DR. MILLER: Yes.

DR. NORMAND: -- fix those, and at that point, the patient is randomized to the sealant or the control group?

DR. MILLER: That's correct.

DR. NORMAND: Okay. So, the patient is randomized to the sealant or control group and then, so, they go in a priority. The surgeon knows how many air leaks are there, that is, that the -- so, either the patient is randomized to the sealant -- sorry.

The patient is randomized, control group, you're done, right?

DR. MILLER: That's --

DR. NORMAND: And so, we know how many intra-operative air leaks there are at that point. That was done prior to randomization?

DR. MILLER: Yes, they -- let's just go back to this one. Password, if someone could come on.

DR. NORMAND: Well, I don't think we

need the slides.

DR. MILLER: Okay, but what happened was, is that when the patient was repaired, then they're randomized into sealant and then in control.

DR. NORMAND: Okay, so, just -- sorry to interrupt you again.

DR. MILLER: Okay.

DR. NORMAND: I just want to make sure at this point, I'm on the same page. So, at that point, we know how many intra-operative air leaks there are?

DR. MILLER: Yes.

DR. NORMAND: Okay, go ahead.

DR. MILLER: And then they were re-tested --

DR. NORMAND: Yes.

DR. MILLER: -- just prior to the time of closure.

DR. NORMAND: Okay.

DR. MILLER: Of closing -- they were re-tested --

DR. NORMAND: Okay.

DR. MILLER: -- for intra-operative air leak for size, for location and so forth.

DR. NORMAND: Okay. So, they're re-tested, so, that means the numbers could have changed for the control group as well as the sealant group?

DR. MILLER: That's correct.

DR. NORMAND: Okay. So, then the sealant is applied and then you're re-tested again for the number of --

DR. MILLER: Yes, and that's when you get that measurement of the intra-operative air leaks that were sealed.

DR. NORMAND: Okay. So, but you've got that for the sealant group, but for the control group, where is that number coming from? Where is the number of intra-operative air leaks count coming from?

DR. MILLER: Well, you have it from the first --

DR. NORMAND: From the first?

DR. MILLER: Yes, and then again at the re-test. There's a second number for that, so, it's when you leave the operating -- - something could have changed when they --

DR. NORMAND: Sure.

DR. MILLER: -- blew up the lung to check for the broncho pleural fistula and so forth.

DR. NORMAND: So, and so, again, for the sealant group, the surgeon can apply the sealant to those that were spotted, in terms of the intra-operative air leak and I also read they could actually apply the sealant to other places.

DR. MILLER: No, only that were recorded.

DR. NORMAND: Only that were recorded?

DR. MILLER: Yes, exactly.

DR. NORMAND: Okay, and so, when you do the count when they leave the room, you're only looking at sort of -- so, for every one

that was spotted, the number of intra-operative air leaks were those that were identified for the -- based on a priority, prior to randomization?

DR. MILLER: Exactly.

DR. NORMAND: I'm sorry this is painful.

DR. MILLER: No, that's all right.

DR. NORMAND: The one last question I have to ask, and this is my not knowing, so, when you look at whether or not the air leak stopped, does everybody get a chest tube who has an air leak?

DR. MILLER: Everybody gets a chest tube with --

DR. NORMAND: Regardless?

DR. MILLER: You have a chest tube to re-expand the lung --

DR. NORMAND: Okay.

DR. MILLER: -- to drain fluid and then --

DR. NORMAND: Okay. So, everybody

has a chest tube?

DR. MILLER: Yes, ma'am.

DR. NORMAND: Okay, sorry, thank you.

DR. MILLER: That's fine.

CHAIR BIRNBACH: Dr. Topoleski.

DR. TOPOLESKI: I have two questions. One is about the burst strength test. How was the burst strength measured and was it the actual material that was bursting or the adhesive bond between the material and tissue?

The second question was on the degradation products. In your slide, you show 3,500 molecular weight. That was initial polymer. Was there a range of molecular weights and was there a range of molecular weights in the degradation products?

DR. PARKS: Okay, the first part on burst strength was the strength of the material. It was not any adhesive burst strength.

The second part, on the polyethylene glycol break down, occasionally we would find a single succinate molecular weight. Otherwise, the polyethylene glycol was 3,500. We found no fractions, no smaller fractions.

DR. TOPOLESKI: Was an adhesive strength test done on the material?

DR. PARKS: I'd have to take a look and see in the PMA, what exactly adhesive we did, but yes, we did adhesive testing as well as part of our development of the burst strength testing profile to make sure we were checking for the burst of the material, as opposed to adhesive failure.

CHAIR BIRNBACH: Yes, go ahead.

DR. LILLARD: One last question regarding the renal failure that you observed. Was there any gender bias or ethnicity bias to the renal failures?

DR. MILLER: No, there was not.

CHAIR BIRNBACH: Dr. Loeb.

DR. LOEB: I have a question. One of the concerns is late complications of either residual volume or pneumothorax and in slide 52, you presented a break down of the different types of surgeries and showed that the sealant group had more extensive surgery.

Was any subsequent analysis done, breaking down those groups? I don't remember seeing it in your written statement, either a separate analysis by magnitude of surgery, breaking it into two groups and looking at the analysis, especially of complications by that type of break down.

DR. MILLER: There is no sub-analysis of that group. It was a very small percentage. The only -- the reason we brought that up, because there was a question from the FDA about residual pleural space, which was higher in that sealant and could it be explained by the extended resection.

But also too, in that one patient who required a chest tube at the one month

follow up, that was in the only patient who had an extended resection, had a bi-lobectomy. But there is no sub-analysis in regards to that.

CHAIR BIRNBACH: Dr. Wiswell, I'm not ignoring you. You're hidden from my view.

DR. WISWELL: In that same group, so, those six that had the prolonged air leak, only one of them had had an extended lung resection, is that what you're saying?

DR. MILLER: To clarify, those weren't prolonged air leaks. Those were patients who were deemed to have a pneumothorax at follow up and out of those, only -- the one that required intervention was an extended resection.

They did not have prolonged air leaks. They just had a residual pleural space.

DR. WISWELL: So, the other five had not had extended --

DR. MILLER: Yes, four of the five

had lobectomies and one had a wedge.

DR. WISWELL: Okay.

DR. MILLER: But all those spaces were decreasing in size.

DR. WISWELL: And I had another question regarding the kidney issues. One is, what were -- for the purposes of this study, what were the definitions of oliguria and acute renal failure?

DR. MILLER: Oliguria was less than 30 cc's an hour of urine output for a 24 hour period, which the majority of us, clinically practice, you know, if it's more than 10 cc's an hour, it's okay. But that was the definition.

Also, acute renal failure is patients requiring dialysis to take care of that, and that was only one patient that required that.

DR. WISWELL: And I guess the last question I would have, regarding the renal function, do you have data concerning the

length of time the patients had oliguria or that they were considered to have "acute renal failure"?

DR. MILLER: Yes, the oliguria resolved within the first one to two days after surgery and that's in that one table. If you can see here, the onset of duration, if you look in the bottom four patients here --

DR. WISWELL: Okay, I think I've got it.

DR. MILLER: Yes, all within the first or second day, and all of them resolved within four days, the oliguria.

DR. WISWELL: Okay, thank you.

CHAIR BIRNBACH: Dr. Jeevanandam?

DR. JEEVANANDAM: I guess I'm going to ask my question again. If you look at -- yes, the air leaks stopped, but all the air leaks stopped.

If you look at the control arm, there were no patients developed broncho pleural fistulas, so there was no reason to

put chest tubes back in those patients. So, those patients who were in the control group really did not have a clinical significance, in terms of not having their air leaks stopped right away.

So, it seems that the air leaks just stopped on their own. It didn't stop faster with the product, as opposed to not having the sealant on the lung.

I'm just trying to find the clinical benefit for this, other than just immediately stopping of the air leak.

DR. MILLER: Yes, well, this study was not powered for complications, but you did see within the control group, there were more pneumonias, there were more deaths.

To power for that, we would have had -- I have the study twice as big to look at that. The primary endpoint and the five -- three of the five segments that we looked at showed there was statistically significant difference in favor of the sealant, and we all

know from the literature of the prolonged air leaks, that you lead to more complications, longer hospital stay into death, and it did show there is more deaths in the control group and more pneumonias.

It was not statistically significant, but it was trending that way. I mean, this study did not power for that. The main thing was air leaks and to control that, which it did successfully.

CHAIR BIRNBACH: Dr. Lillard. I'm sorry, Dr. Normand.

DR. NORMAND: I'm sorry, I'm going to ask this question again. I'm reading from the sponsor's protocol and I'm reading directly from what they're saying on page 11. It says, "The surgeon will go back to each of the sites identified above and apply the patch to those same sites."

So, you identify the air leaks and that's what the indications are. There may be some leaks the surgeon will not choose to

close with the standard technique, i.e., the leak is too small or tissue is too fragile to use sutures or staples. The surgeon will apply the patch to these sites as well.

So, my question before was, you're applying them to sites where there weren't any sutures and I thought you had answered `no', but it seems the protocol says that the surgeon is supposed to apply to those sites as well. Can you please help me understand?

DR. MILLER: What occurs is that, especially down the fissure of the Heimlich, if you develop an air leak there, that's let's say, more than two millimeters or five millimeters, you can't repair that area.

DR. NORMAND: So, the question is just `yes' or `no'. So, could the -- I'm sorry, I just need to understand, I just want to get a sense of -- here's my question.

Is the sealant being used in places where typically, no one would do anything with, and I think you're saying yes, with very

small spots it could be done.

DR. MILLER: Well, it's not -- nothing -- you can't do those -- you can't do anything in those areas.

DR. NORMAND: I know.

DR. MILLER: You just have to let the air leak go.

DR. NORMAND: But in this study, that was my question, are you applying -- it sounds the like the protocol says you're applying the sealant to those hard to get places, is that true or not true?

DR. MILLER: Yes.

DR. NORMAND: Okay. So, the answer should have been `yes' to my question earlier. I'm not chastising you.

DR. MILLER: Okay.

DR. NORMAND: I'm just trying to understand. So, just to -- in the back of my mind, I'm saying, "Okay, this device is being used in air leaks that are typically tended to by sutures or staples, but also too, those

additional leaks that may not have been identified, that may not have been treated, because they're too small to handle.

DR. MILLER: Well, not too small to handle. You just can't treat those.

DR. NORMAND: You can't treat them?

DR. MILLER: Yes, can't treat them.

DR. NORMAND: So, because it's important, because in my mind, because you're also treating new areas -- new things that typically couldn't have been treated before.

DR. MILLER: That's correct.

DR. NORMAND: Okay.

DR. MILLER: Yes, and it wasn't sprayed on the areas that -- you know, for prophylactic, you had to have an air leak.

DR. NORMAND: Okay, thank you.

DR. CERFOLIO: And let me make sure you understand, that's what makes it good.

DR. NORMAND: I understand.

DR. CERFOLIO: That's why we want it, because for those patients without it, I

got nothing, all I got is air leaks and problems.

DR. NORMAND: Well, the question - - -

DR. CERFOLIO: And with the product, I'm able to apply it and treat something that I have no other treatment for besides observation.

DR. NORMAND: No, I understand. I think the question whether that's good or not is for this panel to discuss.

DR. CERFOLIO: Right.

DR. NORMAND: I'm not sure it's necessarily true that something that you couldn't do anything to would ultimately result in a bad outcome. But that's for us to --

DR. CERFOLIO: Well, but I'm here to give you my clinical opinion and my clinical opinion is that those leaks that I can't treat do lead to problems and we have all sorts of data that show that prolonged air leaks lead

to problems, and with a sealant, like I had in the past, which I no longer have, but I would with this product, it may help prevent that problem. So, clinically, it's important.

DR. NORMAND: And statistically, it is as well too, that's my point.

CHAIR BIRNBACH: Dr. Stoller:

DR. STOLLER: One, again, design question. I think it's been addressed, but I want to make sure I'm clear.

So, the primary outcome measures air leak at one month and the ascertainment of that primary outcome measure was completely based on the surgeon's assessment at the one month visit, with no other independent ascertainment of the primary outcome measure, is that correct?

DR. MILLER: That is correct, it was -- at the one month follow up, it's to determine if the patient was air leak free at that time.

DR. STOLLER: Right, and that was

made by the surgeon seeing the patient at the one month follow up visit?

DR. MILLER: Surgeon and the research coordinator who --

DR. STOLLER: Right, both of whom were not blinded to the application of sealant or control, is that correct?

DR. MILLER: That's correct.

DR. STOLLER: Okay.

CHAIR BIRNBACH: Dr. Cassiere, was that you waving before? No, Dr. Brunson.

DR. BRUNSON: This is -- maybe Dr. Cerfolio can answer this. It's about a statement you made about often, there are no leaks in the operating room, but I know that post-op, how would this product impact that, since you have to detect the leaks intra-op to find them?

DR. CERFOLIO; That's a very, very important question and this current study we're talking about, didn't put the product on prophylactically over the staple line.

As you know, there's a lot of surgeons that were using the previous product and currently, non-FDA off-label products and putting it on prophylactically for just that reason.

So, I don't think we have any data to suggest that that's what we should do. But it is frustrating when you see no leaks in the OR and then they have a big leak post-op, that some people might, if this product got approved, then do a prospective study looking at it prophylactically in the patient, that doesn't have an intra-operative leak and seeing if it's cost effective or not, because it might not be. But that's a different question.

DR. WALSH: I'd also like to add that sometimes, what happens when we're testing the product intra-operatively, we're doing it under positive pressure ventilation by the anesthesiologist, under saline and we're looking for bubbles and measuring the

size of the bubbles at the sites that are identified.

The patient then is excavated in the OR, goes to the recovery room, has a chest tube placed and one of the things is, it takes a while, it takes a day or so for the chest cavity to develop a pleura.

So, you basically have an open space with a chest tube that's connected to minus 25 centimeters of water. So, you're evacuating air that may be above the lung, but is just air. It's not leaking from the lung. It's just this potential air space. So, you don't have a tight container.

Also, the patient is breathing spontaneously. They may cough. It may generate a greater pressure than even you generated in -- intra-operatively under 25 centimeter water test.

But that's why there can be discrepancy in the OR. You have no bubbles, but in the recovery room, you have a few

bubbles unnoticed, and I think we have to keep emphasizing, although this study was powered for an endpoint and it was successful in that, and we cannot underestimate how important air leak is, as what we're trying to accomplish here.

Chest tubes stay in for other things, other than just air leaks. Chest tubes can have increased duration, just because of the output of the chest tube and the management of the chest tube by this service.

So, that accounts for not necessarily having chest tubes pulled out when the air leak is taunt.

CHAIR BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I have a question regarding the lymphadenectomy. Could you describe to me what the definition was of partial and complete, and the reason for bringing that up is because in the sealant group, there was no lymphadenectomy done in

29.1 percent of the patients and in the control, it was 19.3.

Then a complete lymphadenectomy in the sealant patients was 41.7 percent and 56.1 percent in the controls, and you think that was of clinical significance?

DR. MILLER: What a lymphadenectomy is, when someone has a primary malignancy within the chest, you must stage the mediastinum and in surgery, we'll either do a complete lymphadenectomy, which removes all lymph nodes from three stations. The peratracheal is a subcarinal in the hilar areas.

If the patient does not have a primary malignancy, such as a -- undergoing wedge extension for metastectomies, lymph nodes are not evaluated at that time.

If you look, in regards to the Z-30 trial, which is a trial that looked at lymph nodes dissection versus lymph node sampling, what a sampling is, is just when you remove

one lymph node for each one of those stations.

There is a slight increase in pleural fluid drainage after the procedure of only 20 cc's a day. But that's why there's a difference in those two patients, because not every patient requires a lymphadenectomy, especially in the patients who are undergoing surgery for emphysema or benign conditions when lymph node is not removed.

DR. CASSIERE: I guess what I'm getting at is it looks like there is more complete lymphadenectomy in the control than the sealant and there is no -- more lymphadenectomies being done in the control group than in the sealant group.

In other words, there's more manipulation of the pleura and the lymph nodes in the chest, the more you manipulate, the more you would think you would have air leaks.

DR. MILLER: That's not correct. It's looking at -- that's a mediastinum lymph node dissection. That doesn't affect the lung

at all. That's what that -- mediastinum lymph node dissections, that's what it implies.

DR. CASSIERE: So, the lymphectomy is totally the mediastinum?

DR. MILLER: Yes, into the lymph nodes.

DR. CASSIERE: Okay.

CHAIR BIRNBACH: Dr. Domino.

DR. DOMINO: Hi, I also had a question for clarification. Some of the patients who were excavated at the end of the case were how many were -- how many had mechanical ventilation. I think we heard, we didn't know what the length of positive pressure ventilation was.

Were there any differences in the groups, who were excavated at the end and didn't have mechanical ventilation versus those who need to intubated for a day or longer?

DR. WALSH: I know there's -- it comes to the point in there, there's concern

raised that this is unblinded. The surgeons understand what was put on the lung, but these -- as I was part of the original design of this with 3M, there are only five centers that did this and there are only, I think, 10 surgeons, and we spent a lot of time going over and meeting, what was going to be our consistent way of managing this patient and we discussed any vagrancies that we may have in our practice and try to be consistent.

All of these patients were extubated at the end of the case. Obviously, we'd have to dig into what the difference in surgical times were, but these are high volume centers. Most of us are going to have times that are fairly close for doing lobectomies or bi-lobectomies.

So, there was consistency in how the patients were treated intra-operatively, what the level of water test was under water, to test for bubbles. We agreed how we would define what the size of the bubble would be

and try to be consistent that way.

Most of us were very consistent in how we managed our patients in the post-operative setting.

So, for a multi-center trial, we selected surgeons who were high volume surgeons, had been doing this for a long time and these are kind of standard ways to managing post-thoracotomy patients. So, we tried to be very consistent across the centers.

DR. DOMINO: So, the answer to the question was, yes, they were extubated at the end of the case and didn't have mechanical ventilation for -- unless they needed it some time later.

DR. WALSH: Yes.

DR. DOMINO: And as far as the CPAP and BiPAP, you said before, you don't have the numbers of people who were on those. Would one expect that one -- with a CPAP or BiPAP device, that you might have a increase in an

air leak at all or is it more of a conventional, mechanical ventilation that might be associated with that?

DR. WALSH: I'd have to go back and look at the data, but obviously, if you're on a CPAP machine or a positive pressure ventilation, you're going to increase your air leak. But to my recollection, there is no differences in the groups and the number of people who needed positive pressure ventilation.

The management and the measure at the time of the recovery room, the air leak sealed intra-operatively, as all of these patients were extubated in the OR. They weren't on positive pressure ventilation when they got to the recovery room.

CHAIR BIRNBACH: I will take the Chair's prerogative to ask a question, Dr. Walsh, before you get too comfortable.

I would just like to follow up briefly with Dr. Normand's line of questions.

In the design of the study, why not exclude patients with renal failure and more importantly, why not blind the study?

DR. WALSH: One more time?

CHAIR BIRNBACH: When you designed the study, did you give any thought to the fact, number one, that the primary endpoint was not blinded and the surgeons who knew what sealant was going to be used were going to be the ones to call the shots and say, "Okay, I still have an air leak here."

Was any thought given to the fact that perhaps, the study should have been designed so that there was some blinding, and since renal failure seems to be an issue, had any thought before the study started, that maybe patients with certain disease states should be excluded, renal failure on the top of the list?

DR. WALSH: Well, it's certainly going back many years, since the original design. But we certainly wanted to have a

spectrum of patients that represented the type of patients that we were operating on, on a routine basis.

So, you can see in the eligibility criteria, these are fairly standard eligibility criteria and we took -- most on the patients that we operated on for lung cancer are sick patients, chronic obstructive pulmonary disease, diabetics, renal failures, so we wanted this to be applicable to the patient population that we deal with.

I think, you know, I think it's just a matter of manpower to run these studies post-operatively. I mean, we thought the most consistent way of assessing the post-operative air leak was to have the surgeon and their research personnel only be the ones that call the shots on whether there is or is not an air leak, because if you start introducing other people into it, it may actually compound it.

So, you know, it is to the surgeon's disadvantage, to say there's no air

leak and pull the chest tube out prematurely because that's going to come back to bite you.

So, if any side that we're going to err on, we always err on the side, even if there's a question of an air leak, we will leave the chest tube in for another 24 hours before discontinuing that tube because if you pull the tube out and you erred on the wrong side and they do, in fact, have an air leak, then you're going to end up with a potential empyemas.

So, most of us have learned to be cautious and leave the chest tubes in a little longer, rather than discontinuing them prematurely.

CHAIR BIRNBACH: Any more questions? Yes, Dr. Ries?

DR. RIES: Just a follow up question about the between center differences. I note that the centers were difference -- there were different numbers, different proportions of patients that were randomized in each center.

In terms of the 114 patients who were enrolled and then not randomized, were the same proportions between centers, was there differences in the selection of patients and the identification of the air leaks? Were the same proportions -- did you look at whether the same proportions of the non-enrolled patients represented the proportions at the centers that were enrolled?

DR. MILLER: Yes, and the majority -- greater than 95 percent of the time, it's because they had no air leak, and that was the same throughout all five centers.

DR. RIES: But were the number of patients who were determined by the surgeon to have no air leaks, the same proportions across the centers?

DR. MILLER: Yes, it was exactly the same.

DR. RIES: And just to address the renal function issue, there is no question about pre-clinical renal toxicity that we were

concerned about. From all the pre-clinical data, there was no concern, even though it was excreted urine. The only reason we brought the renal data today is because it was on the post hoc analysis by the FDA that brought up the question in regards to the renal failure.

CHAIR BIRNBACH: Any other questions?

DR. CERFOLIO: Can I just follow up on one point about the unblindedness, because I think I understand your point very well, but I want to make sure you understand, because as you said, you don't do thoracic surgery.

When you're seeing these patients back at a month, these patients have all been home, their chest tubes have been out for three weeks. So, for the surgeon to say whether they have an air leak or not, although the surgeon was the one saying it, obviously, it's really the radiology report that tells you if they have an air leak or not and the radiologist was blinded.

So, the radiologist is the one reading the films and said, "Hey, that pneumothorax is bigger. There's potentially an air leak there that you've missed."

So, when the surgeon is seeing them at one month, it's just a routine one month follow up. So, really the person reading the chest x-ray was blinded to the study.

Obviously, the surgeon is unblinded. He knows if he used a sealant or not and it was their chest tube management that they ran the same overall, but at one month, whether the surgeon is blinded or unblinded, really didn't make any difference because 99 percent of these patients were home doing well and just came back for another chest x-ray.

CHAIR BIRNBACH: So, the only determinant at one month was the chest x-ray reading?

DR. CERFOLIO: Sure, because if the patient is doing well and there's no

subcutaneous air, no other problems, if they had a pneumothorax when they went home and if that pneumothorax was the same, then there would be no evidence that there was air accumulating in that chest and as Dr. Walsh told you, if there's any question of an air leak, as a surgeon, we're going to leave that tube in because all we're going to have to do is put it back in, if we take it out prematurely.

CHAIR BIRNBACH: Dr. Stoller.

DR. STOLLER: I understand that. Would it then be reasonable to see data on the primary outcome measure as the radiology reports, with regard to the prevalence of air or the pleural space, irrespective of how defined, as residual pleural space or pneumothorax?

Perhaps that ought to be data that we'd like to see later in the afternoon, if it's not identical to the data on air leak free in the surgeon's assessment.

In other words, the prevalence of radiology reports about air in the pleural space, however defined in the compared groups at one month.

DR. SPINDELL: I just wanted to get back to you, Dr. Cerfolio. The determination of air leak in a month was chest x-ray and clinical exam or just chest x-ray?

DR. MILLER: Chest x-ray and clinical exam.

DR. SPINDELL: Okay, all right.

DR. MILLER: Because we examine the incision. We look for subcutaneous emphysema. Also, we discuss with patient if we had any sensory related signs or symptoms related to broncho pleural fistula. So, all that went into the routine post-operative visit.

DR. SPINDELL: And the follow up chest x-ray, getting to Dr. Stoller's point, as you said, as we've seen, it's not uncommon to have some residual space. So, if the person still has residual space, does that

mean they have an air leak or not have an air leak or you can't tell?

DR. MILLER: Well, if it is not increasing in size, it's decreasing in size, then they don't have an air leak.

DR. SPINDELL: So, I guess getting to Dr. Stoller's question, is the data we need to look at follow up chest x-rays and the size of the residual space change, because if we just used the actual residual space, we're not going to get the correct answer?

DR. MILLER: Well, there's no way to accurately -- this was what was brought up in the ad hoc analysis, there's no way to accurately measure that pleural space. You can't do it from a chest x-ray, because it's actually a three dimensional volume.

So, if you tried to measure something from the chest x-ray, you can't do that. You can say if the air space dropped two or three inter-spaces down, then there's a significant problem and only one patient out

of that sub-group analysis in the center group, had an increasing air space, and there's a patient who had the extended resection and that was treated with a chest tube.

CHAIR BIRNBACH: Dr. Stoller.

DR. STOLLER: Under the circumstances, I might suggest that perhaps consideration for a later session be given to presenting the one month follow up data with three endpoints.

One is the prevalence of air in the pleural space, irrespective of any conditions about increasing or decreasing. Two, the prevalence of air in the pleural space that was deemed to be of decreasing size at one month, compared to the prior film, and three, the surgeon's assessment of whether there was or was not an air leak, which would allow an assessment of concordance between the three assessments, with regard to the residual air in the pleural space and would allow the

committee, I think, to better understand discordance between the clinical assessment of air leak free at one month and the radiologic assessment. Does that make sense?

CHAIR BIRNBACH: Okay, we are now going to have a short break. It is about 10:10 a.m. We will resume in 15 minutes at 10:25 a.m. I'd like to remind the panel members that there should be no discussion of the PMA during the break among yourselves with the sponsor, FDA or with the public and we will reconvene at 10:25 a.m. Thank you.

(Whereupon, the above-entitled matter went off the record at approximately 10:10 a.m. and resumed at approximately 10:30 a.m.)

CHAIR BIRNBACH: Welcome back. The sponsor has asked for a few minutes to clarify a few points. Dr. Walsh, you have five minutes.

DR. WALSH: Thank you. I'd like to address a little bit about what was raised

about the methodology of bias in this design. As a surgeon, I want to go over, so it's crystal clear, what was done intra-operatively.

We did the operation. At the end of the operation, the patients were initially enrolled. At the end of the operation, we assessed underwater air leak, to see if there was an air leak. A certain number of the patients, 114 actually, had no air leak, were not part of the study.

Those that were identified to have an air leak intra-operatively, greater than two millimeters, the number of sites that were leaking, we recorded.

At this point, the surgeon does not know what this patient is going to randomize to. They do their best shot at repairing things that can be repaired, suturing small holes or larger holes, trying to repair pleural flaps, anything that we could do.

At that point at the sites, the

patient is randomized. They are randomized either to no further treatment or to the sealant. Those that have the sealant, have the sealant applied to the sites of the repair and the sites that could not be repaired. The patient is reassessed for air leaks and the air leaks are measured.

The patient then goes to the recovery room and the surgeon makes an assessment whether or not there is or is not an air leak. It's really black or white. The surgeon is the one, although they understand whether or not this was a patient who had a sealant or not, is assessing the patient every day thereafter.

If at any time in the follow up days, the patient is identified of having a leak in a chest tube, then they would not qualify as being air leak free.

DR. OST: Good morning. My name is Dr. David Ost. I'm a paid consultant for this study. None of the study was performed at my

institution. I do not own any other stock or have any other conflict of interest with this study.

I wanted to address some of the issues which were brought up. I am a pulmonologist, but I also studied at the Harvard School of Public Health and I can appreciate some of the difficulty of understanding the protocol.

Importantly, as was just pointed out, the randomization occurred after all standard techniques were applied. So, when the standard techniques were applied, no one could know before hand, whether they were treating a control or sealant patient.

The second point I want to emphasize, which was just made, it's correct, the assessment of persistent air leak was not blinded. It was done by a surgeon, but it is a fairly objective thing, meaning, you can -- you know, in terms of a surgeon or a pulmonologist looking at the chest tube, in

the recovery room, post-op day one, post-op day two, you're just looking for bubbles in that chest tube container. They were not grading the size.

So, any bubbles after the recovery room would mean you were not air leak free, and that effect size of 21 percent -- you know, so, that's a number needed to treat only five patients, to be certain of the relatively objective criteria of being air leak free throughout.

So, it was not just assessed at day 30. It was assessed at day 30, but also throughout the hospital stay. So, if you had bubbles on day three, you're done. You're not in that winning category of completely air leak free.

The other question I wanted to address was the clinical significance and I'm going to try to do that briefly and quickly, and the concordance issue, which was a great question.

When I reviewed the protocol, I had a lot of the same questions. From my definitions, pleural space does not necessarily imply air leak. It's the lung partially filling a space.

So, this is the key slide right here. You see the sealant and the control group, those who had complete versus partial lung re-expansion, realizing that partial does not imply air leak.

Note at the bottom, adverse events which were clinically significant pneumothorax, okay, is not every patient who has a partially expanded lung, which really means, partially filled space. The lung -- the remaining lobes could be fully expanded. You just haven't filled the space, like the bird cage.

So, you see there that indeed, you could have partially expanded lung, partially filled space and not have a clinically significant adverse event from pneumothorax

and that's the key.

So, not all persistent spaces are pneumothoraces -- are clinically significant, okay, and for the primary outcome of importance, which is being air leak free for every day from the recovery room onward, the primary outcome measure effect size was there and the effect size wasn't only statistically significant, the effect size is big. The number needed to treat is five. So, that's a big effect size.

I hope that clarifies the procedure, the magnitude of the effect and I think we've dealt with the safety. Thank you.

DR. WALSH: We'd also like to add about the question about consistencies across centers. As you know, there are several ways of measuring, intra-operative, the water test in the recovery room and subsequent post-operative day by the chest tube at 30 days, mostly by radiographic evaluation.

There is consistencies within the

centers between the two surgeons and the centers and there is consistency across all of the centers in this study.

The results were the same, but the sealant patients always did better throughout the entire study.

CHAIR BIRNBACH: Thank you. We will now hear the FDA presentation. The first FDA presenter is Charles Durfor, PhD, the review team leader for this PMA.

DR. DURFOR: Well, good morning to you all and thank you for your time and your effort in reviewing this application. My name is Charles Durfor. I'm a member of the Plastic and Reconstruction Surgery Devices Branch in the Office of the Device Evaluation and I'm introducing the FDA discussion concerning the PMA for ProGEL Surgical Sealant.

The review team for this PMA included myself, and I looked at manufacturing review and lead review. Dr. Roxolana

Horbowyj, Medical Officer and surgeon performed the clinical review. Dr. Chang Lao, the FDA statistician was involved. Dr. Katherine Merritt looked at pre-clinical review. Dr. Kirschbaum, who is a member of the Center for Biologics Evaluation and Research assisted us in looking at both the manufacture of the human serum albumin component, as well as immunological analysis and then there were also members of our compliance staff and our patient labeling staff, who assisted in the review of this application.

The order of presentation is the following: I'm offering you an introduction at this point and then I will provide you some information on pre-clinical studies and clinical immunology.

That will be followed by Dr. Roxolana Horbowyj, who will discuss the study design and patient demographics that were observed in this study. Dr. Chang Lao will

then provided the statistical perspective of the study outcomes and Dr. Roxolana Horbowyj will then conclude our presentation with a clinical perspective of the study outcomes.

As you've already heard, ProGEL Surgical Sealant is comprised of two components. The first is a 30 percent solution of human serum albumin, which is purchased from an FDA license supplier. The second component is a polyethylene glycol cross-linker that has been chemically modified with NHS N-hydroxysuccinimide esters at each end and that facilitates cross-linking of the human serum albumin.

As illustrated in this slide, the final product has both solutions packaged and sealed cartridges within a single syringe. The tip both mixes and sprays the solutions onto the lung tissue.

Once on the tissue, the cross-linker reacts with both human serum albumin to form a patch and to some extent, with the lung

tissue.

Unlike many other products you will review, this one is somewhat different in that the device actually forms within inside the patient on their tissue.

The proposed indication that was provided in the protocol was an as adjunct to standard tissue closure techniques to seal or reduce air leaks during pulmonary surgery.

The sponsor has previously provided you information on the pre-clinical testing of this product and therefore, in the interest of not repeating what they've said, I will focus my comments on specifically, the pre-clinical testing issues, to which we think are worthy of your consideration and that does not include -- we have no concern at this point with the cytotoxicity in sensitization studies, acute systemic toxicity and geno-toxicity, hemolysis and pyrogenicity studies that were presented.

With regard to sub-chronics,

toxicity studies, studies were performed by polymerizing the product interperitoneally in mice and rats. In a mouse study, slight to moderate inflammation was observed at seven days and this reaction was reduced at 14 days after implantation.

When the commercial product was polymerized in situ in rats, the following observations were made. There were no systemic adverse events noted in the animals. At the day eight sacrifice, there were discreet, darkened segments of slight to moderate inflammation on the small intestines of several mid 20 times the anticipate does and high 50 times the anticipated dose animals.

This gross observation corresponded to microscopic findings of inflammation, neo-vascularization, hemorrhage and some volume material at the implant contact sites.

The severity of inflammation was slightly greater for treated sites versus sham

sites within each group and there were similar responses when treated sites were compared across all groups. There were no gender differences observed, in terms of the animal's response. These findings were reversed and not observed in day 29.

In a follow up study, which the sponsor has discussed, the severity of inflammation was reduced by installation of saline into the peritoneal cavity after the product was polymerized.

Thus, the reaction, the inflammation may be related to a chemical reaction of the product with host tissue that's somewhat diluted by saline or it may be of hygroscopic nature of the sealant itself and saline addresses that. This is, to us, unclear.

Regarding product irritation, the product was not an irritant, when in situ polymerization was performed on intact rabbit skin or when extracts of the commercial

product were used in a standard intracutaneous irritation study in rabbits.

Mild irritation was observed when the commercial device was polymerized on the conjunctival sac of a rabbit's eyes and when the product was polymerized intracutaneously in a rabbit, there was moderate to severe irritation observed and this was the commercial product that was polymerized.

In these studies, the center of the injection sites were raised, hardened, somewhat pale and blanche with a palpable device under the skin. Dermal erythema scores of two on a four point scale were recorded at all injection sites at 24 hours and at 14 and 15 sites at 14 days after implantation.

This response may reflect a pressure induced irritation. It may also reflect the hygroscopic nature of the device or once again it may reflect reaction of the product with animal tissue.

To further examine device

performance, the sealant was polymerized on an imperfect staple line after resection of the caudal portion of the cranial lobe of a pig's left lung.

In the first study, which was a seven day study, there was no evidence of an immune response observed in the animals and the criteria for this was lymphocytes in clusters, the presence of plasma cells, multi-nucleated giant cells, Langerhans cells or granulomatous inflammation that was not associated with a foreign body. In addition, there were no air leaks or delays in tissue healing that were observed.

The absence in immune response is actually important because in this study, a commercial product was used in pigs and the absence of immune response suggests that maybe this was a good model and that anything that was observed was not related to an immune response against human serum albumin.

There was however, one of the

findings microscopically was the squamous metaplasia that was observed at the implant site and what I would like to do is just offer you the comments that were in the pathology report associated with that finding.

It's stated that squamous metaplasia was present in the lung to a greater degree than other animals. This response is in keeping with the basic reaction of differentiated tissue to an inflammatory stimulus and the tissue transforms into a less -- essentially, the tissue was transforming to a less metabolically complicated form.

Squamous metaplasia inflammation and fibrosis associated with the wound repair occurred in a fashion similar to those that have been described in humans, and the sighted reference is given for you there.

In a follow up study where pigs were followed for 28 days, healing was described in the following method in a pathology report. At day one, only hemorrhage

was present. By day four, granulation tissue had moved into the pleural and the sealant was largely absent.

By day seven, only isolated fragments of sealant were apparent. By day 14, the sealant was no longer observed. Wound repair in this model did progress normally and there was no indication of a foreign body response or a macrophage response.

As with before, device application lead to inflammation in squamous metaplasia. The pathology report associated with this finding stated that squamous metaplasia involving the lung was identified in the regions of atelectasis and inflammation that were common near the site of surgical closure. Squamous metaplasia was observed only on days four and seven after surgery.

While atelectasis and fibrosis were reported at days 14 and 28 days after surgery, squamous metaplasia was not.

The sponsor also performed two

pharmacokinetic studies to determine the clearance rate of the product and these were performed where they made a carbon 14 labeled cross-linker that was then polymerized in situ with the commercial product.

In the first pilot study, urine was identified as the major route of clearance with 70 percent of the radio labeled product being excreted within one to three days after implantation. There were no gender differences -- gender specific differences noted.

In a follow up study, over 50 percent of the carbon 14 labeled device was excreted in one day and virtually all radio-activity was recovered from rats 14 days post-implant.

As discussed previously, the properties and performance characteristics of the device have been evaluated. The conditions of the final product sterilization do not appear to alter the structure of the human serum albumin. The gel time of eight

seconds was reported for two investigational lobs in the PMA and the burst strength has already been discussed before.

Both the data for the burst strength and the elastic modules appear to be appropriate for the clinical indication of the product.

So, to summarize the pre-clinical studies and in the information that I hope you will take forward, in the sub-chronic toxicity studies, in situ polymerization resulted in slight to moderate inflammation on the small intestines of several mid and high dose animals; rats.

This was associated with microscopic signs of inflammation, neo-vascularization and hemorrhage. Whether this is caused by device reaction with the host tissue or hygroscopic device is unclear.

In a standard irritation study where the product was polymerized intra-cutaneously in rabbits, moderate to severe

irritation was observed when the device was polymerized in rats. In pig lung studies, wound healing was not delayed, but the product was largely absent by four days, with only isolated fragments visible in seven days and was not observed at all by 14 days.

Inflammation fibrosis and squamous metaplasia were common near the site of surgical closure on days four and seven after implantation.

Finally, in pharmacokinetic studies, they were also consistent with the observations in the pig study that the product clears rapidly from animals, and in this case, over 50 percent of this carbon 14 label product was excreted during the first day. Urine was the primary route of clearance, which is what has us paying some attention to the potential for renal toxicity.

To finish this presentation, I'm going to do something that's a little out of order and I apologize, but the clinical data

on immunology testing, at this time, presents no concern to FDA. We want to give you an overview of what was done, so that then, as the other presentations go forward, you can focus on the essential elements.

The concern for this testing was related to a publication involving 65 patients who were undergoing hemodialysis who developed IgE antibodies against ethylene oxide in dialysis tubing, and that resulted in 24 of the 65 patients experiencing anaphylaxis.

Now, FDA recognizes and wants to caution that there are significant differences between the reported observation and ProGEL Surgical Sealant that is being discussed today.

First, ProGEL Surgical Sealant, unlike hemodialysis, is a single exposure and that's obviously important for an immune sensitization, and second of all, polyethylene glycol modification has been used and there are FDA approved products in which

polyethylene glycol modification is used to suppress immune responses against other proteins.

So, with that in mind, we felt it was important to have the sponsor evaluate immunology, but we don't want to try and imply that what was observed in the publication was going to happen here. It was instead, something that needed to be evaluated.

This slide gives you an overview of the studies that were done to look for antibody responses against the product and it also gives you a sense of the sera collection that was determined.

The ELISA assay that was used was developed against the polymerized sealant and the analysis involved testing both pre and pro treatment samples that were collected from 72 percent of the sealant and 76 percent of the control patients.

The results of this study for the pivotal study were that one treatment and one

control subject had post-operative antibodies levels that were suggestive of the formation of antibodies against the sealant.

However, because there was a pre-operative sera at elevated levels as well for both patients, this suggested that these subjects entered the study with a pre-existing antibody titer against the polymerized sealant.

A second immunological study was done to look for cellular responses against the product and that was -- this is outlined here. In this assay, a positive response is done -- is observed when the number of peripheral blood mononuclear cells increases after exposure to a specific antigen.

The way the study was designed, tests were performed for a cellular response to see whether it was impaired or stimulated by the presence of sealant and known antigens and that was the positive control, to see whether the presence of the sealant actually

stimulated or suppressed any sort of immune -- cellular immune response.

Once again, subjects were evaluated both pre and after surgery and antigen samples were available for 69 sealant and 32 control subjects and mitogen antigen samples were obtained for 59 and 34 subjects.

The results of this study, the only statistically significant observation, was that the control group had a lower pre-operative value for tetanus toxoid and this was not deemed to be a critical issue because it was pre-exposure and it was the control group.

However, using the responses for the control samples, 95 percent competence interval was identified and this was an interval that was used then to identify which patients after treatment may have had a cellular response that fell outside the normal range.

Ten sealants and five control

subjects fell outside this normal range and the clinical outcomes of these patients were evaluated with regard to the incidence of the emergence of adverse events that might be possibly related to sealant. This slide shows you the adverse events that were considered in this analysis.

Based on the results of this analysis for the 10 sealant and five control subjects for which the lymphocyte proliferation assay response fell outside the 95 percent competence interval, there was no correlation that appeared to exist between abnormal LPA values and an immune related adverse events for these 10 sealant, five control subjects.

With that, I would like to introduce Dr. Roxolana Horbowyj who will discuss this study design and will also discuss patient demographics.

DR. HORBOWYJ: Good morning. My name is Roxolana Horbowyj and I'm a general

and critical care surgeon, as well as a medical officer for the submission.

This portion of the FDA's presentation highlights ProGEL Surgical Sealant clinical study design, as well as demographics and operative parameters.

Some of the slides presented here may have information that has already been presented by this sponsor this morning, and so, I'll try to present those only very briefly.

ProGEL Surgical Sealant is a two component device which consists of 25 percent pooled human serum and a synthetic cross-linking component of polyethylene glycol, which react to form a clear compliant hydrogel.

This sealant is applied in the sterile single use two component kit with a two cc volume that's to be applied to the external surface of the lung, up to three times per air leak.

Components mix of point of delivery and delivery as such initiates reaction. Polymerization is to occur in 20 to 30 seconds without need for other adjuncts and gel strength is expected to be sufficient to withstand 30 millimeters pressure in two minutes.

As you've heard, the ProGEL Surgical Sealant is intended to be indicated for use as an adjunct to standard tissue closure techniques for sealing or reducing air leaks incurred during pulmonary surgery.

The clinical study in this pre-market application is a prospective, unmasked two to one randomized clinical study. Sample size was calculated to evaluate the proportion of patients who remained air leak free following pulmonary surgery through the duration of one month follow up or through hospital stay, whichever was longer, with a clinically significant difference of 25 percent decrease in patients with post-

operative air leak.

Control with standard of care alone, that is sutures or staples, in the investigational devices you've heard, was the standard of care follow up by a sealant. The study was conducted at five U.S. centers.

Study participants were consented, non-pregnant or breast feeding adults patients with an intra-operative air leak of greater than or equal to two millimeters following lung surgery through open thoracotomy and who were not known to be hypersensitive to albumin or participating in other clinical trials, as per the study design.

Patients were enrolled pre-operatively and reassessed intra-operatively after surgery or before chest -- that is, before chest closure for intra-operative air leaks greater than or equal to two millimeters.

Patients with at least one intra-operative greater than or equal to two

millimeters were then stratified for FEV1 greater than 40 percent or less than or equal to 40 percent.

Patients then had their air leaks identified and stratified by size, received standard care to seal the air leaks, as possible by the standard of care and were randomized two to one ratio.

If randomization to control occurred, then no further treatment was to be done. It was recognized in the protocol that some air leaks would not be closed, that is, air leaks that were potentially too small or too fragile to have the standard of care applied to them. The standard of care again, being the staples or sutures.

If randomization to sealant was to be applied, then all identified air leaks, including air leaks that may have been considered too small or tissue too fragile to apply standard of care, up to three attempts to seal an air leak were permitted and for the

sealant, no maximum device dose or volume was specified. At the conclusion, air leaks were again reassessed before chest closure.

There was perspective consensus on some aspects of chest tube management, as listed here and also as presented by the sponsor this morning. Physician discretion was allowed for use of water for up to 24 hours, for use of Heimlich valves and for the duration of air leak cessation before chest tube removal.

The protocol recognized that patients discharged with the Heimlich valve would affect the accuracy in recording the duration of the post-operative air leaks since patients would not be in the hospital for daily observation, but would return on a weekly basis for assessment of air leakage.

These instances were expected to be wrong and -- rare, excuse me, and that is stated in the protocol and therefore, duration of air leak was planned to use the number of

days elapsed from surgery until the patient returns to clinic with no air leak.

Follow up was from surgery through 30 days post surgery and included evaluation of the chest tube, air leak and drainage, chest x-rays, which included a 30 day post-operative chest x-ray, time to no air leak, time to chest tube removal and time to hospital discharge, laboratory values, including immune responses, this was just described, and adverse events.

In this study, 275 patients were enrolled, 161 of these patients met pre- and intra-operative criteria and were randomized. Nine patients died. Two patients in each group were lost to follow up. Two sealant treated patients were discontinued, one for transplant of the lung and one for lobectomy. Overall, 148 patients completed this study.

Base line demographics where generally considered to be clinically comparable across the cohorts. Please note

there were no differences between the cohorts for pulmonary function tests.

There were slightly more, nearly three percent more control patients that had had previous thoracic surgery as on this slide.

Cohorts were generally also considered to be reasonably comparable for diagnosis profiles, also comparable as to type of surgery, including the rate of right upper lobectomy, left upper lobectomy and all upper lobectomies.

The recently proposed idea to retrospectively regroup patients by procedure, specifically to combine procedures in which partial lobes were resected, was considered inappropriate because the volume of resected lung in partial resections, such as wedge resection, was not recorded and data comparability would therefore be precluded.

Cohorts were also considered comparable as to surgical approaches, as well

as the incidents and severity of pleural adhesions, although the control cohort had 8.5 percent more patients reported to have extensive adhesions.

Overall, the intra-operative air leak profile was also considered to be comparable and the total number of air leaks per cohort was consistent with the two to one randomization.

In patients randomized the standard of care plus sealant, sealant was most commonly applied once, although three applications were allowed.

As to time, time in the operating room and time to skin closure were both considered to be comparable.

At this time, it's my pleasure to introduce Dr. Chang Lao, who will present the FDA statistical perspective on their outcomes.

DR. LAO: Good morning. My name is Chang Lao, Division of Biostatistics and Office of Surveillance and Biostatistics.

My presentation today, this is altering of my the presentation, indication for use, primary and secondary efficacy endpoint, study design and statistical -- and as it results, efficacy and summary.

Indication for use, this adjunct device to stent tissue closure technique, sealing or reducing air leak include preliminary surgery. Study design, this is open label, multi-center, five centers control trial, study of care use as control, two to one randomized by plus size equals size, blocked by investigator or surgeons within sites, stratified by predict FEV1.

Assuming you know the prime efficacy endpoint is a proportion of patients who were air leak free from point of surgery through the one month visit or the duration of hospitalization, which ever is longer.

Five secondary efficacy endpoint, proportion of intra-operative air leak IO areas sealed, proportion of recovery of post-

operative air leak, POAL-free, duration of POAL from time of surgery, in term of days, duration of chest tube placement in days by survival analysis and last one is the duration of hospitalization in days by survival analysis.

Sample size, total 275 patient in load, of 275, 70 patients not randomized due to intro- —- apparent air leaks, 44 patients not randomized for other reasons.

So, with your total of 114 patients not part of -- not randomized, subtract 114 from 275, you have -- we have 161 patient randomized. Of the 161 with sealant group versus 58 in control group, nearly two to one ratio, but not exactly equal two to one.

The superiority trial, two sided type of area equal five percent -- 80 percent, assume control of POAL percentage around 60 to 70 percent, clearly indicate the technical difference, equal 25 percent. Expected drop out rate of about 10 percent.

The patient complete the whole study short of 92 percent versus control of 91 percent and Dr. Horbowyj already told you, patient accountability looks at distribution of complete and not complete patient comparable between the two groups.

There is this randomization centers of vascular with site, five site, the number of surgeons range from one to three, depending on which site and you have the sample size ratio by surgeon.

So, you can see some of them exactly two to one, because this is the plus size of multiple six. So, some samples are not necessarily equal six. For example, the site at number four, you can see that seven days before, surgeon number two, the four to two is a two to one. But not necessarily applied a two to one ratio to all the surgeons.

So, any division of the two to one randomization impacts because this open study

and it impacts to the clinical outcome is --- I don't know, but this is -- can be potential problem if you switch some patients from one group to the other group.

Table two is statistical analysis results for the primary efficacy endpoint, POAL-free by site. With each site, we calculate odd ratio. That's the odd ratio defined at the bottom of the table, probability of success divided by -- probability of failure for the same group, that's for the center group, divided by same as for the control group.

By this definition, if odds ratio greater than one in favor of sealant, otherwise for the control.

The combined odds ratio based on this table, based on our site combined, 3.36. That's calculated from the bottom of table, number of success in the second group divided by number of failure in the control -- number of failure in the sealant group. That's odds

for the sealant divided by the odds for the control group.

So, in this definition, odds were greater than one in favor of sealant group. Three criteria to justify for pooling of a multi-center trial, number one, is there any treatment effect? There's no hypothesis here, no treatment effect across five centers, a guess of hypothesis at the least one treatment effect, surely, at least one or more across five centers.

So, this hypothesis can be tested upon many hazard tests or the Mantel-Haenszel test, basically, two tests per year, pretty similar results, only a different variation of the test.

The Mantel-Haenszel is a condition of the margin for total issued by two tables, unconditional test. If you pass the number one question, then the criteria number two is there any -- if there is a treatment effect, we would like to know, is there any common

treatment effect over five sites.

The can be done by the base load day, how much needed the test, and the base load, the test is a global test. It is done -- these are designed for test recording treatment by center interaction.

So, if your odds ratio goes opposite the ratio of qualified site, this base load test is not very powerful.

Number three, if you pass the criteria, number two, is there is homogeneity, can we get a combined common estimate for odds ratio at a base level of five site.

This can be done Mantel-Haenszel test, it's a fixed effective model. We assume they have passed the homogeneity test already, otherwise --

The results -- three criteria for putting a mulit-center trial number one, is there any treatment effect? The answer is yes, P equals .0039 in favor of sealant to reject a known hypothesis of no treatment

effect.

No hypothesis here is defined as ratio equal one by Mantel-Haenszel test. Number two, if there is a treatment effect, is there any common treatment effect? The answer is yes. Base load day Homogeneity test, the P equaled .39 failed to reject no hypothesis of no common odds ratio.

Note at the bottom, if not homogeneity at our center, we can always try random effect putting various among site to site into the model.

Last, number three, if there is a homogeneity acquired by the center, in terms of prime endpoint, can we get a combined common estimate between the five sites? The answer is yes. Combined odds ratio here is a weight by site to site equals 3.34, 95 competency interval for the true odds ratio 1.429.1 doesn't include one, P value equals .005, which means reject no hypothesis of no common odds ratio, no common treatment effect.

No hypothesis here defines common odds ratio equals one.

At the bottom of the table, I said there were no significant cohort in this analysis, so, in the model we used here, only treatment with only covariable use in the comparison. No other comparable -- the other one --

Table three, this is the five secondary endpoint. Number one is intra-operative ARD IOAL sealed, two different analysis. First one would depend on what event because each patient is some -- more than one IOAL at the beginning.

So, depending on how many of them is sealed-- number per event, second as a patient. Each patient only counted once and 76 percent was 15 percent in favor of the sealant group, P value sponsors .001.

Assuming independence among model event per patient and with this kind of assumption, because I don't have data to

validate that, but because the P value is so small, even if you take care of the independent correlation into consideration, probably won't change the result very much, otherwise we can try different type of collated binomial or cluster binomial or a kind of beta binomial. But here, I didn't try that.

The second analysis is the same, the .9 percent and 10 percent, also of the sealant group, therefore, a Fisher's exact test. The second endpoint that we covered on POAL sealed at 54.4 percent was 32 percent, P equals .022, Fisher's exact test.

Number three, duration of the post-operative leak sealed from time of surgery. This is continuous data, so we used -- it caused some grief with some typical data, not distribution. So, P equals .41, no difference between the two group, mean equals 4.7 days for sealant group versus 3.6 days for the control group.

This is number four, secondary endpoint is a chest tube removal by survival analysis. So, the probability of chest tube removal, this was applied upward because this is a good event. If recurring event, we plus the other curve -- increase the function of time, otherwise it plugs downward, decrease the function of time.

So, here is a meeting of five days each. It means at day five, about 50 percent of the patients had a chest tube removal and the meaning of the meeting is slightly different because this not exactly for the Gaussian distribution and the logged rank test .P .89, not difference.

Again, we're constantly ranking some test .57, no difference between the two groups and the log rank test saw equal weight at each time point, where tests add some more weight at the beginning of study, when more patients under observation.

Number five, probability of

hospital day duration, the sealant is slight above what the control group, median is 7.4 days for sealant group versus 9.3 days for control. Median is about one day shorter than control group. Log rank test .041 statistical significant, but however we say, the test center group where the discharge -- was one patient in the control, when the discharge was having an issue with the valve. But compared to the sub-group analysis in their presentation.

Summary, the primary efficacy endpoint statistically significant combined odds ratio equals 3.34, 95 competency interval 1.4 to 9.1, doesn't include one in favor of the sealant group.

Proportion of POAL-sealed, 35 percent was 13.8 percent control. Summary for five secondary endpoint, number one, intra-operative air leaks, P less than .01, in favor of sealant group, seven day, 70.9 per patient was 10.3 percent for patient Fisher exact

test.

Number two, recovery lung POAL-sealed, P equal .002, also in favor of the sealant group, which was 54 percent for the sealant group versus 32 percent for the control, Fisher exact test.

Number three, no secondary difference duration of POAL-sealed from time of surgery, the main 4.7 days for sealant, 3.6 days for control, P equal .41, but we're constantly ranking some number test.

Number four, no secondary difference in probability chest tube removal, five days each for the median.

Number five, hospitalization, log rank test is .041, favor of the sealant group. This is a summary of the efficacy data, but I want to add one comment for the same calculation. One or three patient will versus 58 patients control-and these remedies are based on efficacy, not based on safety.

For safety, for such a small sample

size, not enough power to detect the real event between the two groups. This end my talk. Thank you very much.

DR. HORBOWYJ: This section of the FDA presentation addresses the outcomes from the clinical perspective and issues and FDA questions to the Panel.

FDA questions to the Panel will request your comment on the following: potential clinical impact of product resident's time, potential clinical outcome of renal clearance and/or toxicity, overall assurance of product effectiveness and overall assurance of a reasonable risk -- reasonable level of risk -- that risk of adverse events, illness or injury associated with the use of ProGEL Surgical Sealant for its intended uses and conditions of use.

This presentation provides a clinical complement to Dr. Chang's statistical prospective on the effectiveness endpoints, namely incidence of air leak-free patients,

time to hospital discharge days, time to air leak sealed days, time to chest tube removal days, as well as specific pulmonary renal questions, issues and FDA questions to the Panel.

As Dr. Chang has described, a primary effectiveness endpoint of no air leak through one month post-operative was met, as was the secondary effectiveness endpoints of no air leak in the operating room and the recovery room.

The column labeled difference on these slides represents the difference between cohorts. The notation next to the number notes for which cohort the difference was greater.

Review finds that there was a 60 percent difference between cohorts for air leaks sealed per patients in the operating room and the incidences change between the OR and the recovery room because in both groups, there were patients without an air leak in the operating room who developed an air leak in

the recovery room and there were patients with an air leak in the operating whose air leak was not present in the recovery room.

Therefore, the difference between -- - therefore, the 60 percent difference between cohorts for no air leak in the operating room changed to a difference of 23.9 percent in the recovery room.

These changes in instances of air leak between the operating room and recovery room are clinically notable.

From the OR through one month follow up, there was a 30.1 percent difference favoring the investigational cohort. From the recovery room through one month follow up, there was a 21.6 percent difference, favoring the investigational advice cohort.

Time to hospital discharge data is presented here and this data is based upon FDA statistician recount of per patient data. Differences between investigational device and cohort are presented, since the study was not

powered to endpoints other than the primary effectiveness endpoint, which you saw on the other slide.

The data was reported in increments of two days through 11 days and then is greater than 11 days.

For this endpoint that is time to hospital discharge days, 3.8 and 7.9, or a total of 11.7 percent, more investigational device patients in control were discharged home by day six.

However, eight percent more investigational device patients with a post-operative air leak at more than five days received a Heimlich valve and were discharged with a Heimlich valve.

As you've heard, the use of the Heimlich valve was for physician discretion, not per prospective guidelines defined in the protocol. Four sealant patients received a Heimlich valve for persistent and symptomatic air leak and were consider to have a

pneumothorax as an adverse event. No control patients received a Heimlich valve for a persistent or symptomatic air leak.

Seven other sealant and one control patient received a Heimlich valve for a persistent asymptomatic air leak alone and were not considered to have an adverse event.

Heimlich valves used in these patients decreased time to hospital discharge for these patients. However, as Heimlich valve use criteria were not prospectively declined, Heimlich valve use confounds interpretation of time to hospital discharge, due to the lack of information to support uniform application of consensus criteria for Heimlich valve use during this clinical trial. Data excluding patients discharged with the Heimlich valve has not been reviewed by FDA.

Time to no air leak data is presented here. This data demonstrates that 2.4 percent of more investigational device patients had no air leak at zero to two days.

However, 6.6 and 3.5 or a total of 10.1 were control patients had no air leak at three to six days.

Data also demonstrates a 7.4 percent more investigational device patients, time to no air leak endpoint occurred at more than 11 days.

Since patients were discharged with the Heimlich valve and were re-evaluated at one week increments, rather than daily, patient discharge from the hospital with Heimlich valve and weekly rather than daily increments confounded a determination of the true number of days to no air leak in these patients.

Nonetheless, the data does say that four percent more investigational device patients, time to no air leak occurred in more than 11 days.

This slide presents time to chest tube removal. The data here demonstrates that while there was a 1.9 percent difference in

favor of the investigational device at zero to two days, most patients in both groups had chest tubes removed at three to six days.

However, thereafter, more control patients had chest tubes removed through 11 days, while more investigational device patients had chest tubes removed after 11 days.

Again, since patients discharged with the Heimlich valve were re-evaluated at one-week increments rather than daily, discharge from the hospital with a Heimlich valve and weekly rather than daily assessments confound a determination of the true days to no air leak in these patients and may have also affected time to chest tube removal determination.

Nonetheless, 7.4 percent more investigational device patients time to chest tube removal was at more than 11 days.

In addition to the pulmonary parameters just discussed, the following four

issues were presented by the sponsor and form the basis of FDA questions to the Panel, as these represent clinical outcomes that may impact patient safety.

Delayed air leaks were defined as an air leak that occurred first on or after post-operative day two. Data demonstrated that six percent more sealant-treated patients than control experience air leak that occurred in this way.

Prolonged air leaks were defined as any air leak that was present in the recovery room on post-operative day zero or on post-operative day one and was still present after post-operative day seven.

Data demonstrated that two percent more investigational device compared to control patients have prolonged air leak at day seven and that 7.5 percent more investigational device patients compared to control have prolonged air leak through and after 11 days.

Pneumothorax was considered symptomatic -- when considered symptomatic, was presented as an adverse event. In the standard care plus sealant cohort, pneumothorax as an adverse event was reported in nine of 103 patients.

Five of these nine patients required intervention, such as a chest tube or Heimlich valve to be placed. One of these patients died. Also, one patient who presented with a pneumothorax three weeks post surgery was reported by the investigator to have a serious, unexpected device-related adverse effect due to the temporal relationship of the event with the use of the sealant and this information is related in the sponsor's executive summary in your Panel pack.

In the standard care control group, pneumothorax as an adverse event was reported in five of 58 standard care control patients. One of these five control patients required chest tube re-insertion. None of these

patients died.

As to incomplete lung expansion at one month follow up, the sponsor reported these results for the treating investigator and the sponsor's medical monitor's review of 149 patients.

In this review, complete lung expansion and one month follow-up was reported in 62 out of 96 patients, that is 67 percent in the investigational group and 41 out of 53 patients, that is 78 percent in the control group. The difference here is 11 percent. So, 11 percent more control treated patients had complete lung expansion by this assessment.

Of patients who received a Heimlich valve on post-operative one month chest x-ray, seven of 11 sealant patients had incomplete expansion. Five stayed the same compared to the chest tube pull, one increase compared to the chest tube pull chest x-ray. Eleven of four sealant patients and one of one control

patients had complete expansion at one month follow up.

Incomplete lung expansion sequellae beyond one month follow up are unknown in patients treated with sealants.

To further evaluate the occurrence in 30-day outcome of the pneumothorax partial expansion or residual space findings on chest x-rays, a follow-up chest x-ray evaluation protocol was designed by FDA and the sponsor during PMA review.

In this analysis, chest x-rays from the recovery room within 24 hours of chest tube removal and at 30 days post-op were reviewed for 60 patients randomly selected at three to five investigational sites.

This sample size was considered to be sufficiently useful for us to gain information, but also, least burdensome for the sponsor and so, it was agreed upon.

Assessment of the chest x-rays, explicitly specified method of determining

partial expansion size, to assure uniform measurement of each chest x-ray.

Subjects were selected in a two sealant to one control ratio and chest x-rays were read by an independent master radiologist. Data demonstrated that while two percent more control patients in the recovery room and 11 percent more control patients at chest tube pull had incomplete expansion at one month follow-up, 17 percent more investigational device patients had incomplete expansion. No control treated patients had incomplete expansion.

For the six sealant patients with incomplete lung expansion and one month follow up that were part of the random cohort assessed by an independent master radiologist, the size or extent of incomplete expansion at the time of chest tube pull and one month follow-up is presented here.

For patient number one, the data is incomplete and therefore, change cannot be

determined. For patient number three, the incomplete air space had increased from 1.2 centimeters at the time of chest tube removal to 3.5 centimeters at one month follow-up.

For the other four of these patients, the incomplete air space was decreasing, but not resolved, from the time of chest tube pull at one month follow up. The data demonstrates incomplete chest x-ray a size ranging from .2 to 4.8 centimeters. In control patients, only complete expansion had resolved.

In considering the composition of ProGEL Surgical Sealant, known renal excretion and the potential for immune reaction to the chemically modified human albumin component in the sealant, the difference between investigational and control cohort patients' change in renal parameters was noted.

Data demonstrated the nine percent standard care plus sealant and 8.3 percent standard care-alone patients had renal adverse

event. That is 5.7 more investigational device patients than control patients had renal adverse events.

Data for pre-op and one month BUN in serum creatinine levels, as well as the severity of the adverse events were reported. Data demonstrated that six of nine patients had a rise in serum creatinine from the sealant group. One of nine patients did not have a rise in serum creatinine and two of the nine patients died, and this comparison is from the pre-op time to the one-month follow up time.

There was pre-existing renal disease in pre-investigational device patients and one control patients who had an adverse event. There was also no pre-existing renal disease in six investigational device and one control patient who had a renal adverse event.

Severe renal adverse events occurred in five investigational device patients without pre-existing disease and two

of those patients died. Severe renal adverse events occurred in one control device patients with pre-existing disease and that patient died.

In assessment of the cause of death, data reported that all five patients in the investigational cohort had pulmonary etiology and two of these were associated with multi-organ failure. Data reported that the four death in control treated patients had a mixed etiology and no multi-organ failure.

In summary, the incidents of air leak free patients through one month follow up as determined from the recovery room through one month was 21 percent greater in the investigational group than in control. When determined from the OR through one month, this was 30.1 percent. So the primary effectiveness endpoint was met.

Incidents of air leak free status in the OR was 60 percent greater in the sealant group than in control; in the recovery

room, 23.9 percent greater in the sealant group than in control. The endpoint was met statistically, however, the air leak recurrence rate is clinically notable.

The time to hospital discharge endpoint was met. However, the evaluation has been confounded and potentially biased by Heimlich valve use without a perspective plan. The time to air leak seal than time to chest tube removal was not found to have difference and the evaluation was also potentially confounded and biased by Heimlich valve without a perspective plan.

As to specific issues in our questions to the Panel, the following are noted again here in summary.

Late on-set air leak occurred in six percent more investigational device patients than in control. Prolonged air leak occurred in two percent more investigational device patients than in control at post-operative day seven and in 7.5 percent more

investigational device patients than in control through post-op day 11 and thereafter.

Pneumothorax as an adverse event occurred at a comparable incidence. However, five of nine standard of care plus sealant patients and one of five standard of care or control patients required invasive intervention and one of these investigational device patients died.

As compared to incomplete lung expansion at one month follow up, treating physicians and the monitor, the sponsor's monitor, found 11 percent more patients in the investigational group compared to control who had incomplete expansion at one month follow up.

Independent radiologic assessment, which was masked, found 17 percent more patients in the investigational group compared to control to also have incomplete lung expansion. We considered these to be comparable.