing data, certainly the previous  
12 pediatric data, to say that things are in the same  
13 direction on these kinds of outcomes.

14 So, somehow, if this trial had not  
15 existed, one would have just this data alone, so  
16 there is some previous data, which we somehow need  
17 to factor into our thinking about the particular  
18 trial we are reviewing today.

19 I haven't done that formally, but at least  
20 I think we should keep it in mind.

21 [Slide.]

22 This is my final transparency. So, one,  
23 the good news is that the results are consistent  
24 with the pediatric data for a similar device. Non-  
25 inferiority is "established" perhaps for these

1 secondary outcomes, but we did not achieve or did  
2 not establish non-inferiority in a formal sense for  
3 the primary outcome and certainly had no evidence  
4 for superiority in this particular trial.

5 At any rate, I raised a couple of  
6 questions that perhaps the sponsor might want to  
7 respond to, but I think those are in some sense the  
8 essence of the statistical issues as I see them.

9 MR. BACHMAN: The first point you raise  
10 was with I think another reason why what you call  
11 the disease-free survival was not a good outcome  
12 measure or the softness of it was not only the  
13 range from death to just being on nasal oxygen, but  
14 things like nasal oxygen or time that you wean are  
15 somewhat subjective anyway, and they weren't  
16 protocolized, so I think we would all agree that  
17 that was another reason why that wasn't the optimum  
18 endpoint for the study. Nevertheless, it was the  
19 one we ended with.

20 I am not sure I understood your question  
21 about power analysis, which was the other thing  
22 that we put down. We started off with the results  
23 of the pediatric trial and then assumed if the  
24 difference wasn't as large, and that was an  
25 arbitrary selection, that 148 patients would have

1 been enough power to approve this, but because  
2 there were so many patients ended up on extended  
3 mechanical ventilation that it kind of went out the  
4 window.

5 DR. DeMETS: Well, typically, you would  
6 like to see an argument that said we agreed on a  
7 delta of 0.1, and that is an arbitrary decision  
8 that is based on clinical and a whole bunch of  
9 other things, we all understand that.

10 But then you would like to, before you  
11 started at least, assure yourself that the trial  
12 you were going to conduct with the outcome you  
13 picked, for better or for worse, had something like  
14 a 90 percent power to find differences of that  
15 size. Otherwise, you are guaranteed to have  
16 equivalence of non-inferiority.

17 It goes back to the issue that obtaining  
18 nonsignificance is not enough. I have to obtain  
19 nonsignificance with a confidence interval of a  
20 certain size to rule out differences that we have  
21 specified, so that discussion I didn't see. I am  
22 not saying your sample size was wrong, I am just  
23 saying I didn't see a discussion that would  
24 convince me that this trial was adequately sized  
25 for the outcome you chose to begin with.

1           So, I am not disputing whether it is or  
2 isn't, I just didn't see the argument presented.

3           A comment on the first outcome, I am not  
4 so willing to say that the outcome you picked is a  
5 bad outcome. I mean you can go through steps to  
6 have definitions what an event is that could be  
7 less biased. I am not saying unbiased but less  
8 biased.

9           Oncologists use disease-free survival all  
10 the time, for better or for worse, and they go  
11 through some steps about having independent graders  
12 of chest x-rays, whatever the outcome might be, so  
13 there is some process you can go through to make it  
14 less biased, and I was just curious what procedures  
15 you went through to say this outcome didn't get  
16 biased by the investigator's own personal take on  
17 high-frequency ventilation versus conventional  
18 ventilation.

19           MR. STENZLER: I think on the bias aspect,  
20 a lot of the outcome measures, obviously you can't  
21 blind what the patient is on, but we lumped any  
22 form of respiratory support including down to nasal  
23 cannula oxygen that is respiratory support.

24           So this in a way eliminated the bias that  
25 they may have put them on a cannula versus a CPAP

1 device, which would have been mechanical  
2 ventilation, or on the basis of mechanical  
3 ventilation. We took all respiratory support and  
4 lumped it into a bad outcome, which kind of limited  
5 the bias, we believe.

6 DR. PROUGH: Dr. DeMets, did you have any  
7 more questions?

8 DR. DeMETS: No.

9 DR. PROUGH: At this time, I would like to  
10 ask each panel member starting with Dr. Kirton and  
11 moving to Dr. Kirton's left to ask any questions  
12 that they might have for the sponsors or to make  
13 any comments that they would like to make.

14 DR. KIRTON: I just have one question for  
15 the sponsors in regards I am a little concerned  
16 with the failure of the diaphragm component of the  
17 ventilator. I was just intrigued that it is  
18 earmarked as a failure, typically about 2,000 or  
19 2,500 hours, but yet within the trial, it failed  
20 earlier than that, but yet it was of no significant  
21 consequence.

22 I was wondering, are you planning to  
23 change just how you will report that aspect of the  
24 machine and what safeguards in training will be  
25 addressed, so that the consumer obviously is well

1 aware and can act appropriately.

2 MR. STENZLER: As far as the diaphragm  
3 failure, two points. We have since the beginning  
4 of the 3100B trial, we have had significant  
5 engineering efforts placed at redesigning the  
6 driver, and there will be another submission  
7 probably maybe on the way to you with changes to  
8 the driver that we believe will extend the hours  
9 out to 4,000 hours.

10 But the other important aspect of it is  
11 that the diaphragm from the very first slide I put  
12 up, there is actually two pieces of the driver.  
13 The diaphragm that fails is on the part that is  
14 isolated from the patient circuit, so the patient  
15 really doesn't see that component of it.

16 When the diaphragm fails, it is not a  
17 catastrophic failure, so it is a rubber diaphragm  
18 that develops tears in it, and you can have large  
19 tears and still deliver significant volume.

20 We have submitted I believe additional  
21 data in one of the supplements showing tests that  
22 have been run on failed diaphragms. The driver  
23 doesn't fail, but the diaphragm shows a tear. The  
24 users are trained to inspect the diaphragms between  
25 patients, so the likelihood you will have a

1 catastrophic failure is very small even with a  
2 diaphragm failure.

3 DR. KIRTON: That was my only question.  
4 Dr. DeMets and Dr. Sessler basically summarize my  
5 questions and concerns.

6 DR. PROUGH: Dr. Schroeder.

7 DR. SCHROEDER: Just one quick question  
8 about the failure rate. Is it any different from  
9 the failure rate you have with the 3100 and 3100A?  
10 I mean I would think a failure in a neonate is much  
11 more catastrophic on a timely basis than in an  
12 adult.

13 MR. STENZLER: Again, the failure rate, as  
14 you are moving in an adult, you move the diaphragm  
15 a greater distance, so the stress failures are  
16 greater, but once again, there are almost no  
17 failures of the diaphragm in the neonates. It is  
18 really the distance you ask the driver to move.  
19 Again, it is not a catastrophic failure. You  
20 normally see the tear in the diaphragm in between  
21 circuit changes, so you are basically looking at  
22 the diaphragm typically at least once every 5 to 7  
23 days, and you would pick it up.

24 DR. SCHROEDER: I guess my only other  
25 comment, it is not really a question, is I was

1 impressed with the study that was done, the design.  
2 I am not a statistician, so I am glad to hear that  
3 reiterated by someone who is. My concern is  
4 comparing it to historical controls, comparing it  
5 to a constantly dynamic treatment environment,  
6 where we are changing every year what it is we do,  
7 and the inconsistencies across the industry as to  
8 what is used and what is not used, I think which  
9 was alluded to, that 10 cc per kilo may actually be  
10 a little bit lower than what a lot of patients are  
11 actually getting.

12 Also, the variability or the difficulties  
13 in comparing it to studies with vastly different  
14 etiologies of ARDS, patients with vastly different  
15 clinical presentations and clinical courses.

16 I mean I understand the issues behind the  
17 ARDSNet study and the relevance to the current  
18 question. That is just my comment.

19 DR. PROUGH: I don't have a question of  
20 the sponsors, I do have a question for Dr. DeMets.  
21 On page 130 of the book, there is a list of the  
22 criteria by which something other than no  
23 respiratory support required is defined. I am  
24 wondering if those definitions are sufficiently  
25 precise.

1 DR. DeMETS: Not being a pulmonary  
2 physician, what I do know is you can turn a lot of  
3 knobs and you can adjust a lot of things, so  
4 whether these definitions are manipulatable or not,  
5 I don't know. My only question was do you have a  
6 definition of an event that is pretty robust to  
7 whatever maneuvering one might do. I am not  
8 capable of assessing that.

9 DR. PROUGH: Would anyone else care to  
10 comment on robustness?

11 DR. DeMETS: My point was suppose I have  
12 it in for the high-frequency ventilator for some  
13 reason, I don't like them, I just don't like the  
14 system, so every time I have a choice to make as a  
15 clinician, I adjust the system to make it worse for  
16 that ventilator, and therefore I make it fail. I  
17 mean I am oversimplifying because I don't know  
18 enough about it.

19 DR. STEWART: The point that Alex made I  
20 think was a good one. Doing clinical trials in  
21 ARDS, I have a real concern that people can adjust  
22 P to F ratio, but since need for supplemental  
23 oxygen was included in the definition, you can't  
24 manipulate, at least that I know of, someone's  
25 saturation.

1 DR. DeMETS: Well, that's the answer.

2 DR. STEWART: I think it is better than a  
3 lot of trials that have been done to date in  
4 mechanical ventilation.

5 DR. PROUGH: Dr. Garman.

6 DR. GARMAN: What labeling suggestions  
7 might you offer in view of the comments you have  
8 received?

9 MR. STENZLER: Well, I believe that all of  
10 the text that is in the Operator's Manual covers  
11 most of the material and discussions today. Again,  
12 we also produce on a fairly regular basis, critical  
13 care reviews, which our clinical documents provide  
14 to clinicians as we develop strategies to use our  
15 device better.

16 But as far as the labeling and the  
17 Operator's Manual itself, I think it is fairly  
18 complete as is, has been through discussions with  
19 the FDA, CDRH, to fine-tune it to meet what they  
20 expect to see in a device labeling.

21 DR. PROUGH: Mr. Amato.

22 MR. AMATO: I have no comments at this  
23 time.

24 DR. PROUGH: Dr. Sessler.

25 DR. SESSLER: I just have a quick

1 question, again coming back to the weaning from  
2 high frequency, just in the sense that again I  
3 think it is the difference between efficacy and  
4 effectiveness, the translation of this in terms of  
5 taking it to the marketplace, not just people who  
6 have lived with it investigatively, but busy  
7 clinicians working with it.

8           The question I have I guess is when you  
9 are talking about weaning, there are criteria that  
10 are laid out here, when the  $FiO_2$  is less than 0.5,  
11 and the mean airway pressure less than 24, what are  
12 those really based on? Is that based on pediatric  
13 data, is it clinical experience thus far, and how  
14 can we again I guess best tweak that, so that there  
15 is as much guidance that we can give to clinicians  
16 as possible?

17           DR. STEWART: We have now--I just called  
18 when we were at lunch--83 patients, adults with HFO  
19 in our center, and to be honest, what I learned  
20 about it was from working with the company and all  
21 the pediatric and neonatal folks that have done it  
22 both in Toronto and abroad.

23           They have just given us advice. So, there  
24 is a real need for us to determine in adults what  
25 is the ideal timing to get them off the oscillator.

1 Currently, we are sitting at a mean airway pressure  
2 of 22 or 24 range, which is still pretty aggressive  
3 conventional mechanical ventilation.

4 You are talking about PEEPs up around 10  
5 to 15 range for sure, and reasonable, maybe 1 to 1  
6 I:E ratio to get them to that range. So, they are  
7 still on some conventional for a period of time.

8 At that level, my experience--and I don't  
9 know Steve's completely--most patients will  
10 transition nicely to conventional, and not have to  
11 go back to high-frequency oscillation, but a  
12 burning question in the future is should we leave  
13 them on HFO even longer and get better survival in  
14 a group that we even go lower on, on HFO.

15 I think what you will find, though, when  
16 they are improved that much is they start to  
17 develop respiratory alkalosis, and they are blowing  
18 off a lot of their CO<sub>2</sub> quite aggressively, so you  
19 can manage them a little bit easier perhaps with  
20 conventional.

21 DR. PROUGH: Steve.

22 DR. DERDAK: I believe the oscillator is  
23 predominantly a device to improve oxygenation and  
24 hopefully a nontoxic FiO<sub>2</sub> level and hopefully  
25 minimizing lung injury while doing it. The weaning

1 strategy of first decreasing  $FiO_2$ , I think is the  
2 same as in conventional ventilation. We try to go  
3 to whatever the threshold of toxicity might be,  
4 whether it is 60 percent, 40 percent, I don't think  
5 we really know that in individual patients, but 40  
6 or 50 percent, my preference is 40 percent if you  
7 are asking for an opinion, prior to taking down  
8 mean airway pressure.

9 At the mean airway pressure range on an  
10 oscillator of 22 to 24 range, remember, that when  
11 we switch from conventional ventilation to high-  
12 frequency, we are usually increasing the mean  
13 airway pressure by 5 cm or so.

14 When we go off the oscillator, what we  
15 find is that with mean airway pressures in the  
16 range of 22 to 24, if you go much below that in an  
17 adult patient, I think, it is my impression there  
18 is some danger of the lungs starting to derecruit,  
19 and we also find that it is very easy to set up a  
20 conventional ventilator to achieve a mean airway  
21 pressure in the high teens or in the 20 range plus  
22 or minus 2, when you have achieved 40 percent on  
23 that oscillator and gotten to a mean airway  
24 pressure of 24.

25 The tempo, the speed at which you take

1 down mean airway pressure I think is a very good  
2 question that we don't know yet. I worked with Dr.  
3 Null and Dr. Delemos, who had a lot of experience  
4 using high-frequency in neonates and pediatrics,  
5 and their teaching is always come down very slowly  
6 and cautiously. You can go up quickly, but come  
7 down slowly, must like we do with PEEP.

8 I think documentation perhaps explaining  
9 how people with experience have used the oscillator  
10 may be another format other than the Operator's  
11 Manual, but perhaps in review articles or how we do  
12 it type of reviews would be supplemental to what is  
13 in the Manual. You can probably read the article,  
14 the manuscript that we are going to be doing in  
15 this paper and come away with precise notions of  
16 how exactly to use it and when to use it, but I  
17 think there is a need for that kind of supplemental  
18 information.

19 Someone raised the question of safety.  
20 One of the things that we do in the ICU is we  
21 always have a bag mask at the head of the bed with  
22 oxygen going through and a PEEP valve, so that if  
23 there is a sudden stoppage of the oscillator, it is  
24 not a big deal, you disconnect the ventilator,  
25 immediately attach the bag and troubleshoot, so it

1 is immediately there. That is not a bad idea for  
2 any sick patient on a ventilator, but definitely  
3 with high-frequency, there is an apnea mode backup,  
4 for example, if the machine was to malfunction.

5 So, those are items that I think need to  
6 be part of the teaching package on how we use it,  
7 but there is still clearly questions, I don't think  
8 for conventional either.

9 DR. STEWART: I have had a few people say  
10 to me if it is really lung-protective, why not,  
11 like they do in the neonatal world, just wean them  
12 right down the HFO to spontaneous breathing, and I  
13 just think it is an adult mind-set because from the  
14 nurses' perspective and from the family's  
15 perspective, their patient is being managed  
16 differently and looks different, so we should be  
17 getting them off as soon as it is feasible to get  
18 them off. Again, a question for the future.

19 DR. PROUGH: Dr. Sessler?

20 DR. SESSLER: One other follow-up I guess,  
21 and that is, a lot of our patients who require  
22 nonconventional ventilatory support need more  
23 sedation, more intramuscular blockade, those have  
24 their problems related to those interventions.  
25 Could you comment on our experiences either in the

1 clinical trial or at the bedside, the frequency of  
2 using those drugs, does it differ?

3 DR. STEWART: That is an excellent  
4 question. I remember being at--I don't know  
5 whether it was Snowbird or one of the high-  
6 frequency meetings, I got up there and I said the  
7 pluses and minus of HFO in adults, and I said one  
8 of the minuses, you have got to paralyze the  
9 patient.

10 I remember someone in the crowd said to me  
11 why do you have to paralyze, I have tried it on  
12 myself, and I didn't feel that need to a drive to  
13 breathe. Since then, we have started to just see  
14 if there is patients we could take off. Again, at  
15 lunch, I called and our research RT told me we have  
16 some experience, usually during the time they are  
17 on HFO, of stopping the process in 12 to 14 of the  
18 patients, but the other side of it from my  
19 perspective, if you really think you can save a  
20 life, which I think from our rescue data, which we  
21 didn't even get into, I think you can save some  
22 lives with this device a lot.

23 Is there really a down side to be  
24 paralyzed if you using it properly and if you are  
25 monitoring how much you are paralyzing a patient?

1 I am not sure it is really a down side.

2 DR. DERDAK: If I could just make a quick  
3 comment on that. I think for the initiation of  
4 high frequency, from switching from conventional to  
5 high frequency, virtually all patients are  
6 paralyzed. Often, they are paralyzed already on  
7 conventional ventilation prior to going on to high  
8 frequency at that severity of ARDS.

9 Clearly, patients can be taken off  
10 paralysis during the weaning phase of high  
11 frequency and maintained on sedation. Both of us  
12 have had experience in patients we have been able  
13 to completely stop the paralytic agent.

14 But during the initiation phase, I think  
15 it is an essential part of the therapy. The other  
16 thing to point out is that there are all grades of  
17 paralysis obviously, and patients don't have to be  
18 in deep paralysis, just sufficient to have  
19 relaxation of the chest wall and avoiding agitation  
20 with the ventilator, but the level of paralysis  
21 obviously can be modified, and they can be taken  
22 off sometimes and just maintained on sedation as  
23 you transition into the mid-20s mean airway  
24 pressure and getting ready to put them back on  
25 conventional ventilation.

1 DR. PROUGH: Dr. Mueller.

2 DR. MUELLER: Every drug and every  
3 intervention has some side effects with it, as well  
4 as benefits. As you probably know, there are  
5 several cell types now that are plated on  
6 expandable membrane as opposed to the rigid  
7 support. If one then stretches the cell just a few  
8 percent, you can achieve changes in the expression  
9 of the genome and the proteins that are synthesized  
10 in the cell.

11 Do you have any information about the  
12 frequency of response range with which you, let's  
13 say, stimulate all the cells of the airway,  
14 neutrophils, and so forth, who are trying to chew  
15 up things, and make our patient better.

16 Are there any negative effects that you  
17 might see in vitro?

18 It is not purely a theoretical question.  
19 If you think about, depending on your statistician  
20 and interpretation, that the results at one month  
21 may be better than six months. Maybe the reason  
22 the six months is not so good is because you have  
23 also done something to your inflammatory response  
24 or your replication of alveolar cells or something  
25 which puts that patient at a disadvantage. In