the colonoscopy study does have a larger percent of patients who are greater than 90 kilograms. The weight range in that study did go all the way up to 154 kilograms. But some of the most obese patients that you might see would be excluded for difficult airways. So, that is specifically to the higher weight patients.

As Dr. Kline indicated, in terms of ASA status, we did enroll patients with an ASA of three. The ASA classification in four we had no patients. That is probably consistent with the guidelines followed by gastroenterologists, in terms of who they are performing moderate sedation on without the presence of an anesthesiologist. We also have a breakout by greater than 75.

The number of patients enrolled both in the colonoscopy and the bronchoscopy study who are over age 75 was a relatively small number and I think we would like to ask Dr. Larry Cohen up to speak to the kind to the

kind of patients that he sees in his colonoscopy practice.

DR. COHEN: Thank you. I would agree with the comments that have been made. This does represent sort of the broad spectrum of patients that we see in an outpatient setting. We have looked carefully at our practice, for example, we have 95 percent of the patients that come in for a screening colonoscopy are ASA I's and II's.

In terms of the weight distribution, I think that this is fairly representative as well as for age. The average age of all patients presenting in our practice in New York for a colonoscopy is about 57 years of age. So, I think this is a fairly representative picture of what we see in the broader practice.

CHAIR FARRAR: Did that answer your question, Dr. Nussmeier?

DR. NUSSMEIER: Partially. Thank you.

CHAIR FARRAR: And Dr. Buchman?

DR. BUCHMAN: I have two questions. The first, actually, is specifically for Dr. Cohen.

Dr. Cohen, in your presentation, in your needs assessment for the medication, you listed two items. One is that there is evidence that propofol, or fospropofol, decrease the patient's fears for sedation and would lead to an increased utilization of colonoscopy for colon cancer screening. The other is that patients preferred propofol or fospropofol, over conventional sedation.

Now, in a brief review of publications in Pub. Med., I was unable actually to find any data on that. And I noted on your presentation, that you didn't list any data. Is that simply speculation or do you actually have data to support that?

DR. KLINE: Dr. Cohen?

DR. COHEN: Thank you. Regarding the first question, concerning fear and

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anxiety, let me first point out that in my presentation on the needs for sedation, it was a general discussion related to the benefits of sedation in general wasn't specific to the needs or the benefits of fospropofol. In terms of the issue of barriers to patient acceptance, there are data and we can supply the references that indicate that the single greatest barrier today that exists for patients to accept the colonoscopy is in fact a fear of discomfort.

Regarding your second question as to patient preferences, there are six studies in the literature that are randomized prospective trials that have compared standard sedation with benzo/opioids to sedation with propofol. And four of the six studies actually do demonstrate that patients preferred that their experience and their preference was improved with propofol over standard benzo/opioids.

DR. BUCHMAN: Can I just follow

up? I should have actually prefaced by question by blinded data in terms of preference. The data that I have seen has been largely unblinded data where either the physician and/or the patient was unblinded to the procedure versus having a pharmacist, for example, that was unblinded with both the physician and patient unblinded or blinded. So is there any actual blinded data --

DR. COHEN: Yes.

DR. BUCHMAN: -- that would indicate --

DR. COHEN: The studies that I am referring to, these are randomized controlled, double-blind trials.

CHAIR FARRAR: If I could just follow up with one question. How was patient satisfaction measured in this study? That doesn't need to be to Dr. Cohen specifically. So, we didn't see any of the measures presented here. I mean, obviously, the protocols are available but if you could

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clarify that for me.

DR. KLINE: We asked a question at the end of the procedure, asked the patients to rate on a scale of one to ten what their satisfaction level was with the procedure.

CHAIR FARRAR: And there was mention of patients indicating that they wouldn't mind undergoing it again. Was that asked in a formal way?

DR. KLINE: Yes. That was one of our secondary endpoints. And at the end of the procedure, we asked patients if you were undergoing a colonoscopy or a bronchoscopy again, would you be willing to be treated with the same study sedative that you received. That endpoint reached statistical significance in the bronchoscopy study and it trended in favor of our dose in the colonoscopy study but did not reach significance.

This slide shows the data for patients willing to be treated again. Again, similar rates in the colonoscopy study.

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Higher rates seen at our proposed dose in the bronchoscopy study. And important to remember that results in the two milligram per kilogram arm are confounded by the fact that these patients received an alternative sedative per the site standard of care. So the rating that those patients are responding to includes having received that alternative sedative.

CHAIR FARRAR: Just as a comment, the fact that the two milligram group did receive alternate care suggests that, at least in the population that you looked at, not a large difference in preference between receiving propofol only or the new formulation, as well as other medications.

Dr. Soriano?

DR. SORIANO: Yes, I have to second Dr. Leslie's concern about dose stacking. Certainly, in my practice, when I use propofol to sedate some of my patients, these are pediatric patients, as well as teenagers who can be considered adults, the

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procedurist wants a quick anesthetic because frequently these procedures will be 10 minutes, 15 minutes long. So, if the process of sedation will take even longer than the procedure itself, then there is no benefit.

This question is to the Applicant then, what are you doing to, in your risk mitigation program, to reassure that dose stacking doesn't occur? Certainly, there will be a temptation to just give more to get a larger effect.

DR. KLINE: We believe that the risk mitigation begins with the package insert as the focal point for instructing physicians. And I would like to ask Dr. Sirek to provide further information on those plans.

But also while she is coming up, I would also like to point out that we look to information from our high dose studies to provide information on what happens when the four minute interval that we recommend is not followed. And if you look at the patients who

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received doses that are 11 milligrams per kilogram or greater which, as Dr. Cullen pointed out, are equivalent to receiving a proposed dose plus three supplemental doses simultaneously, we did see a higher incidence of sedation-related events. These were all easily managed by the proceduralists providing sedation.

DR. SORIANO: One other issue. One other piece of data does not, I did not see covered in your presentations, was the duration of these procedures. I just reviewed it quickly again and I didn't see any comparison to duration. So whether or not this is real life, whether these were quick, I guess, screening procedures or whether they were more complicated than traditional colonoscopies or bronchoscopies.

DR. KLINE: The median procedure duration in the colonoscopy study was 11 minutes. And that was 10 minutes in the bronchoscopy study. I would like to ask Dr.

Cohen to provide context for how that fits for a typical procedure that he may do and follow that up with Dr. Silvestri to give his experience in bronchoscopy.

DR. COHEN: Thank you. I think that the average period of 11 minutes basically reflects, I think, the period of time that is spent. I think one can argue, obviously, there is a lot of individual variation in practice. But I think a period, one average I think that across the country you would see in numbers ranging from 15 to 20 minutes. Eleven minutes may be a little bit shorter than average but it certainly is not off the curve.

DR. SILVESTRI: I am Gerard Silvestri. I am a pulmonologist and professor of medicine at the Medical University of South Carolina at Charleston. I am a clinician scientist. Mostly my practice is lung cancer. I see seven to 10 new lung cancers per week. I enrolled 27 patients on this trial.

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And to answer your question specifically, I think the procedural time was a little bit shorter than we would expect in clinical practice, although I would say that in the bronchoscopy trial, if you look at the overall time, some of them were well over that 10 minute mark, specifically in our institution where we do a procedure called endobronchial ultrasound to stage patients. It is a larger scope, by the way, and we did that in a number of our patients in those 27 and we went well over the 10 minute time frame.

I would suggest that the 10 minutes is both for endobronchial biopsies and bronchoalveolar lavage, so your shorter case is airway inspections. But remembering that these patients all had a diagnostic reason. We do not have a screening test in bronchoscopy, per se. So every one of those patients went to bronchoscopy for the specific indication of a diagnosis of an underlying

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abnormal chest x-ray or the like.

DR. KLINE: If I may as well, you asked a question about the risk management and I would like to ask Dr. Sirek to address that.

DR. SIREK: We believe, as you indicate, that it is very, very important that we be proactive in educating prescribers as to the appropriate use of fospropofol. Slide up, please.

So, the emphasis of our educational program will really be three-fold. It will be pre-procedure patient assessment consistent with the ASA guidelines and other guidelines for moderate sedation, proper dosing and administration with emphasis on the initial dose, the supplemental doses and the dosing interval, as you indicate, as well as dose reductions for the elderly in ASA III or IV.

We also will be highlighting the monitoring expectations that are true for all moderate sedation procedures, regardless of

the product that is being used. So, these will be the points that we will be emphasizing.

And then the questions is, how will we be getting that out into the community? Next slide up, please.

So, first let me start by saying that fospropofol is intended for use by physicians who are routinely performing moderate sedation procedures. So there will be that target audience. And, as indicated, numerous societies, organizations, both national and local, already publish sedation guidelines and sedation training and we really will work proactively with these organizations so that immediately upon approval, we will be disseminating all of the fospropofol information to these organizations, so that they can incorporate them into guidelines as appropriate and into training as appropriate. We will also be providing financial support to help them get that out.

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We are also going to follow up with our medical affairs personnel at all levels, to be sure that we can work as effectively as possible to get those messages out. But we realize that that is not enough. We also will be very proactively training our own staff so that every encounter with a prescriber who might use fospropofol emphasizes those three main points and we will be providing a variety of tools, whether they are hard copy dosing cards or posters, whether they are guides to patient assessment and monitoring, they will be given in terms of interactive tools available online, web training, other monitoring tools, possibly sedation simulation programs. Many, many multi-pronged messages out there, just to emphasize those points.

CHAIR FARRAR: Before you sit down, if I could follow up with a question. You specify exclusion criteria or criteria to be considered as being ASA and airway

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difficulties. And specific with regards to airways, clearly in the trial you had experts who considered these issues before patients were enrolled. As it moves into a general population, I am wondering how you would approach the concept of airway problems, especially with regards to Dr. Nussmeier's question in the growing obesity problem and problems with sleep apnea and so on, which might lead to respiratory problems with any kind of sedation.

DR. SIREK: Slide up, please. The exclusion of patients with difficult airways is consistent with ASA practice guidelines. But to your point, it is important to reemphasize that to individuals performing moderate sedation, regardless of the sedative agent that they are using. And so, examples of tools that could be used are pictures of the Mallampati score to help proceduralists as a reminder as to how to judge difficult airways and, you know, just continuing to work

with all of the organizations out there to train in identifying difficult airways. And we believe that this is true again, regardless of the sedative agent that is used. It is important.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I have a safety concern which I think would be probably best addressed by Dr. Leslie.

I am originally trained as an anesthesiologist but practice as a neurointensivist, and was repeatedly amazed that when doing brain death exams on the length of time in which one could stay well oxygenated while not ventilated during a brain death exam. I am struck by the use of pulse oximetry as a main indicator of adequacy of ventilation. And I think you would probably agree that oxygenation or the pulse oximeter is not a good indicator of ventilation but rather of oxygenation.

So, my specific question is why

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have you decided not to use, apparently, end-tidal CO2 monitoring as a primary indicator of ventilation. And second, as a practicing anesthesiologist who should know that patients can respond to questions do purposeful things yet not ventilate under the influence of narcotics or other sedatives, what meaning does the thumbs up sign mean with regards to adequacy of ventilation?

DR. LESLIE: First, let me qualify. I was not involved in the design or completion of the studies. I was just contacted about a month ago to begin to review the NDA and provide sort of, as you are seeing now, my concerns about the risks and benefits. Clearly, as you stated, the pulse oximeter only measures the current concentration of the oxygen there. It is not an indication of adequate ventilation. It is a predictor of disaster. Perhaps we should look at it that way.

CO2 is what I would routinely use

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in all monitoring in anesthesia care situations. That is not a monitor that is available or routinely used in the majority of these other situations of procedural sedation.

And I think that is part of the concern is what do you actually use as a measure of a patient's interactivity? I believe the company chose, and I think it is rightfully so that we even, as the ASA proposed, as an indicator of a level of sedation is appropriate responsiveness, they chose to use the thumbs up. Different people use different things, asking questions, ask them to do things, simple yes and no answer questions. I think it all comes down to that is the measure we use some sort of what we judge as an appropriate response to gauge a patient's level of sedation.

I don't know of any other better way to do the level of sedation. MOAA/S, perhaps is a little more scientific but not well standardized and not practiced in most

places.

DR. KIRSCH: One of the other hats that I have worn in my professional career is providing anesthesia services in an office-based practice in actually rural Maryland, 40 miles north of Baltimore. And in that setting, the standard of practice that we had was used in end tidal CO2 hooked up to the nasal cannula.

And I'm wondering, don't you think these patients who are going to receive this medication deserve that level of monitoring?

DR. LESLIE: I think anytime an anesthesiologist is practicing, that is generally considered part of our routine care. When we provide monitored anesthesia care because we quite often do take patients to deep levels of sedation, it is absolutely appropriate.

I would also say that, you know, because I would use propofol over fospropofol for most of these situations because I do like

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the rapid onset and I do think the offset will be a little bit faster. But again, it is more if an anesthesiologist, I think I am required to measure end tidal CO2. That is part of my accepted guidelines of monitoring. When I provide an anesthesia management, CO2 is in part that. But that really is not the standard that people are implied or recommended by our guidelines for doing mild to moderate sedation.

DR. KLINE: If I may?

CHAIR FARRAR: Yes.

DR. KLINE: Just to add to what Dr. Leslie has said, the ASA guidelines for moderate sedation recommend the use of capnography for patients undergoing MAC sedation. There is not a recommendation that it be routinely used in patients undergoing moderate sedation. And what we are proposing for monitoring is consistent with those guidelines.

CHAIR FARRAR: Dr. Chang?

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DR. CHANG: Yes, I had two questions. I think you stated the failure, if you had to use supplemental analgesics or, I guess other sedatives.

DR. KLINE: Not analgesics.

DR. CHANG: I'm sorry. And you had one table, it looked like 55 percent of patients on a 6.5 milligram dose needed a supplemental sedative but you called a treatment success in the 88 percent. So only 12 percent required that. So I wasn't sure on the difference.

DR. KLINE: So the definition actually of -- they weren't considered a sedation failure if they needed a supplement. They were considered a failure if the drug that they were randomized to failed to adequately sedate them and an alternative sedative was administered. So the investigator, at that point, would choose no longer to use study drug but go to something per their site standard of care.

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DR. CHANG: So the 55 percent that required a supplement, it wasn't necessarily another sedative like midazolam. Is that true?

DR. KLINE: No. When we say supplement -- actually, I believe the data you are specifically referring to from the presentation was specific to the analgesic used. And that was not part of the definition of a sedation's success or failure but also to clarify the need for supplemental doses of study sedative medication was also not just the need for an alternative sedative.

DR. CHANG: Yes, well, that gets to my second question. I was trying to figure out what is your actual indication? If you are using it in colonoscopy, I would have thought you would want to use it in place of an opioid and an midazolam or sedative. But it sounds like in your studies, everyone got fentanyl at the beginning and that 52.5 percent of those on 6.5 milligrams actually

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reported procedural pain.

So, even though you are stating that maybe this is a good alternative because people don't want to undergo a colonoscopy because of the pain, that over 50 percent actually reported pain.

So, are you saying that you are going to use this drug but endoscopists are still going to give an opioid?

DR. KLINE: We tested this drug with the use of fentanyl in all of our patients. So, we would recommend the use of an opioid to manage pain and fospropofol to provide sedation.

To clarify, the dose of fentanyl that we used was 50 micrograms. If during the procedure the patient reported pain, and that would be as assessed by the investigator, they were allowed a supplemental dose of fentanyl. So, that is how it was recorded when we looked at patient's willingness to be treated again, it was not adversely affected by that.

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CHAIR FARRAR: Dr. Epstein?

DR. EPSTEIN: Yes, thank you. Also for Dr. Kline, can you expand a little bit or tell us how many subjects received a second dose of the medicine in certain of the study? Obviously, you had some fixed dose studies, too.

DR. KLINE: Yes. We did look at the breakdown of patients who required supplemental doses.

Slide on, please. This is a histogram. This is our proposed label dose in the colonoscopy study and the bronchoscopy study. And it shows the number of supplemental doses of study sedative required by patients in these groups. So, you can see that 11 percent of patients in the colonoscopy study, 25 percent in the bronchoscopy study, completed their procedures with just the initial bolus. An additional 16 percent in colonoscopy and 30 percent in bronchoscopy required one supplement and so forth.

DR. EPSTEIN: And a follow-on question. Did you have any data, I know we talked a little bit about comorbidities, did you have any specific data on patients that were dialysis dependent with renal failure?

DR. KLINE: I would like to ask Dr. Michael Cullen to speak to that.

DR. CULLEN: We did. We looked at patients with severe renal failure with the creatinine clearance of less than 30. And we also actually looked at patients with hepatic impairment with a child B or C class. Slide on, please. And as you can see, the safety profile here is pretty comparable. There was a single adverse event in that total population that required airway assistance.

DR. EPSTEIN: Can you put that slide back on just one more time? I was just looking at the hepatic --

DR. KLINE: Slide up. Sorry.

DR. EPSTEIN: -- too while you had that up.

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Can you describe what the -- can you expand on the SAEs in both those categories?

DR. CULLEN: I believe that was -- oh, right. That was a patient who had an AV fistula plate -- no, not the hepatic one. The renal SAE was a patient who had a bleeding complication from the AV fistula. I believe for the hepatic, it was a hypoxemia and a hypotension, but we will check on that.

CHAIR FARRAR: Dr. McLeskey?

DR. McLESKEY: This is mostly about clarification. Dr. Leslie mentioned in one of his slides that patients were fully awake within five minutes and reached an Aldrete greater than nine in 10 minutes or less. And I just wondered, five minutes or 10 minutes from what end point? Was that the end of the procedure or some other endpoint? And then related to the question that just preceded this, is there also some kind of guideline that you all have concluded that

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would be the time to wakefulness like that, following the last dose, for example. Could you elaborate on that just a bit?

DR. KLINE: The recovery period we looked at the time to reach fully alert status, which we defined as the time to the first of three consecutive MOAA/S scores of five. And that was the five minutes that Dr. Leslie referred to. So five minutes from the removal of the scope.

In the colonoscopy study, the time to an Aldrete score of nine or greater was seven minutes, the median time. And that also is from time of removal to scope. Our proposed dosing guidelines call for monitoring the patient through recovery. They are not specific to the alertness status or the Aldrete score in the proposed package insert but certainly continued monitoring of the patient during the recovery period.

DR. McLESKEY: And again, just by clarification. So, the time periods that John

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mentioned were after removal of the scope. Is there any similar kind of information following time from the last dose?

DR. KLINE: We did not analyze from time from last dose.

CHAIR FARRAR: Dr. Sang?

DR. SANG: Thanks. I'm just wondering, do you have plans to -- or are you now scheduled to look at PK in the pediatric population?

DR. KLINE: We currently have only studied fospropofol in adult patients. We certainly plan to study fospropofol in pediatric patients and we would look to our FDA colleagues and develop a pediatric program jointly with them.

DR. SANG: And I have a second question that has to do with the formaldehyde metabolite following fospropofol. So formaldehyde rapidly breaks down to formate but there are now new data in the pain arena to show that formaldehyde targets TRPA1

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receptors. And you know, TRPA1 is a major sensor for chemical irritation in the peripheral nerve endings, as well as in the respiratory tract.

So, it leads me to ask, number one, understanding the rapid metabolism of formaldehyde to formate, I think the half life is approximately one and a half minutes, the transient paresthesias that you have described with fospropofol administration, and certainly what has been described with fosphenytoin, can be in part associated with formaldehyde metabolite.

So now, I have to ask you, the respiratory events that have occurred in the few hundred patients that you studied, was it possible at all to look specifically at a risk of the development of bronchospasm and how might you, especially in the context of bronchopulmonary lavage, how might this be addressed?

DR. KLINE: I would like to ask

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Dr. Cullen to address your questions.

DR. CULLEN: First, if I may address the question about the paresthesias in the formaldehyde. The paresthesia and pruritus that we have seen with fospropofol is identical to what is seen with dexamethasone as well as fosphenytoin. And of course, dexamethasone shares the phosphate moiety but not the formaldehyde generation.

Secondly, slide up please, the potential for changing formate levels, which is rapidly produced by metabolism from the formaldehyde has been looked at very carefully in this early study with doses up to five times the recommended dose. And formate measured over time, you can see on the graph here, that there was no real change from baseline, even at those very high doses.

DR. SANG: And I understand, certainly formaldehyde is ubiquitous in the environment and there is a large environmental exposure plus formaldehyde that is endogenous

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as well, but since the respiratory tract is full of TRPA1 receptors, I was wondering specifically about bronchospasm. And number two, I am not sure how formaldehyde levels answers the question necessarily.

DR. KLINE: I would like to ask Dr. Silvestri to address your question regarding bronchospasms.

DR. SILVESTRI: Thank you. I think the hypothesis is a very interesting one. I don't know that the clinical data available, in terms of formate levels can answer that. What I can say is in the 27 patients we enrolled, we saw no evidence of bronchospasm.

In evaluating the data on the 252 patients and writing the manuscript, we saw no evidence of increased bronchospasm in those patients under a variety of conditions in a variety of procedures.

So while I think it is clearly a hypothetical consideration, we saw no evidence

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of it in practice. Thank you.

DR. KLINE: If I may, to follow up on your question regarding formaldehyde, I would like to ask Dr. Waters to address that.

CHAIR FARRAR: If you could identify yourself, please?

DR. WATERS: Steve Waters, MGI Pharma.

To your question, formaldehyde is produced as a metabolite but it is very rapidly metabolized to formate. Therefore, we cannot measure formaldehyde levels. It is formate that we measure and that is why we show that data.

And you are also correct, endogenous production of formaldehyde actually exceeds what we would produce by a given dose of fospropofol. Endogenous metabolists from amino acid metabolism and purine and pyrimidine metabolism, as well as oxidative demethylation steps produce a far greater endogenous load of formaldehyde than does drug

delivery.

CHAIR FARRAR: It is 10:15 and other people that would like to ask questions will do so after the break. Following the break, the FDA will present briefly and then we will have a lot of time for further discussion.

Before we go to break, I would like to remind folks that we will reconvene at 10:30. Panel members, please remember that there should be no discussion of the topic during the break amongst ourselves or with any member of the audience. And I will see you at 10:30.

(Whereupon, the above-entitled meeting went off the record at 10:16 a.m. and went back on the record at 10:31 a.m.)

CHAIR FARRAR: Moving ahead with the program, Dr. Lex Schultheis will present the FDA perspective.

DR. SCHULTHEIS: Good morning. My name is Lex Schultheis and I am a medical

officer in the Division of Anesthesia, Analgesia and Rheumatology Products at FDA. I will present some of the preliminary findings of our review team's evaluation of the applicant's submission of fospropofol.

This presentation will focus on the indication for fospropofol proposed by the Applicant and the efficacy database supporting this proposal, including the blinded and randomized dose ranging study 0520 in colonoscopy patients, the dose controlled studies, 0522 in colonoscopy patients, and study 0524 in bronchoscopy patients.

I will also discuss some of the safety findings of 0523, a study of fospropofol among patients having a wider range of procedures requiring sedation. As we review these studies, I will ask you to keep in mind several points for later discussion. We will deliberate the adequacy of purposeful responsiveness as assigned to support the safety of supplemental dosing of fospropofol.

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We will discus safety information that may affect the dosing of certain subpopulations. Also, you will be asked to consider how the available data suggests what assessment and interventional skills are needed to safely manage patients with fospropofol.

The indication proposed by the applicant is sedation in adult patients undergoing diagnostic or therapeutic procedures. And this is slightly different than the indication for propofol, which was for MAC sedation.

Fospropofol was developed based on the hypothesis that the pharmacokinetic profile of a prodrug, which is slower timed onset of active drug affect and reduced Tmax would allow intravenous bolus injection to be managed safely while enabling a rapid recovery from sedation.

The entire safety database consists of approximately 1,600 patients. However, the approach of early studies

utilizing a dosing regimen that attempted to manage sedation with a high initial bolus determined by a weight range was abandoned for a milligram per kilogram dosing regimen because several patients experienced apnea and required support.

The applicant's proposed dosing regimen is an initial bolus followed by supplemental doses, all prescribed on a milligram per kilogram basis, as needed, with an obligatory interval of at least four minutes. Geriatric patients and patients with serious comorbidities are to receive reduced doses.

Based upon the pharmacokinetic information presented earlier by the Applicant, patients are to receive a dose calculated for a 60 kilogram body weight, even if they weigh less than 60 kilograms. Similarly, the maximum dose is based upon a 90 kilogram body weight, even if the patient's weight exceeds 90 kilograms.

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The three studies that are being reviewed to evaluate efficacy of fospropofol are studies 0520, 0522, and 0524. The total number of patients exposed to the proposed dosing in these studies is 334 patients. The number of patients exposed at the approved dosing was 26 in 0520, 158 patients in study 0522, and 150 patients in study 0524.

These studies and the open label safety study of 0523 were conducted with certain safeguards. First of all, an airways expert was immediately available at all times, as stipulated by the protocol. Also, patients were excluded if they were prospectively identified as having an airway that would be expected to pose difficulty if advanced techniques such as an emergently needed laryngoscopy were likely to be required.

The principal tool used to measure depth of sedation was the Modified Sedation Assessment of Alertness and Sedation Score. The scale categorizes patient responsiveness

to various levels of stimulation by the sedation health care provider. On this categorical scale, a score of five corresponds to a patient who appears alert and zero corresponds to a patient who is unresponsive to a painful stimulus. As you recall from the Applicant's presentation, the primary sedation endpoint for efficacy studies was three consecutive sedation scores below the sedation score corresponding to an alert state and completion of the diagnostic or therapeutic procedure without requiring an alternative sedation product for manual or mechanical ventilation.

The Applicant has already described the efficacy findings. Our preliminary review indicates that fospropofol met its primary efficacy endpoint of sedation success. The yellow highlighted numbers illustrate that there was a dose-related increase in sedation success. Secondary endpoints, including completion of treatment,

patient and physician satisfaction evaluations and lack of patient recall of the procedure also indicated that here was a clinical benefit of sedation with fospropofol. Therefore, fospropofol was efficacious when used as a sedative in these studies.

This slide summarizes data from patients who failed to achieve sedation success and the reasons for failure are listed in the same order as the requirements to meet the primary efficacy endpoint. Most failures were as a result of having to use an alternative sedation product because the patient did not maintain a level of sedation adequate to conduct the procedure. Again, highlighted in yellow.

At this point of our review, we also agree substantively with the Applicant's key safety findings. Preliminary evaluation of patient deaths and the other adverse events as reported by the applicant as serious adverse events in randomized, blinded, and

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controlled studies suggest that these events were not attributable to fospropofol. Of the adverse events that resulted in discontinuation of the procedure, the Applicant reported that one was caused by fospropofol. This event coded as paresthesia was basically a discomfort associated with injection of the product. Common adverse events tended to be mild or moderate in intensity and were readily managed.

The potential for abuse of fospropofol is evaluated as part of the review process and is mentioned here because fospropofol is an aqueous formulation and was bioavailable when the product was studied following oral administration. Euphoria was reported as an adverse event in studies of healthy volunteers. So the possibility of scheduling fospropofol is being considered.

Now, in order to understand how patients respond to fospropofol, it is helpful to examine the timing of sedation onset. In

this figure, data were abstracted from the Applicant's study of bronchoscopy patients who received the proposed dosing of an initial bolus of 6.5 milligrams per kilogram of fospropofol and supplementary doses of 1.6 milligrams per kilogram at intervals not less than four minutes, as needed.

The horizontal access is time in minutes. The vertical access if the percent of all patients treated with the proposed dosing. Each colored curve illustrates the patient subpopulation having a specific sedation score at each time point. Therefore, at five minutes before administration of fospropofol, 100 percent of the patients were alert. This time point also corresponds to the timing of administration of 50 micrograms of fentanyl.

As you can then see, the percentage of patients retaining a sedation score corresponding to an alert state is maintained at nearly 100 percent until the

initial dose of fospropofol is administered at time zero. Thereafter, the percentage of patients who are alert, score of five on the sedation scale, falls to approximately ten percent after ten minutes. Most of the remaining patients have a sedation score of three or four but some patients achieve a sedation score of two or below.

Recovery from sedation resulting from fospropofol is illustrated on this slide. Again, the information depicted is abstracted from the Applicant's reported data from patients in the 6.5 milligram per kilogram arm of the bronchoscopy study. After the last dose of fospropofol was administered, the percentage of patients who have a sedation score of four or lower on the sedation scale gradually declined and the percentage of patients who were alert increased so that by approximately 25 minutes after the last dose of fospropofol, nearly every patient was alert.

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As I indicated in my introduction, one of the features of fospropofol sedation that I asked you to consider was patient responsiveness as a sign of sedation depth. In this slide, the applicant has compared the incidence of various sedation related adverse events associated with sedation to the sedation score measurement. And the sedation score was the one most closely associated in time with the adverse event. If we focus on the finding of hypoxia defined here as a peripheral saturation, less than 90 percent for greater than 30 seconds, we see that the highest incidents of events occurred when patients scored a three, the middle range of the sedation scale. At this level, patients required that their name be called loudly and repeatedly before they would respond. Manual ventilation for two events was also required at this moderate level. It is particularly notable that hypoxic events were also reported among patients who were even less sedated,

according to the sedation scale.

In this slide, we see an analysis by the Applicant relating the incidence of hypoxia to a retention of purposeful responsiveness. In many cases, patients were able to produce the thumbs up sign or wiggle their toes when investigators responded that the patient do so, even in association with signs of hypoxia. The ability to respond purposefully was required in order for patients to receive supplemental fospropofol for sedation.

Now, your handout had a typo up in the upper right-hand corner, which has been corrected. From these data and in the previous slide, we see that retention of purposeful responsiveness did not exclude an associated finding of hypoxia as measured by peripheral desaturation on an oximeter.

Now, the Applicant's findings are interesting, when considered in view of the ASA Guidelines for Sedation and Analgesia by

Non-Anesthesiologists from 2001 and the continuum of depth of sedation, definition of general anesthesia and levels of sedation analgesia approved by the ASA House of Delegates in 1999 and amended in 2004. In these statements, retention of purposeful responsiveness was used to demarcate various depths of sedation and the associated risk associated with sedation depth. According to these definitions, reflex withdrawal from a painful stimulus was not considered a purposeful response. Patients who retained purposeful responsiveness to verbal or tactile stimulation are expected to maintain spontaneous ventilation and are not expected to require interventions to support their airway. This corresponded to an MOAA/S level of four or three. Purposeful responsiveness to vigorous or painful stimulation corresponded to MOAA/S levels of two or one, respectively.

In summary, the Applicant's data

suggests that hypoxia occurred at levels of sedation where interventions may not have been expected because patients were still responding purposefully. We ask you to consider this finding when deliberating how a clinical assessment of purposeful responsiveness may affect the safety of a decision to administer a supplemental dose of fospropofol in clinical practice.

This slide lists various types of airway maneuvers required to manage sedation with fospropofol from studies 0520, 0522, and 0524. Some patients received more than one intervention. The most common intervention was a dose-related increase in the flow of nasal oxygen. However, mechanical intervention such as chin lift or suctioning were sometimes also used. Manual ventilation was needed in one patient.

The incidence of hypoxia observed in these studies appeared to be primarily driven by event rates in the bronchoscopy

study 0524. Because the incidence of hypoxia was dose-related, it is likely to be caused, in part, by fospropofol and cannot be entirely attributed to the presence of an instrument in the airway. In this study, patients tended to be older and have more serious comorbidities than in colonoscopy studies.

In the next few slides, we will examine various subsets of patients by age, ASA categorization, and body weight who had a more frequent incidence of hypoxia. I should also mention that your handout may have had a typographical error as well, which has been corrected in these slides.

In this analysis of pool data from randomized, blinded and controlled colonoscopy and bronchoscopy studies, we see that there appears to be a dose-related increase in the incidence of hypoxia associated with a geriatric age group. However, we also acknowledge that the number of patients in each category is small, so that the addition

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of a few patients could shift the apparent percentages considerably.

In this slide, we observe a similar dose-related increase in the incidence of hypoxia associated with high ASA physical classifications, that is three and four, compared with patients over the entire ASA classification scheme one through four. Again, the number of patients are small, so that moving a few patients between groups could shift the relative percentages between ASA categories.

This slide contains an analysis of the incidence of hypoxia compared with patients' body weight. These data suggest that there is a dose-related increase in the incidence of hypoxia that is associated with patient body weight below 60 kilograms. You recall that dosing was prescribed on a milligram per kilogram basis but was bounded for patients weighing less than 60 kilograms. Therefore, patients weighing less than 60

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kilograms received a higher dose on a milligram per kilogram basis than patients weighing 60 kilograms or more.

We note, as in the previous slides, that the number of patients in each of these subgroups is small, so that the shift of a few patients will change the incidence of hypoxia associated with each subgroup.

In an effort to further elucidate whether a safety signal associated with geriatric age group, high ASA physical classification or body weight below 60 kilograms was present, data at the proposed dosing from open label safety study 0523 was pooled with the data at the same dosing from blinded, randomized and controlled studies 0520, 0522, and 0524. The population in the safety study, 0523 consisted of 123 patients undergoing a wider range of diagnostic and therapeutic procedures, including transesophageal echocardiography, upper endoscopy, and hysteroscopy compared with

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patients having only colonoscopy or bronchoscopy in the controlled studies. The extent of exposure was similar in this analysis because the dosing was the same and the duration of procedures were similar.

In this analysis, the incidence of all airway intervention was compared by subpopulations of age, ASA classification and body weight. The trend in the incidence of hypoxia based upon small numbers of patients in the data from blinded, randomized, and controlled studies was also noted in the incidence of required airway assistance and pool data that included patients having a broader range of procedures.

Now, let's take another look at the continuum of depth of sedation, definition of general anesthesia and levels of sedation and anesthesia suggested by the ASA. Here, patients who withdraw from a painful stimulus are not considered to exhibit a purposeful response. Patients who are unarousable even

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with pain, are considered to be under general anesthesia.

According to the ASA recommendations for sedation an analgesia by non-anesthesiologists, rescue of a patient from a deeper level of sedation than intended is an intervention by a practitioner proficient in airway management and advanced life support. Quoting from this document, the qualified practitioner corrects adverse physiological consequences of the deeper-than-intended level of sedation such as hypoventilation, hypoxia and hypotension and returns the patient to the originally intended level of sedation, end quote.

In studies of fospropofol, an MOAA/S level of one indicated that the patient only responded to painful stimulation and patients having an MOAA/S level of zero were unresponsive.

The next slide reviews the incidence of patients having an MOAA/S score

of one or zero and the range of time spent at these levels of sedation. Overall, approximately four percent of patients in studies of colonoscopy, that is studies 0520 and 0522, achieved a sedation score of zero or one during the conduct of sedation. Among bronchoscopy patients in study 0524, 16 percent of the patients achieved a score of zero or one. When these data were pooled, the overall incidence of patients having a sedation score at any time during the procedure was nine percent. A sedation score of zero or one was nine percent. The maximum duration of patient having a sedation score of zero or one was 20 minutes and that was only in one patient. Most of the patients had those scores for shorter periods of time.

As you recall from my earlier slide, patients having achieved these deep levels of sedation rarely required rescue with a bag and mask or more advanced intervention. The nature of airway interventions among the

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most deeply sedated patients was similar to those required for patients who were more easily aroused.

As the Applicant noted in their presentation, some patients who achieve low MOAA/S scores had -- required rescue sedation with an alternative to fospropofol in order to continue conducting the procedure.

In summary, hypoxia, defined as hypoxemia on the basis of a peripheral monitor, occurred in patients who were able to respond purposefully to verbal and tactile stimulation.

Hypoxia and airway interventions occurred more frequently among geriatric patients, patients categorized as ASA III or IV and patients weighing less than 60 kilograms.

The most frequent intervention to manage the airway, ventilation and respiratory gas exchange was to increase oxygen flow.

Some patients responded only to

pain or became unresponsive during the conduct of sedation.

This concludes my presentation and I appreciate your attention. I will entertain questions from the Committee at this time.

CHAIR FARRAR: Okay. So, let me open the floor for discussion. We will start by going back to the three people who had wanted to ask questions before the break. I would ask that you remain there but the questions may have been oriented originally towards the sponsor.

Dr. Prough?

DR. PROUGH: I'm still curious about the --

CHAIR FARRAR: If you could use your -- thank you.

DR. PROUGH: I'm still curious about the number of patients who were excluded because of anticipated airway difficulties and exactly what criteria were used.

CHAIR FARRAR: I'm sorry, could

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you -- that is directed to the sponsors?

DR. PROUGH: Yes.

CHAIR FARRAR: Okay.

DR. KLINE: The inclusion/exclusion criteria in the study specific to airway stipulated that if a patient had a Mallampati score of four or a Mallampati score of three and a thyromental distance of four centimeters or less, or in the assessment of the investigator had a difficult airway, they were excluded.

When we look at the numbers of screen failures -- while we are pulling that up, I would like to point out that the practitioners, the investigators in our study made this assessment on their own. There was no outside expert doing this assessment for them. And this is, a routine assessment of the airway is, something that they typically do before providing moderate sedation to their patients. Not necessarily the specific way we have done it, but they do look at the

assessment of the airway.

Slide up, please. This is in the colonoscopy study. So, there were 31 screen failures overall. Two patients were noted to not meet the inclusion/exclusion criteria of those 31 patients. So, that could be either a difficult airway or it could also be a hypersensitivity from earlier sedative medications they received.

CHAIR FARRAR: Did you have a follow-up, Dr. Prough?

DR. PROUGH: No. Thank you.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: In terms of the gastrointestinal procedures, I am surprised -- this is for the sponsor -- that you did not include ERCP, given that it is a procedure that takes longer, the patients is in an uncomfortable position and, in fact, actually many of those cases today are done with propofol and that, with the upper endoscopies, you only had 26 cases, given that the

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literature is replete with data showing that hypoxia occurs to a greater degree and in a greater percentage of patients than with colonoscopy.

But my question, actually, is in regard to colonoscopy but you can also comment on those two as well. One of the biggest concerns with colonoscopy is the risk of perforation. The published risk of perforation is one in every 1200. Now, I have done about 8,000, I have had one, but I have also reviewed cases in which a physician, for example, one that I can remember had ten perforations in 2,000.

And one of the ways in which perforation is prevented is when the patient has discomfort. When the patient has discomfort, it tells you to stop shoving the scope in and get your finger off the air button. And when a patient is sedated heavily and they don't respond with pain, that will significantly increase that risk.

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Now, in your studies, you basically showed a dichotomy. Either patients were more heavily sedated and they had no pain or they weren't sedated enough and required another agent and had significant pain. And in addition, given the percentages that I gave you for perforation, you had very, very few patients. Now, if there are 23 million endoscopy cases, for safety data, where did you ever come up with the idea that less than 300 patients was adequate? Because with that, you wouldn't have any perforations and you would need a study, you know, probably five times this size. And I am really concerned about this safety issue. We only address the hypoxia issue. But I am concerned about the procedural issues.

DR. KLINE: I would like to ask Dr. Larry Cohen to address some of your specific questions about ERCP and colonoscopy.

In terms of our safety database, we have studied our proposed dose in 455

patients. And in addition, we have significant experience in patients who receive a higher initial dose. And the total size of our database is consistent with that of other drugs that are submitted for consideration to the FDA.

Dr. Cohen?

DR. COHEN: Thank you. I think we have to break the question down into several components because I think, if I am hearing you, there really are several issues. There is the issue of why was colonoscopy chosen as the procedure rather than, perhaps, some of the other, perhaps, more advanced endoscopic procedures.

The second question you raise is the safety vis-a-vis the procedure itself and the risk of perforation, as opposed to the safety of the drug. So, let's talk about each of those individually.

First of all, let me answer the second question. I think that is more cogent

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to the reason we are here, which is the safety of the drug with regard to the procedure that is being performed.

Keep in mind that this drug is being developed for moderate sedation by use by non-anesthesiologists and there is no reason inherently to think that the risk of an endoscopic complication that is not sedation-related would be any greater than for any other endoscopic complication, assuming it is not related to the sedation.

In the very early literature of propofol use for endoscopy, there was some suggestion of an increased risk of perforation and it was speculated that it was related to deeper sedation and the fact that patients were less able to participate. I think as endoscopists have gotten more experience, we have learned that the risk of complications, specifically perforation, is no different in the literature today with propofol than it is with standard benzodiazepine.

The issue of different procedures, I can't speak to why colonoscopy was chosen and why they didn't use more advanced therapeutic procedures, I do think that we do need to keep in mind that, again, this was being developed for moderate sedation by non-anesthesiologists. As has been pointed out previously, there will always be a role for MAC sedation during these procedures and I personally believe that some of the more advanced diagnostic and therapeutic procedures are best performed and will probably always been best performed with the use of an anesthesia provider.

DR. BUCHMAN: And if you could address how the number of subjects was chosen to address the safety issues. I didn't actually see how the number was chosen for the efficacy data but I'm sure you did some sort of power calculation, but I'm not so concerned about that.

I don't think there are any

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questions on efficacy but the question in terms of safety, how did you choose the number that you thought would be adequate to show both hypoxia as well as procedure-related effects that are at least indirectly related to the level of sedation?

DR. KLINE: We powered the studies, as you mentioned on efficacy endpoints. They are not powered on safety endpoints. The size of the studies was predicted to gain experience in the drug. We have 455 patients at our proposed dose and again, that was selected because we felt that it gave a good representation of the sedation-related events we would expect to see in the population.

DR. BUCHMAN: Do you think 26 patients that had upper endoscopies is adequate to assess the safety of the use of your medication in patients undergoing that procedure?

DR. KLINE: Certainly 26 patients

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to prove one point would not be, but we do have experience in similar procedures. So, the procedure you mentioned is a shared airway procedure. We have experience in the bronchoscopy study. I think you can appreciate the difficulty in studying sedation agents, selecting procedure types, and, you know, you can't study every single procedure where moderate sedation may be used.

DR. BUCHMAN: I would like to ask one additional question. One of the other concerns that I have is that I have actually seen the absence of any controlled data presented today. In the primary study that you are using, one of your two studies for the efficacy in Phase 3, I see the comparison of two experimental groups. I don't see any control group. A control group would have been using, obviously you can't use a placebo in this situation, but a control group would have been using conventional therapy, and I am a little bit mystified the absence of why

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conventional therapy was not an arm of the study. We really have nothing to compare it to, except a low does that doesn't work as well that is still an experimental group. Why did you not compare the 6.5 milligram per kilogram dose, for example, to conventional dosing of fentanyl and benzodiazepine? As I mentioned before, that could easily be blinded by the pharmacist being blinded and the patient and the physician still being blinded. So that would not be an excuse for excluding a real control arm in this study.

DR. KLINE: We elected to conduct our studies as dose-controlled studies. And we did so because of the occurrence of paresthesia and pruritus occurring at high incidence. We used a blinded pharmacist, as you mentioned. However, even receiving those study drugs blinded, if the patient reports the paresthesia and pruritus, you can pretty well identify what group they have been in.

Further, we don't think that it is

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necessary to do an active comparator to demonstrate that fospropofol is an effective sedative. And as you see in our data, in colonoscopy patients, 88 percent and in bronchoscopy, 91 percent, and in the minor procedure study, 95 percent of patients completed their procedure without requiring alternative sedative and without requiring manual or mechanical ventilation.

Further, we did include midazolam as an outside comparator in our colonoscopy study. It was not intended for formal efficacy comparisons such that we would look to draw comparative claim from that data. But when you look at our colonoscopy study, our Phase 3 colonoscopy study, you can see that our sedation success rate was higher than midazolam. And when you look at the secondary endpoints, they do trend in favor of fospropofol.

CHAIR FARRAR: Dr. Nussmeier.

DR. BUCHMAN: Just to be fair,

though, very few endoscopists would use midazolam alone without an opiate for sedation. So that is a completely unfair comparison.

DR. KLINE: We did use fentanyl in combination with midazolam. All patients in the study received a pre-dose with fentanyl. So, it was a comparison against fentanyl midazolam.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: Yes. This is a question for any of the gastroenterologists who may care to answer it. I'm not so concerned about the pulmonologists because I think they are likely to quite facile with airway management. But for the gastroenterologist, in current practice today, how long does one usually wait between supplemental doses of midazolam for fentanyl until the next supplemental dose?

And I'll tell you why I am asking. We sell data, I believe that said that most

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frequently three supplemental doses of fospropofol were required. And that would be perhaps as much as half a minute for the actual injection and then the protocol called for waiting a full four minutes before supplementing again. So, almost five minutes between doses. And I think you are correct in stating that that is a very important part of the protocol or part of the practice to minimize risk but, if four minutes is longer than would be typical in current practice, have you considered how difficult it might be to teach patients in a non-study setting, keeping in mind that there is no reversal agent?

DR. KLINE: Dr. Cohen?

DR. COHEN: Thank you. If I understood the question correctly, I think you are asking what is standard practice in terms of dosing intervals using the drugs that are currently in use.

And I think that, as

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proceduralists, we dose our medications really based upon understanding of their pharmacology, their pharmacokinetic profile so that, for example, if one is using benzodiazepine such as midazolam, that would normally be dosed at two or three minute intervals at a minimum, again, looking at the pharmacokinetic profile, but, obviously, it's going to be dictated by the kinetics of each drug.

CHAIR FARRAR: Is that an answer to your question?

DR. NUSSMEIER: Yes. I'm just still concerned that following the protocol as it should be followed would lengthen the duration of the procedure in total and that it is going to be difficult to achieve compliance with the protocol in a clinical setting.

DR. KLINE: If we can address that. Can you put up the timeline slide for colonoscopy? And I would like to ask Dr. Brill to speak to how this compares to typical

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colonoscopy times.

CHAIR FARRAR: Please identify yourself.

DR. BRILL: I am Joel Brill. I am a gastroenterologist in Phoenix. I was not an investigator in this study, however, I am the GI representative to the RUC and I have done that for over 11 years' time. Most recently in 2005, the RUC, the RBRS Update Committee reviewed the amount of time that it takes to perform endoscopic procedures, specifically focusing on the base code for colonoscopy. And the RUC found that procedure time for a colonoscopy is 30 minutes of intraservice time. Intraservice time is defined from when the intravenous line is started and sedation is first administered until when the endoscope is withdrawn.

So, within that time, as you can see here in the procedural milestones, you can see that even if the patient required a second or a third dose, that time for performance of

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the procedure would certainly be well within what has been established by and recognized by the centers for Medicare and Medicaid services for the intraprocedure time for an endoscopic procedure, such as a colonoscopy in screening.

CHAIR FARRAR: Ms. Krivacic?

MS. KRIVACIC: Yes, I had a question about the safety information and specifically the age groups, the subgroups.

When you look at, for colonoscopy in particular, when you look at the age groups between 18 and 65, did you sort of weight that in terms of more on the higher end being the older patients, given that, you know, the standard treatment guidelines, and I guess in terms of insurance, are 50 and older? Can you kind of comment on that?

DR. KLINE: Dr. Sirek?

DR. SIREK: Consistent with the guidelines, the median age for the screening colonoscopy, slide up please, oh no, I'm sorry, wrong slide, the median age was a

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little over 50. And that would be consistent with the guidelines as to when patients start their screening colonoscopies. So yes, it was weighted towards the older part of that.

MS. KRIVACIC: I had another question about the alertness component of the study, with regard to being alert five minutes after the procedure. Was there any information regarding recall after that five-minute period in terms of, did the patient understand what the gastroenterologist might have said five minutes or ten minutes after the procedure to that patient? Was there anything done regarding recall?

DR. KLINE: We did. We did a measure of verbal learning and memory recall in both the colonoscopy and bronchoscopy study. Slide on.

The instrument that we used is referred to as the Hopkins Verbal Learning Test and it is specifically used to assess verbal learning and memory recall. And in

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this test, you read a list of 12 words to a patient and then immediately ask them to recall how many they remember and you do that three times in a row. Twenty minutes after that, those learning trials as they are referred to, you go back to the patient, and you say tell me how many of those 12 words you can remember.

So we use this assessment and we did the initial test, the learning trials were administered 15 minutes after the end of procedure, so 15 minutes after the scope was removed. Slide on. And when we look at the retention score, the retention score is simply a ratio of the number that the patients could recall at 20 minutes versus their best score in the second and third learning trials expressed as a percentage. We see that the retention percentage for patients receiving fospropofol at our proposed dose was about 67 percent. And as a marker, the midazolam arm, which you are certainly more familiar with,

had a score of 41 percent in that study.

MS. KRIVACIC: Then I had one final question. In non-opioid-tolerant patients, what would you suggest using or could you, have you thought about that?

DR. KLINE: A specific for analgesia or -- in our studies, we used 50 micrograms of fentanyl as the initial fentanyl dose. If patients required further supplemental doses of analgesic medicine, they were allowed 25 micrograms to manage the intraprocedure pain. So that is what we tested, and that is what we would recommend.

MS. KRIVACIC: But isn't fentanyl an opioid?

DR. KLINE: I'm sorry, maybe I didn't understand your question.

MS. KRIVACIC: In, say, non-opioid-tolerant patients, patients that have allergic reactions --

DR. KLINE: I'm sorry. I misunderstood the question. I would like to

ask Dr. Larry Cohen to speak to that.

DR. COHEN: Thank you. As I understand it, I think what you are asking, what does one do in the situation of having a patient who doesn't tolerate using opioids. We traditionally are using opioids and benzos. What we do typically in practice, we give a sedative without the opioid, recognizing that it is going to require somewhat more on the sedation side. There, we are relying upon the amnesia affect, since we can't use the combination for the balanced affect of analgesia and amnesia. So we are using a little bit more of the sedative trying to capitalize, if you will, on the amnestic affect of the benzodiazepines, or in this case, fospropofol.

MS. KRIVACIC: So would you use that then with fospropofol?

DR. COHEN: Yes. So then I think in a situation where someone was intolerant or allergic to an opioid, one would simply use,

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presumably use fospropofol as a single agent.

CHAIR FARRAR: Dr. Chang?

DR. CHANG: I wanted to ask Dr. Schultheis, I'm sorry, if I am pronouncing your name wrong, just the comment that you made or the data that you showed that most of the patients with hypoxia or hypotension actually had purposeful response. And I am just wondering, is that asking for a purposeful response at the time they were hypoxic, since it had to be more than 30 seconds, which is not long in the whole procedure, or hypotension. I just wanted to make sure the correlation was at the time of the actual adverse event.

DR. SCHULTHEIS: The sedation scores and the purposeful assessments could not be conducted exactly at the same point, but they were conducted at the same frequency so that the assessments were made at the nearest point to when the hypoxic event was recorded.

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DR. CHANG: So you took that one time point that was the closest?

DR. SCHULTHEIS: Yes.

DR. CHANG: I see.

DR. KLINE: If we may, to further address the hypoxia to when a purposeful response was delayed, we think it is important to take it in the overall context of the opportunity to have an event at a certain MOAA/S score or purposeful response. I would like to ask Dr. Sirek to speak to that.

DR. SIREK: Slide up, please. The recommendation, both in the ASA guidelines and in our dosing concerning purposeful response, is not that a supplemental dose should be given when there is purposeful response, but a supplemental dose should not be given if there is no purposeful response.

So, this includes the same data presented, sort of, with a control for the time when you had purposeful response versus no purposeful response given, as you can see

if you look on the right-hand column, that for all the times that we measured purposeful response, 19,000 of those times the patients had a purposeful response consistent with moderate sedation, whereas there was a much lower rate of no purposeful response.

So, in that context it still is true, of course, that most of the sedation-related events occurred when a patient had purposeful response. But when you consider the risk of a sedation-related adverse event, it is greatly increased when you have no purposeful response, consistent with the ASA guidelines, consistent with what we know about sedation in general. And that is the rate there, you see the 1.04 per 100 patient-minutes' exposure, as opposed to the 0.25 rate when you have a purposeful response. A four-fold increase.

And the way we understand this is consistent with what, I believe, one of the advisory members said earlier is that a

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purposeful response does not preclude you from having hypoxia. So, it is not a sign. If you can give a thumbs up, it is not a sign that you don't have some element of hypoxemia. And so before you dose, you need to have both, that a patient has purposeful response and that they are otherwise stable, taking in all of the information that you have for monitoring the patient.

DR. CHANG: It just doesn't help you, I guess, to look at -- if you are considering giving a supplemental dose that a patient gives you thumbs up sign, it doesn't necessarily mean that you are going to prevent hypoxia or hypotension with that additional dose.

DR. KLINE: That is correct. But if I could, I would like to ask Dr. Candiotti to speak to the idea of purposeful response and the role it plays in determining patient status.

DR. CANDIOTTI: Keith Candiotti,

University of Miami. I am an anesthesiologist.

In the ASA guidelines, they basically stipulate that mild to moderate sedation of purposeful response is considered to be an adequate indicator of adequate ventilation. We know that it certainly doesn't preclude the possibility of mild hypoventilation or some hypoxia to occur, but it certainly is a good indicator that it is less likely to exist and, I would say, is used pretty much as a standard both in the OR as well as in other areas to help guide dosing of medication. As you are well aware, capnography certainly has limitations in MAC patients, non-intubated patients and whatnot, but can also be a source of supplementation.

CHAIR FARRAR: I think Dr. Kirsch would like to follow up on that.

DR. KIRSCH: So, I'm sorry, I'm confused. Could you help me understand what data you are referencing or is it just your

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personal experience with regards to the relationship between someone having a purposeful response and demonstrating adequate ventilation?

DR. CANDIOTTI: The literature. As a matter of fact, in the ASA guidelines, they even specifically state that the literature is lacking in particular control trials or a demonstration of this. It was a result of a survey, as you are well aware, when the ASA does the policies and whatnot or the guidelines. It is based on consultant recommendations as well as "expert opinion." So I am not quoting from a specific article. I am taking that directly from the ASA guidelines.

DR. KIRSCH: And in your own practice, when you give patients narcotics, for example, I suspect you have practicing for some time now, can you estimate how frequent it is that someone can receive a pre-medication of even just a narcotic and respond

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to your questions yet not be ventilated?

DR. CANDIOTTI: Well, they can't verbally respond to me if they are not ventilating at all, obviously. But certainly, as we are both well aware, hypoventilation can occur as a spectrum and to a degree. I think with any form of sedation, some degree including the classical benzodiazepines and opioids, some degree of hypoventilation can easily occur, especially as sleep apnics. In many people it is unrecognized.

DR. KIRSCH: And just my last question is just for clarification. What are the monitoring modalities that are suggested by the sponsor to assess ventilation?

DR. CANDIOTTI: I am not going to speak on behalf of the sponsor but they do endorse the ASA guidelines. The ASA guidelines specifically indicate, they do specifically say a thumbs up in responsiveness is adequate for moderate sedation. For deeper sedation, they do recommend capnography.

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DR. KLINE: The monitoring that we have listed here are the specific monitoring guidelines that we have included in our proposed package insert and these are consistent with ASA guidelines for monitoring during moderate sedation.

CHAIR FARRAR: Doctor --

DR. KLINE: Further, --

CHAIR FARRAR: Oh, sorry.

DR. KLINE: -- I would like to just read to you from the practice guidelines on how the ASA recommends viewing purposeful response. And what they say is that "The ability to give a thumbs up or other indication of consciousness in response to verbal or light tactile stimulation," which is how we also define it, "suggests that the patient will be able to control his airway and take deep breaths, if necessary, corresponding to moderate sedation."

CHAIR FARRAR: Dr. Epstein.

DR. EPSTEIN: Yes, I had a

question for Dr. Schultheis.

Regarding the hypoxemia in the combined data on the slide set that you showed and knowing that the sponsor also had a midazolam fentanyl arm, how did those numbers compare across those two different groups?

DR. SCHULTHEIS: Okay. My safety evaluation is preliminary and the sponsor may have different numbers. But if you could compare the incidence of peripheral hypoxemia defined by desaturation below 90 percent, just in the studies, the colonoscopy studies, the 0520 and the 0522, there were 78 midazolam patients studied. There was no desaturation below 90 percent and of the 184 fospropofol patients, there were six patients that desaturated below 90 percent. That is three percent. And you may correct those numbers, but that is what I have in my preliminary safety evaluation.

DR. KLINE: That sounds consistent with our findings on desaturation. What we

did see was in the studies desaturation that led to a sedation-related event of hypoxemia as we defined. So, less than 90 for greater than 30 seconds occurred at a very low rate. I believe one patient in our proposed label dose group. So, while it was greater than not seeing any in the midazolam, it was certainly more. Also, I think, to put the results in the proper context, I would like to point out that the dose of midazolam that we used was the dose that is recommended per label and, as such, was much lower than what is commonly used in practice.

Do you want to speak to exactly what those sources are, Dr. Cullen?

DR. CULLEN: Slide up. The results here are from the individual trials, not pool data and I think it does make a difference. But as you can see here in the pivotal trial at the recommended dose of 6.5 milligrams per kilo, there was a single instance of hypoxemia. And also a reminder,

there are three-to-two-to-one ratio in the randomization.

So, it looks like the incidence of hypoxemia is pretty comparable if you are talking apples to apples. When you pool the studies, you may have included, for example, in the dose response study, both higher and lower doses.

If you have a question on the amount of midazolam, slide up please, the midazolam arm, it is important to remember that the initial dose was 0.02 milligrams per kilo for midazolam, which is much lower than is commonly used. The cumulative total dose oftentimes is comparable to what is given all at once in the initial dose. But you can see here the initial dose for midazolam.

DR. KLINE: Thank you. And if I could ask Dr. Cohen to talk about what typical doses of midazolam are that he sees used in practice or is familiar with in the literature.

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DR. COHEN: Thank you. In practice, during colonoscopy at least, the standard doses of a benzo/opioid would be somewhere between 75 and 100 micrograms of fentanyl and between three and five milligrams of midazolam.

DR. CHANG: See, that is a little bit of a concern. If we are all using higher doses than the recommended for your clinical practice application, don't you think there might be some difficulty even if you do some type of education that endoscopists will use more than the recommended dose of fospropofol?

DR. KLINE: We don't think more than the recommended doses is required to appropriately sedate patients and I would like to ask Dr. Sirek to speak to how we will get that message out.

DR. SIREK: I think that the information that Dr. Cullen provided, that three to five milligram range, is consistent with what was actually given in our study for

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midazolam. So that was four milligrams, which is within the range of 0.02 milligrams per kilogram because that is how it was given in our study and what is in the label.

So, I do think that physicians certainly can and should follow the label. And all of our efforts will be directed towards making sure that they understand the label and understand the importance of dosing properly with our product.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: So, it appears that actually what you are seeking for an indication is the combined use of fentanyl and fospropofol, rather than just fospropofol alone. And in addition, many of these patients will receive midazolam.

So, now what you are doing, instead of having two agents to sedate a patient, we are going to three. And there are different dosing intervals. Every four minutes for fospropofol, every two minutes, at

least is our practice, with fentanyl or midazolam.

So, my question is, do you think that training is sufficient, given the added potential for confusion in the GI lab? And also, the faster we can sedate patients, the faster we, maybe I shouldn't say we, but the faster that patients can be sedated and turned over, the more money that is made. And there is a huge push to get these patients in and out. Do you think that training alone is going to be sufficient to prevent any complications here that are seen in the real world outside of a research setting or do you need a full RiskMAP strategy?

Now for example, there was a study published a number of years ago from Canber with over 28,000 patients. And most of these patients receive sedation with propofol. And numerically, there were substantially more patients that had anesthesia-related sedation-related complications when administered by the

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so-called GPs there, rather than when compared with those that had sedation administered by anesthesiologists.

Now, they didn't look at actually why that may have occurred but I wonder if it had something to do with confusion or the like. And so again, just to repeat my question. Do you think training is sufficient or do you really need a full RiskMAP strategy with certification and the like?

DR. KLINE: Let me first address your question about the agents used and then ask Dr. Sirek to follow up on your questions regarding training.

I would like to clarify that approximately 90 percent of patients in the colonoscopy and bronchoscopy studies completed their procedures with only fentanyl given as an analgesic and fospropofol given as a sedative. That was somewhat protocol driven because we only allowed up to three supplemental doses in the initiation period

before patients were eligible to receive an alternative sedative.

So when you look at, for example, our minor procedure study and that additional requirement wasn't included in the protocol, you saw 95 percent of patients completing their procedure with fospropofol given as an analgesic or fentanyl given as an analgesic and fospropofol given as a sedative. And Dr. Sirek can address the training aspects.

DR. SIREK: We agree that training is important. We also agree with the Agency that the label is always the first step in that aspect, making sure that the label is very clear to the prescribers as to appropriate dosing. In terms of a formal RiskMAP, we will, of course, engage in active discussions with the Agency as to what is the most appropriate.

In terms of RiskMAPs in particular, part of the criteria, obviously, is whether or not there is a safety margin.

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And we believe that our high dose study, studies, I should say, do give a good indication of the safety margin for this product. So we are not depending entirely, while we will actively, actively be right out there training everybody that we can in how to dose this properly, we are not depending solely on that.

We also do have the safety margin that says for those patients who receive greater than 11 milligrams per kilogram across all of the 400 series, all of the events that were seen were able to be managed by the proceduralist.

DR. KLINE: And I would like to ask Dr. Brill to address the third aspect of your comment.

DR. BRILL: As the distinguished panelists will recognize, faster endoscopy does not result in an increase lesion detection. In actuality, the study in the New England Journal of Medicine December of 2006

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from Rockford Gastroenterology, which is the greater Illinois area, definitely shows a correlation between the amount of time spent in performing the procedure and the detection of lesions. More recently, a study by Sateco and Associates at Stanford University published in JAMA in March of this year, also shows the issue of flat lesions in the right side of the colon and emphasizing the need for a careful examination of the colon.

Certainly, I recognize that there may be some of our colleagues who may be motivated by factors other than patient safety. However, I will emphasize that the primary concern of the physician first and foremost when performing a screening procedure, should be a careful and complete examination of the colon. And that is what guides us.

Last but not least, I will also point out that yes, there are instances where a physician may choose that based on the

endoscopist's pre-endoscopic evaluation of the patient, that it may be appropriate for the patient to have monitored anesthesia care provided by a second individual. In fact, that is inherent within the statement issued by the three gastroenterology societies in March of 2004 and has also been incorporated in guidelines established by the majority of the Medicare contractors in this country, as well as a number of the larger commercial insurance companies which look very carefully at the ASA criteria that were published in anesthesiology in 2002, when the use of moderate sedation by non-anesthesiologists as well as by the criteria published by the group at OHSU, the gastroenterology group, published in Gastrointestinal Endoscopy, in 2002, and others, in order to help physicians establish when an anesthesia professional should be used when the endoscopists should be able to safely administer moderate sedation.

DR. BUCHMAN: Just a quick follow-

up on that, Dr. Brill, though. As you know, the Rockford Group or the ones that originally recommended a 10 minute withdrawal time, which means that given the median time for your colonoscopy of 11 minutes, the average patient had a scope in their secum at one minute. And whether that is perpetuated, the quickness, by the ability to sedate the patient quickly and perhaps to maybe lead to an inadequate exam is not clear because clearly, what was done in your study would not have been, well not your study, but in these studies, the 0520 study for example, would not have been appropriate standard of care if the mean is 11 minutes, when 100 percent of patients should be at least 11 minutes.

DR. BRILL: Slide up, please. As you will see, sedation initiation nine minutes. At that point, the scope is inserted. So you have 11 minutes of procedure time. That's nine and 11, that's 20 there, that was preceded in the study. And as I

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previously indicated, the definition of intraservice times starts when the scope, pardon me, when the intravenous line is started, and sedation is initiated.

So, scope inserted in this study here, they have 11 minutes. You have quoted the Rockford study which actually talks about a six to eight minute withdrawal time. So, I don't think those numbers, they may be a little bit showing the experience of the endoscopists, but they are certainly not at the realm of ordinary, sir.

CHAIR FARRAR: It is my turn. And I wonder if I could ask, I believe it was Dr. Cohen presented slides relative to the number of procedures that are currently done and the number that are done with airway monitoring or airway specialists in the room. And if you could just review those slides with us because I think part of the issue here this morning is that there is concern about, with the approval of this particular medication and the testing

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that you have done, that it will increase the number of procedures that are performed without someone present who has specific training in airway monitoring and/or airway care. And so I would like to know what the current status is, review the current status and then come back with another question.

DR. COHEN: Thank you. And perhaps I need to make a little bit more clear exactly what it is that we are discussing. We are talking about procedural sedation. If I can go to my slides. Go back a little bit. No?

CHAIR FARRAR: Slide number nine of yours, I think, --

DR. COHEN: Okay.

CHAIR FARRAR: -- is where you presented the CORI database study.

DR. COHEN: Well, this particular, I think, let me go back and we can talk to it. I think the first numbers we talked about were 40 million cases of procedural sedation. And

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when we talk about procedural sedation, I am referring to sedation that is being provided by the proceduralists in general, that is, in the absence of an anesthesia specialist. And that was not referring specifically to cases in which an anesthesia specialist has been asked to be present.

Regarding the CORI data, this is a national endoscopic database, the 324,000 cases, these were performed by a number of sites throughout the country. There are about 87 sites that contribute cases to this database. And it is not possible in the database to extract out how many of these cases were being performed with an anesthesia specialist versus how many were performed where the sedation was given by the gastroenterologist proceduralist. And we recall can't analyze the subsets within this study.

CHAIR FARRAR: So, let me ask specifically. Is there any data published

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that indicates the potential risk where the proceduralist is doing the sedation versus having an anesthesiologist involved in the process?

DR. COHEN: I will actually ask Dr. Brill to address that.

DR. BRILL: Two things. One is that the GAO, the Government Accountability Office, published an evaluation of endoscopic procedures performed in a variety of settings. And several years ago looked specifically, for example, at endoscopy performed in non-hospital settings, in the office setting and concluded that endoscopic procedures could be safely performed in an office setting, which is one of the reasons why Medicare pays for endoscopic procedures in the office setting, such as screening colonoscopy, colonoscopy with biopsy, colonoscopy with polypectomy and the like.

Second of all, if one looks at the Medicare database, one will see that in terms

of the volume of where procedures were performed, approximately five percent of procedures are performed in the office setting, approximately 29 percent of the procedures are performed in an ambulatory surgery setting. And the remainder of procedures are performed in the hospital, whether the inpatient or the outpatient hospital setting. One would note that the hospital settings are almost uniformly joint commission accredited. The ASC settings are credited by one of four entities; either the joint commission, the AAAC, the American Association of Accreditation of Healthcare Facilities, the AAAASF, or in California, the Institute of Medical Quality. And all of those four entities have specific standards that the facility must meet for accreditation which speaks specifically to the presence of anesthesia rescue training of individuals performing procedures. The individual facility, obviously will set its own standards

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and the like.

With regards to the office setting, the majority of office procedures are performed in two states, New York and Virginia. And we'll note that the State of New York is in the process of enacting, at this point, a requirement that requires all office settings in New York to be credentialed by one of those three entities, again, the Joint Commission, AAAC or AAAASF by June of 2009.

So, in short, a long answer but there are adequate standards in place that a credentialed facility will have personnel in place who should be able to manage the airway and the complications.

CHAIR FARRAR: So the second question relates to actually the next slide of Dr. Cohen's, which indicated that currently, 40 percent of the endoscopy procedures, at least the slide says the de facto standard of care, that 40 percent of the procedures are

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