currently conducted with propofol. Is that of all endoscopic procedures?

DR. KLINE: Dr. Cohen?

CHAIR FARRAR: Could you just to clarify that?

DR. COHEN: Yes, the numbers have gone up over the last several years, as I think many of us are aware. But it is estimated, at the current time, that 38 percent of all endoscopies in the U.S. are performed with propofol being given by an anesthesia provider.

CHAIR FARRAR: Being given by an anesthesia provider. So those would be taken care of, in the settings that were just described, they would be taken care of, they would not be office procedures. Is that correct?

DR. COHEN: No. In fact, if you look at utilization of anesthesia provider or MAC sedation by site it is probably is higher in the office settings than it is in either an

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ambulatory or surgical center or hospital but in fact it is really across the board. Using MAC sedation given by an anesthesia provider can occur in any of those three settings.

CHAIR FARRAR: Okay. And just, so the second part of that slide talks about the difficulties or potential difficulties in using propofol; burning on injection, risk associated with lipid emulsions. Is the propofol, the 38 percent here, only part of MAC and -- or is it used for less complex anesthesia procedures now?

I guess what I am asking is, propofol can only be used with an anesthesiologist present. Is that correct?

DR. COHEN: There is some use of propofol by non-anesthesia providers. And there are a small percentage, somewhere in the range of five to seven percent, of propofol use is being given currently by non-anesthesiologists.

CHAIR FARRAR: Which brings me to

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the last question which is really directed at the company. Which is, that in terms of ongoing obviously any clinical development procedure process will involve a relatively small number of patients because of the way in which it is conducted. The question then about what happens when it is introduced into the general population is something that can only answered, and what happens with large numbers of patients exposed, can only be answered at the time when it is actually given in a larger population, usually after approval.

And I wonder if you could be clear. You have talked about the educational roles that you hope to play. What about the monitoring roles and the ongoing monitoring to try to help to answer some of the questions that have been asked here. Not simply about your products but about sedation in general.

DR. KLINE: I would like to ask Dr. Sirek to speak to pharmacovigilance.

DR. SIREK: We will, of course, be practicing good pharmaco vigilance and so we will be collecting spontaneous reports but we will not be dependent on that. We will be also proactively looking to gather information from other sources. We don't yet have formal contracts in place with anybody awaiting what the final product label will be, so that we can judge appropriately. Slide up, please.

You have already heard though about the CORI initiative, that is the leading endoscopic research and data repository on which some of the information that Dr. Cohen based his slides on. And we believe either this particular one or something similar will serve to give us some very early feedback on the success of training, on the actual rates of sedation-related adverse events added a much broader population. As you can see, the sites were both community and academic. So that is just one example of how we will seek to gather additional safety data, once the

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product is marketed.

CHAIR FARRAR: Okay, thank you. Ms. Aronson.

MS. ARONSON: My two questions relate to the benefit versus the risk. In slide CM-6, I note that 25 percent of patients with the standard sedation utilized propofol. And given that the sponsor's one of the primary benefits is risk of bacteria infection, I wonder in the retrospective study that is listed in CM-11, whether you have the statistics on risk of bacteria infection for propofol.

DR. KLINE: For propofol?

MS. ARONSON: Yes.

DR. KLINE: Dr. Cohen, can you speak to that?

DR. COHEN: One of the problems of performing a retrospective study on a database is that you are limited to whatever has been entered into the database and, unfortunately, this particular database does not capture some

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of the, sort of the delayed complications, which infection will certainly be.

I mean, if you look at some of the earlier literature in propofol, there were reported cases of sepsis, even death, related to the use of propofol, before it was recognized that there were certain good use practices that would reduce or minimize the risk of complication.

But to answer your question, in short, the answer is no, that was not captured in the CORI database. So we don't have the information, unfortunately.

MS. ARONSON: And to follow up, what about a comparison of hypoxemia?

DR. COHEN: Asking about hypoxemia in this -- well, I think that if you look at the data shown in the slide, the incidence of all cardiopulmonary complications, which included all of the complications listed here, plus others, including -- slide up please -- and they included both transient hypoxemia, as

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well as -- included hypoxemia. The overall incidence was 1.1 percent in the colonoscopy population. It was not broken down further in terms of the specific complications.

MS. ARONSON: You don't have propofol.

DR. COHEN: I'm sorry?

MS. ARONSON: I guess I am missing a comparison.

DR. COHEN: I see. Looking at the other study that looks specifically at propofol, I think you have to recognize there were 11,000 cases. It was a separate study that was published looking at the use of propofol.

You have to recognize in that particular analysis, also that was based on the CORI data, they did not, they did not specifically report on the specific complications. Again, the incidence being somewhere in the range of about one percent, plus or minus for all complications but it was

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not broken down into specifically the specific complication.

MS. ARONSON: Okay. And just finally, the issue that the FDA raised about the potential of reclassification of this drug, I'm just wondering about any risk management, whether the sponsor has considered that at all.

DR. KLINE: The classification that you are talking about, the controlled, certainly the risk plan that we will adapt will be appropriate to the scheduling class that is assigned to fospropofol.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: So that was actually exactly my question. The data that Dr. Schultheis showed us demonstrating euphoria in individuals who drink your compound, that is data from your place, so I assume that you must have something in the works to try to mitigate the risk of diversion of that compound. Could you share with us what your

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preliminary plans are?

DR. KLINE: Certainly risk of diversion will be very important with the product. I don't believe we have specific slides that can address that now but we absolutely will put the appropriate controls on the supply chain to minimize that risk of diversion. We are very aware of it and we will proactively do all we can to minimize the risk for diversion.

CHAIR FARRAR: Dr. Epstein.

DR. EPSTEIN: Yes, I have a question directed to Dr. Leslie.

Dr. Leslie, in a perfect world, if this drug was being used for moderate sedation analgesia, what specific training or guidelines would you like to see implemented or would be your recommendation for implementation, if this drug was available commercially?

DR. LESLIE: Certainly. I think they have listed for you as to what the

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company had put in the original proposal for their PI but it really comes down to the simple, three-part plan that they have. And number one is that I want to make sure that the patient really does fit the bill for mild to moderate sedation. And that, unfortunately, relies on the actual physician's experience and their expertise. In other words, I will see pulmonologists who will do what I would call ASA IV's routinely sedate them themselves, and manage patients who start with hypoxia to begin with and feel perfectly comfortable managing that. I don't see a gastroenterologist or another endoscopist doing it that way. So, patient assessment and their experience in knowing what they can and cannot safely do with a particular patient and a particular procedure type.

The second aspect is the education of the clinicians as to the specific differences between this sedative and the ones

that they may be currently using. And it really relates to the fact that this is a prodrug. It does not have a rapid onset. There is metabolism required and so their whole timing has to readjusted. It is no different than we learn any new drug. You have got to learn when you can give it, how long does it take to peak, and when can you re-dose it. It will take specific instructions.

The third important part is going to be how you actually monitor the person, look for the predictable side effects and the training of that person who is present in the room. Number one is, I do believe you need a person who is primarily dedicated, as designed in the ASA recommendations primarily managing the patient and their sedation. Yes, they can break away for a little this, little that. Not to say they can't assist for short periods, but primarily they are to manage the patient's sedation. That person needs to have

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basic airway management skills at least to that level.

I think in backup, either the physician who is directing the sedation by the other health care professional must have ACLS certification or immediately available someone in the office, someone within a few hundred feet, has that capability in case they need to go to further advanced airway support, such as bag-mask-valve, or maybe even intubation.

Now, the data as done in the studies show that they never needed that ACLS person. But in fact, I think, for safety reasons because it is going to take a little bit of learning period, as with any new drug, you need to err on that side.

One other point that didn't come out, you realize they did it in 24 sites for colonoscopy, 26 or so for the bronchoscopy. And if you look at the numbers, that means that they really did 10 or 11 cases per site. So, I am actually encouraged by that sort of

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lack of steep learning curve that they didn't have trouble with the first or second patient. I do a lot of clinical studies and quite often, we kind of struggle the first few times to get it right.

So I was actually, you know, I thought that was a good sign that whoever was doing the drug administration, whatever airway training skills they had, whatever backup they had from the start seemed to work. But I do emphasize, as I said, in several spots in my risk management presentation, it is extremely important that they follow all of the guidelines that the ASA has clearly laid out, that you have got to have basic airway skills. You can't let people give this who are not skilled and privileged to do that and have got to have backup that can extend beyond that because sedation is a continuum. And it can happen that that hypoxia can be persistent and they have got to have somebody immediately available to rescue them.

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DR. EPSTEIN: As a follow-on question, do you believe that ACLS is adequate for airway management, as it is currently designed?

DR. LESLIE: I think as long as you have done an appropriate airway assessment prior to getting into that situation, yes. A simple insertion of an airway, bag-mask ventilation, if that is appropriate, yes.

I do think that there is going to be a challenge from time to time of what is an appropriate airway. I think Dr. Nussmeier's question and others about the morbidly obese patients, those are difficult to assess. The incidence of obstructive sleep apnea and where does that fit. Different institutions have different policies there. And we will have to rely on a lot of local and institutional policies that have already worked a lot of these details out as to where they feel comfortable.

I know in our institution, we have

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seen a lot more need for MAC anesthesia in the endoscopy suite. And it really relates to older patients, massively obese patients, much sicker patients. And the choice to use MAC, I think is the right choice. It would not be a right choice to say well, let's make fospropofol work here. Those patients still should receive the current care that they are getting.

CHAIR FARRAR: Dr. Sang.

DR. SANG: Thank you. This is for Dr. Cohen. What proportion of the 60 plus endoscopies that do not involve an anesthesiologist require the reversal of either benzo or an opioid? I may have missed it.

And then how are these captured? Are these captured under the category of cardiopulmonary events or are they captured separately, so you can actually answer this question?

DR. COHEN: Now, you are referring

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to practice in general?

DR. SANG: Yes.

DR. COHEN: To the best of my knowledge, there really are no data indicating what the use of reversal agents is. I can tell you that in our personal practice, it is extraordinarily small. In fact, we recently have, we have reviewed our own personal experience and we have actually had to use antagonists only three times in the past five years, performing somewhere in the range of 15,000 endoscopic exams. So I think that going to a reversal agent is actually quite uncommon.

DR. SANG: Okay, thank you. I have a second question which is, I may have heard incorrectly, is it standard of care to allow the person primarily managing sedation in the endoscopy suite to be pulled and assist in the procedure. Is that standard of care?

The reason I ask is because, as you know, the temporal resolution of the

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monitors in the operating room are not as good as our eyes. And if that is the case, if no one is watching a patient at every second, I am not sure I understand. If you could just explain.

DR. KLINE: Yes. The ASA guidelines for moderate sedation, which we have attempted to be consistent with, we are consistent with in our proposed label, indicate that for moderate sedation, as we are proposing, a designated individual monitor the patient and that that individual can assist with brief interruptible tasks. So that is per the ASA Guidelines for Sedation by Non-Anesthesiologists.

CHAIR FARRAR: So actually, I think we are going to end this morning's session with Dr. Nallani and then we will speak about how we will conduct this afternoon. But there will be time for additional questions after lunch.

DR. NALLANI: I have a question

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for the sponsor. It relates to slide CP-9, if you can get that up.

DR. KLINE: Slide up.

DR. NALLANI: Thanks. It is indicated the five percent of subjects had plasma concentrations of about two micrograms per mL. Do the sponsors have any idea of the demographics of these subjects with respect to body weight or age?

DR. CULLEN: We do. The patients who exceeded two micrograms per milliliter, there were 22 samples that exceeded that level. We looked at all those patients represented by those samples. Those samples, I would remind you, represent a PK level from the population PK study that was drawn after as few as one or as many as seven supplemental doses.

And to answer your question, of the patients whose level exceeded two, only three patients all in the bronchoscopy study reached a MOAA/S level of one. And only two

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patients with a high level had sedation-related adverse events of one hypoxemia and one hypotension. Actually not the same three but different two.

CHAIR FARRAR: Okay. I will ask Teresa to make some announcements before we call the session to a close.

DR. WATKINS: All members that had previously registered for the open public hearing, regardless of whether you have already checked in at the front desk, please stop by at the meeting registration desk before you go to lunch.

Thank you.

CHAIR FARRAR: Before we end, I would like just to make a comment about this afternoon. We will have the open public hearing beginning promptly at 1:00 and I would like to ask the panel members, the committee members to please, before you duck out for lunch, review the questions that are in your packet. There are four slides that are there.

And prepare any questions that you may have that you would like answered in order to be able to deal with those questions, to be sure that we cover them in the discussion section this afternoon, so that we can move expeditiously through this process.

We will now break for lunch. We will reconvene again in approximately an hour, promptly at 1:00. So please try and be here a few minutes early.

Please take any personal belongings with you that you need at this time, although the room will remain secured with FDA personnel present. You will not be allowed, necessarily, back into the room until close to the time of reconvening.

Panel members, please remember that there should be no discussion of the topic during lunch amongst ourselves or with any member of the audience. Thank you.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

CHAIR FARRAR: If we could get started, we are beginning the open public hearing section. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency, at the open public hearing session of the Advisory Committee meeting, the FDA believes it is important to understand that the context of an individual's presentation should be known.

For this reason, the FDA encourages you, the open public speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship you may have with the sponsor, its products and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment

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of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee places great importance on the open public hearing process. The insights and comments provided can help the agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair way, an open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the

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chair. Thank you for your cooperation.

DR. WATKINS: Our first speaker is Atul Shah.

DR. SHAH: Thank you. I would like to thank FDA to allow me to speak to Anesthetic and Life Support Drugs Advisory Committee. MGI Pharma has agreed to pay for my time and travel expenses in connection with today's meeting.

I am a board certified gastroenterologist practicing in a private group practice in southern Maryland, and we have performed more than 100,000 endoscopies in the last 20 years between me and my colleagues. And I also had an opportunity to participate in 0522 study as a primary investigator and enrolled 30 out of 314 patients in that study.

Just to explain to you, 90 percent of endoscopies that are done in our endoscopy center, which is on the hospital grounds. And we have ability to get anesthesia within two

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to three minutes and they have been very fortunate to accommodate us in a timely fashion.

Currently, only sedation we have available is benzodiazepines with the aids of narcotics. We have faced tremendous problems with inadequate pain control, which is our primary concern, in almost 25 percent of our cases. And patients have been dissatisfied with the available sedation to the gastroenterologists to us and to the country.

Colonoscopy requires heavier sedation than upper endoscopies in our practice. And we have not been able to provide adequate sedation at this point. Deep sedation, prolonged deep sedation we have noticed in benzodiazepines currently, with as little as 122 milligrams in elderly population. And on other side, we have seen hypotension, unpredictable responses, even in high dose of ten milligram of benzodiazepines.

And propofol, which has been

currently increasingly used by the gastroenterologists throughout the country and worldwide, with more than half a million experiences not given by an anesthesiologist or what we call as NAPs with no complication, no deaths noted so far.

Fospropofol in the recommended dose of 6.5 milligram per kilogram, provided mild to moderate sedation in adult patients undergoing short diagnostic therapeutic procedures in colonoscopy and bronchoscopy, with adequate acceptable safety performance. The most common adverse reaction which we noticed were paresthesia and pruritus, which is very transient, and most patients did not recall these events.

Both physicians and patients recorded a high level of satisfaction in our study. And almost all of our patients were willing to be treated again with fospropofol again.

I strongly believe there is a need

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to train physicians and nurses with strict adherence to the protocol, which has been published, and to avoid repeating the same mistakes we have made following the use of midazolam two decades ago.

Despite the lack of reversal agent at this time for fospropofol and intended dose of 6.5 milligram per kilogram, it should be made available to the physicians and with the assistance of trained personnel who are one-on-one monitoring the patient for mild to moderate sedation, we should have it made available without the bolded statement as being done 20 years ago with propofol.

We do need future Phase 4 studies and disseminating guidance to train the physicians who can properly guide their assistant in use of fospropofol. And also there should be a caution exercised when used in conjunction with benzodiazepines, which may have a synergistic effect.

The use of capnography and

transcultaneous carbon dioxide monitoring might help to aid in Phase 4 trials in effectively recognizing hypoventilation, compared to use of pulse ox which is not even available when we used to give benzodiazepines in our hospitals.

DR. WATKINS: Thank you. Our next speaker is Stanford Plavin.

DR. PLAVIN: I paid my own way. I'm here to talk. I'm an advocate for patient safety. And the first thing that struck me about this was the fact that I was wondering why an anesthesiologist did not speak on the medical need of an anesthetic drug to the Anesthesia and Advanced Life Support Committee. But, irrespective of that, first slide.

I represent the National Coalition for Quality Colorectal Screening and Care. It is a broad spectrum approach. Gastroenterologists, surgeons, primary care physicians, anesthesiologists, patient

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advocacy groups. We are deeply concerned that the improper labeling of this type of drug will not promote the safe and colon cancer screening tests that are readily needed in our society.

The FDA's stated mission is to protect the consumer in advanced technology. I think to protect the consumer is the most important thing. Fospropofol is considered a prodrug form of propofol. And just a definition, a prodrug is a medication that is administered in its active or less active form and then metabolized to an in vivo form as an active metabolite. In this case, propofol.

This is from an excerpt from Drugs of the Future back in 2006. It has a description of fospropofol, which showed that it was a water-soluble prodrug of propofol designed to overcome some of the disadvantages of the lipid-based form which were, obviously, pain on injection and hyperlipidemia. The key statement here is that fospropofol is released

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to form propofol from the prodrug and equilibrates rapidly into the brain tissue to exert a dose-dependent anesthetic effect. These Phase 1 studies, obviously we have done Phase 2 and Phase 3, the sponsor has, but it showed even greater potency than the lipid-based propofol.

As far as the future of gastroenterology and fospropofol, obviously, it will inevitably find its wide-spread use amongst gastroenterologists, as represented by the interest groups here today. But if approved without the appropriate warning and labeling, leading to what catastrophic events that I am sure the FDA and the panel here doesn't want to happen. In fact, the AGA Institute, which represents the family of people here today, says "In many instances, sedation-related education is under-represented in the United States. Most mid-level professional training and moreover sedation-related continuing education is not

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commonly available to mid-career endoscopists." I'm sure that a lot of the people here meet that criteria.

So, this will potentially expose millions of patients to a drug that gastroenterologists, even by their own assessment of their own AGA Institute are not appropriately trained to employ and administer safely.

So, our role is to advocate for better sedation options but with the safety and quality necessary. Sedation success has been shown that percentages in the 90 plus range with fospropofol had more than 25 percent who were considered in deep sedation or greater. We need to improve patient access to screening, and this drug may do just that, but it needs to be studied further and properly labeled as as to protect the patients it is designed to serve.

Just some brief observations. The onset of all narcotics and anxiolytics are

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different, yet the labeling is essentially the same. Therefore, the use of fospropofol, which has different pharmacokinetics and dynamics which has been elicited here today should be labeled and shown the same respect of its parent drug.

The Institute for Safe Medical Practices showed that fospropofol, its predecessor propofol, should have strict product labeling. I'm sure we are all familiar with this and I don't see any reason why this current formulation of the medication should be looked at otherwise.

So I would like to thank you on behalf of the thousands of physicians and patients who aren't here to hear their voice heard. And I would also like to thank you because I am sure you are aware of all of the data that has come out recently, and some of it is obviously extremely concerning, but it is in the best interest to have this drug studied more.

We as physicians all have medical licenses. But I don't want a person who has a driver's license flying my airplane when I travel, nor do I want someone with no expertise --

DR. WATKINS: Thank you. Our next presenter is Kumar Belani.

DR. BELANI: Thank you. My visit here has been sponsored by MGI. I also have consulting and speaking agreements with several other pharmaceuticals and biomedical companies.

I am an anesthesiologist and, over the last 30 years of experience is being dictated here, I not only administer general anesthesia but I also sedate patients undergoing diagnostic and therapeutic procedures. I have participated in training programs that train nurses and physicians that provide sedation for patients needing diagnostic procedures.

At my institutions, sedation

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services are always supervised and ordered by a physician. During sedation, a care team approach is used and includes the full-time presence of a trained nurse with or without a physician or the training that is solely dedicated to the care and monitoring of the patient needing sedation. Along with the supervising physician, this team is skilled and undergone advanced training in the continuum of sedation and monitoring. A pre-sedation assessment and care plan is documented for each patient. This screening allows to exclude patients that need the services of an anesthesiologist.

For sedation, all patients follow their institutional NPO guidelines and coordinate the cardiopulmonary monitoring that is carried out and documented. I would like to indicate, and this is well-supported by the literature that we still do not have an ideal drug that provides safe and satisfactory sedation for all patients.

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Drugs such as chloral hydrate and the demerol-fentora-thorazine combination have been shown to be associated with a significant risk of serious adverse events. In addition, the pharmacokinetic profile of these drugs, namely chloral hydrate and DPT is extremely unfavorable resulting in a significantly delayed recovery.

Chloral hydrate and DPT were soon replaced by the introduction of benzodiazepines. Previously diazepine was used but was associated with significant pain on injection and delayed recovery because of active metabolites. Water soluble, painless to inject midazolam then became available and is currently one of the mainstay drugs for providing anxiolysis, amnesia and sedation. Unfortunately, midazolam, as you have heard today, by itself is not very important and has often been associated with patient and provider dissatisfaction and requiring larger doses.

Most commonly, a second drug like fentanyl, a rapidly acting sharp duration opioid is added to increase its success rates. Doing this, as one would expect, would add to the side effect profile and induces the potential for respiratory depression.

Practitioners and proceduralists who use this combination have learned to fine-tune sequencing and dosing to achieve maximum benefit with the goal to minimize unwanted effects. In the last decade, endoscopists and other proceduralists have found the superiority of propofol for sedation. When used in the proper setting, propofol provides excellent sedation, patient and provider satisfaction, when compared to midazolam meperidine combination.

However, propofol is still not an ideal drug. It is soluble only in lipids and uniformly causes significant pain and discomfort on injection. It has a very narrow therapeutic window and, hence, it gets a very

rapid onset with quickly achieved blood level that results in significant cardiopulmonary depression most commonly seen with induction of anesthesia. This is not surprising because propofol was introduced for inducing general anesthesia, and practitioners have learned how to maximize its use for moderate sedation.

What we actually need is a better propofol. Aquavan or fospropofol, I believe, is one such option. And the reasons I believe this is the case is because firstly, it is water soluble. Secondly, it is a prodrug. This means it takes a little bit longer in onset than the doses studied. This induces a smooth sedation effect, without the rapid high peaks that are observed with the lipid emulsion of propofol.

Next, unlike propofol, the drug is being introduced as a drug for sedation and has been studied for sedation for this purpose.

DR. WATKINS: Thank you. Our next

presenter is Momen Wahidi.

DR. WAHIDI: Good afternoon and thank you for allowing me to speak today. I am a pulmonologist an intensivist, as well as a clinical researcher and a director of bronchoscopy at Duke University Medical Center. I was an investigator on the bronchoscopy study. I have no financial relationship with MGI Pharma; however, they did pay my expenses today.

I want to talk to you about my practice. We do over 2,000 bronchoscopies a year at Duke, and I personally do about 500 of those. We currently use a moderate sedation with midazolam and fentanyl. And although it is an effective regimen, unfortunately, it falls short of keeping my patients comfortable in about 15 to 20 percent of the patients. The problem with this regimen is that we don't get predictable sedation. It is always a guessing game in the bronchoscopy suite about what patient is going to need one milligram

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Versed and what patient is going to need seven milligram Versed and so forth.

I am also concerned about the delayed recovery of this regimen. It is always burdensome for us and for the the family to wait to talk to them. It interferes with the flow for patients and ourselves.

I want to also point to some changes in the landscape of bronchoscopy. The bronchoscopy field is undergoing tremendous growth. We have a lot of new technologies emerging in the last five years. We have endobronchial ultrasound. We have more and more complicated procedures that require better sedation and more effective sedation. And we are also doing more procedures on patients because of the effects of the tobacco abuse, the epidemic in the last 50 years, as you know.

Fospropofol provides very smooth and effective sedation and it is dose-dependant. It is predictable and it would

help us do our procedures more effectively. From the side effect discussion, the relevant side effects to me, as a bronchoscopist and a pulmonologist are the hypoxia and the, potentially, drifting into deep sedation. What I can tell you is today, with the current regimen that we use, this is not uncommon. Unfortunately, bronchoscopy is not studied well. We don't have a lot of studies and we take it upon ourselves, myself and other colleagues, to do better bronchoscopy research.

And what we see today in the bronchoscopy suite is that these are common occurrences. Most of the hypoxia that we see is treated easily with simple maneuvers like increasing the oxygen flow or repositioning. Similarly, deep sedation is not common but when we encounter it, it is usually handled efficiently, quickly, and our nurses, trained nurses and physicians handle it very effectively. But it does happen today and it

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is not different than fospropofol.

So, I am hoping that this drug would be approved because it will help my patients, it will help my practice and, hopefully, it will help a lot of patients.

Thank you.

DR. WATKINS: Thank you very much. The next presenter is David Lubarsky.

DR. LUBARSKY: Thank you. My name is David Lubarsky. I am the Chair at the University of Miami and MGI did pay for my expenses and time to be here. My total consulting fees, I have been working with them probably for four years, represent significantly less than one percent of my income. They occasionally consult with me.

My practice consists of nine different surgical suites in seven different facilities, including the largest public and the largest hospital in the United States of America, as well as a VA, a private hospital and ambulatory surgery center, the number one

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eye hospital in America. And in each and every single facility, as I am sure some of the sitting chairs who are on this committee understand, I am constantly assaulted with the push for various practitioners to use propofol. And I believe that this drug is a reasonable compromise where I can say yes to one and no to the other, if this drug were approved for this purpose. I am only speaking personally, from my experience, which is in the hospital where anesthesia backup is readily available. And I believe that the use of this drug with its slower onset and perhaps easier recognition of deep sedation will allow for an easier call for help, if that is the case.

I will tell you that, around my hospital system, it is difficult to control the use of propofol despite having written all of the sedation guidelines for the system after I got there.

There are many patients who

actually would benefit from a propofol-like level of sedation. It is more pleasant than some of the other drugs that we currently use. And right now, people either bootleg propofol or they use drugs that might be sub-optimal for a particular experience. And I think that this drug provides that opportunity to address that.

I also think that I have been constrained in teaching other specialties how to manage airways. Because the implication has been constantly that you are, essentially, going around the FDA, around the black box warning on propofol. You are teaching people how to rescue airways so that they feel comfortable using propofol. And I want to say, I do not want any proceduralist using propofol, which induces a quick general anesthetic, without an anesthesiologist present. And I think that this drug offers a potential alternative to that and allows for additional cooperation between the societies,

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which frankly, to this endpoint, has been lacking. The reason that the AGA has no anesthesiologist teaching the GI doctors how to manage airways and do deep sedation is because we frankly don't believe that it is safe for them to use propofol on a regular basis. Perhaps this is a bridge to greater cooperation, to greater education, to greater patient safety, and perhaps it is not. I don't know the answer to that. I think that post-marketing studies are going to have to be done. There is the potential danger that we will see midazolam-like arrests, et cetera, when the drug is first introduced. We can't know that.

And I would also like to say that as a chair of an extremely large training program, I defer to the ASA and their statement and their position but I think that offering perhaps a different perspective because I currently do not currently cover GI endoscopy. So, I don't have any economic

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interest as a practice in actually pursuing or maintaining that practice. And when you work in a public hospital, you can't actually afford to send an anesthesiologist down to do every sedation. So, in some cases, this may really be better for the patients.

And unlike everybody else, I am going to stop before my time is up. Thank you very much.

DR. WATKINS: Thank you. Our next presenter is Todd Baron.

DR. BARON: Hello. I am a gastroenterologist at Mayo Clinic, Rochester. I am the Director of Pancreatic and Biliary Endoscopy there. I am here to represent the ASGE. I am also the Chair of the Standards of Practice Committee for the ASGE. Neither myself nor the ASGE has any financial conflicts with regard to this.

In the landscape of endoscopic sedation, monitored anesthesia care, accounts as you heard between 33 and 40 percent of all

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endoscopic sedation, up to 67 percent, for example, in New York, as we have also heard, midazolam and opiates comprise the majority of sedation given for gastrointestinal endoscopy.

GI-directed propofol, despite the fact that it is generally not accepted, as been published, in over 500,000 patients with excellent safety and efficacy. Unfortunately, there is a restricted label for propofol. State nursing board rules limit the administration by a GI nurse team. The economics of MAC anesthesia then have led to higher costs per case, up to $440 per case, a billion dollars of health care. Costs and there are payers that are refusing to reimburse now for use of propofol.

Sedation levels. There are, obviously, various levels of sedation that can be obtained by any drug or any drug combination. Anesthesia provides probably deep sedation in use of propofol, whereas the GI nurse sedation delivered propofol targets

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moderate sedation. You have also heard earlier by Dr. Cohen, and this is part of his data, looking at satisfaction with propofol compared to benzodiazepine and opioids with regards to colonoscopy sedation showing that there is better patient satisfaction with propofol.

So, fospropofol, as you know, is a water-soluble prodrug without restricted label may allow propofol superior type of sedation experience but administered by a GI nursing and a GI nurse team. The potential decreased use of anesthesia providers may also result in cost savings.

There are concerns about fospropofol that you have heard. And this talk was obviously put together before any of the data that was presented today. There is not a comparison to a gold standard. There is limited data on use in upper endoscopy. It does have a longer half life than propofol and we talked about dose stacking, paresthesias

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and perhaps insufficient data in the sickest of patients.

So in summary, future studies are needed, obviously, for upper endoscopy, in addition to other, perhaps, complex endoscopies such as ERCP/EUS and those with advanced anesthesia grade levels. Certainly, it is mentioned today, training and procedural staff are needed prior to implementation of this drug. But the ASGE's position is that appropriately trained gastroenterologists and nurses under the direction of gastroenterologists can safely administer, not only propofol, but also fospropofol for sedation during endoscopic procedures.

Thank you.

DR. WATKINS: Thank you. Our next presenter is Philip Grossman.

DR. GROSSMAN: Thank you. I am Dr. Philip Grossman, a practicing gastroenterologist in Miami, Florida. I am a voluntary associate professor of

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gastroenterology and epidemiology in public health as well as medical director of an ambulatory surgery center. In addition, I have served as a consultant to MGI and have been compensated for it. And the opinions that I express today are mine and not of any of the organizations that I have just mentioned.

I am going to try to make my remarks simple and to the point. And that is, fospropofol is not a good or a bad drug, per se. It is no different from penicillin or any other drug when measured for appropriate usage. The real issue surrounding fospropofol is that there now exists a gap, particularly in the outpatient interventional world. We have midazolam and narcotics at one end of the spectrum. We have anesthesia-administered propofol on the other end of the spectrum and a very large gap in between that heretofore has been unmet. The data available to date suggests that fospropofol would meet that gap

very well.

You know, this is not a wonder drug. I don't think it is meant to replace any of the other choices. I think its benefit is that it provides the clinician an alternative in the appropriate setting.

We know that the usual combination of fentanyl and Versed are not often adequate for patient sedation. You have seen the slides from speakers before me, as well as the fact that the rise in propofol use is growing at about 25 percent each year, not by coincidence, but because there is a gap that is being administered now with the only alternative.

Safety is, of course, the number one issue. And the comments that I have seen and read to date talk about the drug, per se but I think the real safety issue is around the clinician and not the drug, that with adequate training, with adequate patient assessment, the drug is safe and fills an

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important role.

If you look at midazolam, as has been mentioned and you turn the clock back and look at all the respiratory arrests, you would have said that is a horribly unsafe drug and should be pulled from the market. Yet, today it is widely used and is a safe drug in the same hands. The difference is that the drug didn't change but what changed was the education and assessment and understanding of the drug.

There has been criticism or concern that, if fospropofol were approved as requested, that there would be a danger in the office environment. That already there is a concern about procedures in the office being done in an unsafe manner. My answer is simple. The problem is not the drug; it is the doctor. If things are being done with improper safety, they are simply being done improperly and that is not a product of the drug.

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Propofol provides a very beneficial patient experience but it is not perfect. There are storage issues. There are sepsis issues, there is pain on injection and this fospropofol provides what I believe to be an excellent balance between the two extremes. At a time when two of our greatest challenges in health care in this country are access to care and colorectal cancer screening, this is a time when clinicians need a broader choice to match the patient's need for a safe and effective examination with available drugs. I believe fospropofol should be approved for that reason.

DR. WATKINS: Thank you. Our next presenter is Michael Weinstein.

DR. WEINSTEIN: Members of the Committee, I am Dr. Michael Weinstein, a practicing gastroenterologist in the region for more than 23 years. As a disclosure, I have participated in fospropofol clinical trials for Guilford Pharmaceuticals beginning

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in 2003 and later for MGI Pharma. I was compensated by these companies as a principal investigator. In order for me to appear here today, I am being compensated for my time away from my practice. My comments are my personal comments.

As an additional disclosure, I currently serve on the governing board of the American Gastroenterological Association but I am not here in that capacity and my comments are not official comments of the AGA.

I thank you for the opportunity to appear before you.

Pertinent to this new drug application, I am the founder of two endoscopy centers in the region that have performed more than 150,000 procedures over the last 20 years. We have used a combination of midazolam and meperidine or fentanyl sedative combinations without a single intubation in more than 20 years. I have seen dramatic improvements in advances in medical technology

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and medicines for digestive disorders. The ambulatory endoscopy center accreditation process has changed over the last two decades and the credentialing for physicians and training requirements for our nursing and technical staff have changed with them. Related to the administration of sedation, we now require all physicians and endoscopic nurses to maintain ACLS certification.

In addition to the gastroenterologists, endoscopic procedures are staffed by both a nurse dedicated to assisting with monitoring of patient sedation level and a technician to assist in therapeutic procedures. Over the years, we have added equipment to help us monitor patient responses to sedatives, including automated vital sign assessors, pulse oximetry and routine EKG monitoring.

Our patients expect that their procedures will be performed in a comfortable and safe manor. Combining midazolam and an

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opioid leads to a reliable induction of sedation with high rates of procedure completion and high patient satisfaction levels. There are, however, some less-than-ideal aspects to the use of these agents, as you have heard. These include the delayed onset of sedation and lingering sedative effects that may delay recovery and discharge.

Diprivan was not used by gastroenterologists for the routine performance of endoscopic procedures, when it was first introduced nearly 20 years ago. Accordingly, the restriction on the use of propofol by non-anesthesiologists did not impose a clinical care hindrance. However, times and technology have changed and my hair has fallen out.

I will not reiterate all of the arguments about whether the labeling of propofol should be changed, except to say that in 2008, the published data on worldwide experience with trained, non-anesthesiologist-

administered propofol now exceeds half a million cases performed safely.

I wish to highlight a couple of the most important points from the perspective of an investigator of propofol. My experience was limited to male and female patients between the ages of 18 and 85 with ASA class I or II, scheduled to undergo elective outpatient colonoscopy. We did not have the opportunity to study fospropofol in patients with severe systemic disease, ASA class III or IV. These are patients that we would not normally schedule in an ambulatory endoscopy center for non-anesthesiologist-administered sedation. As a basis for comparison, I have had the experience of observing the sedation effect of propofol combinations in hundreds of patients under the direction of anesthesiologists. I have sedated thousands of patients with benzodiazepine/opioid combinations and I personally directed the use of propofol for 75 cases in another clinical

trial.

My personal observations with fospropofol/fentanyl combination is that the sedation achieved in patients was characterized by a more gentle onset --

DR. WATKINS: Thank you. Our next presenter is Gordon Downie.

DR. DOWNIE: I would like to thank the panel for this opportunity. My name is Gordon Downie. I am an M.D. Ph.D., a Ph.D. in experimental pathology. I am a board-certified pulmonologist. My travel here was supported by MGI Pharma. I have no other financial relationship. I am a practicing interventional pulmonologist in Northeast Texas. At the time of the Phase 3 trial, I was an associate professor at East Carolina University and a site principal investigator for the trial.

I am here in support of the use of fospropofol in advanced interventional pulmonary techniques. My current practice

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employs Versed and fentanyl in small, repeatable aliquots to achieve and maintain moderate sedation. I am ACLS-certified and moderate sedation-certified. However, there are several gaps which I have found in my practice. These usually occur in patients with high metabolic rates secondary to drug abuse or in my lung cancer clinical experience, patients with narcotic usage for uncontrollable refractory pain. Fentanyl and Versed is inadequate in inducing and sustaining moderate sedation in these patients.

As Dr. Wahidi from Duke intimated, advanced interventional techniques in pulmonology is the largest growing facet of bronchoscopy. We have prolonged procedures lasting from a half hour to an hour and a half. And as we go longer, we need a repeatable, predictable sedation which will not have patients dipping into deep sedation, which occurs readily with Versed and fentanyl.

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My personal experience with fospropofol, we followed ten patients in the study. Six of these ten patients had lung cancer at our group and, to address some of the panel's questions from earlier, my procedures lasted between 20 minutes and 50 minutes so, much longer than the mean that was reported.

Three of the four cancer patients used a 6.5 milligram dosing. We had no deeper sedation than three -- excuse me. One patient with two, most were three. It was predictable and very useful in that setting.

In conclusion, I think fospropofol would be very useful in my practice, especially in advanced interventional techniques. In Northeast Texas, where I now practice, we only have two anesthesiologists in our practice and three CRNAs. We have a new cancer center, which is our magnet for drawing in patients. We just do not have the manpower to have anesthesia-trained personnel

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at these procedures. So, I think fospropofol has attributes not available in the other sedating medications and I think this would improve safety and comfort in the cohort that I have just described.

It is my profound hope that political and financial concerns will not unduly influence the approval of this drug, which is proven to have scientific merit, especially in the cohort that I mentioned. Thank you.

DR. WATKINS: Thank you. Our next presenter is Thomas Henthorn.

DR. HENTHORN: Thank you very much. I am here to represent the American Society of Anesthesiologists, to bring their comments to this Committee and I thank you for that. They paid for my travel.

What I have to say deals with some of the real concerns with the clinical pharmacologic data for propofol and fospropofol. I also have some remarks

regarding the ASA's recommendations regarding the needed training and education for safe administration of anesthetic drugs.

The first red flag has to do with fospropofol's variability. This figure shows the plasma propofol concentrations resulting from an infusion of the emulsion formulation and from fospropofol and as plotted on identical axes. The C-max of the emulsion varied no more than approximately 25 percent, while the fospropofol varied over a three-fold range. Some of the reason for this may be related to its conversion.

Due to the increased molecular weight of the phosphate group, the milligram dose of fospropofol would be expected to be 1.86 times larger than the equipotent dose of propofol. Instead, the actual equipotent dose in this study was 6.32. Data presented today from the sponsor showed similar dose ratio.

In contrast, fosphenytoin, using the same mechanism, has a molecular weight

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that is 1.5 times that of phenytoin and the equipotent dose is exactly 1.5 times.

The situation with fospropofol is not so straightforward. There is metabolism variability and metabolism in the liver that probably goes straight to the glucuronide and prevents it from going into the blood.

However the true kinetics of the conversion of prodrug to propofol plays out, anesthesia providers, familiar with the dosing of propofol in their current literature about fospropofol need to be educated. Furthermore, the potential for highly variable conditions strongly argue for the presence of personnel sufficiently educated and trained to deal with the full continuum of sedation and anesthesia.

The other red flag is the very steep response curve for propofol. The gamma for midazolam is much smaller than that for propofol. And what that translates into is that small doses of propofol can produce large increments of effect. Quite the opposite of

what happens with midazolam, where repeated large doses do not give you significant changes in effect. This will be a different situation.

In this 1928 or 1908 publication by Dr. Cohen, who we saw earlier today, we see that the proposed 6.5 milligram dose of fospropofol was successful only 69 percent of the time. This study also shows the steep nature of the dose response curve, where an increase of only 1.5 milligram per kilogram changes the sedation success from 35 percent to 69 percent and up to 96 percent. Dr. Cohen termed that the larger dose as having safety concerns, which we saw today was an incidence of 25 percent of deep sedation or frank anesthesia. Note that the midazolam was successful about 80 percent of the time. I am not so worried about patients that failed in midazolam. I am more worried about adding drug.

And I have run out of time. Thank

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you.

DR. WATKINS: Our final presenter is Julie Cantor-Weinberg.

DR. CANTOR-WEINBERG: I am the Vice President of Public Policy at the American College of Gastroenterology and we are pleased to be here today. MGI Pharma has been an exhibitor at ACG educational conferences. ACG is a physician organization representing more than 11,000 gastroenterologists.

I think that it is important to realize that we work so hard to increase colon cancer screening rates, and fear of discomfort during the procedure can be an important barrier to colonoscopy screening. And our members consider sedation during endoscopic procedures, including colonoscopies a medical necessity, with more than 98 percent utilizing sedation during these procedures.

The profession of gastroenterologists has more than four decades

of experience in using a wide range of sedation agents. Gastroenterologists are well trained to respond to the rare complications that may occur using these agents.

I am not going to repeat some of the comments of the other GI group. So, I think it is important to recognize that there is ample scientific evidence demonstrating the safety of propofol under the supervision of gastroenterologists. And in 2004, along with our sister societies, we issued a joint statement on the use of sedation in endoscopy. And the statement found that there is ample data to support the use of propofol by adequately trained anesthesiologists.

Nonetheless, the current FDA-approved labeling contains a warning specifying that it should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of surgical or diagnostic procedures. And this has led some states and institutions

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to limit the use of propofol by gastroenterologists.

Given the significant data on the safety of gastroenterologist-administered or -supervised propofol in 2005, the College filed a proposed labeling change for propofol through the FDA. Three years later, we are still waiting for an answer, despite the fact that there have been almost 500,000 cases of non-anesthesiologist-administered propofol documented in the literature. And the non-anesthesiologist-administered propofol is one feasible solution to the high cost associated with anesthesiologist-delivered sedation for endoscopy.

Obviously, patient safety is key to quality care in any recommendation this Committee makes. And it is important to note that there is no studies to date demonstrating that NAP exhibits a higher incidence of cardiopulmonary or procedural complications than standard sedation by

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endoscopic procedures. The College believes that training and clinical education are a key function, and some of our training does involve assessing and monitoring patients with restricted airways.

It is important to note that all of the pivotal studies conducted pursuant to the NDA with fospropofol performed without anesthesiologists, including those done in association with colonoscopy. We are pleased that the NDA and clinical trial application for this sedation agent. Especially the trial data on colonoscopy patients shows that it can be safely used by non-anesthesiologists, including gastroenterologists, with appropriate patient selection and patient monitoring.

We, therefore, urge the Committee to, if it approves the product, to allow for non-anesthesiologist-administered propofol and seek your help in moving our 2005 petition forward on propofol. The health care system

can't afford to wait any longer than it already has. Thank you.

DR. WATKINS: Thank you very much.

CHAIR FARRAR: That concludes the open public hearing. The open public hearing portion of the meeting is now concluded and we will no longer take comments from the audience. The Committee will now turn its attention to addressing the task at hand, the careful consideration of the data before the Committee, as well as the public comments.

What I would like to propose to the Committee is that I had asked you before lunch to look at the questions that we have. We have one more question which basically asks, in summary, how you feel about the data that has been presented. We will provide you with that question in a minute. And what I would like to do is to open the floor for discussion. Clearly, if you have thought of other questions over the course of lunch that you are interested in asking about, we are

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very interested in making sure that we cover all of the topics that we have heard this morning.

And Dr. McLeskey, you had a question before lunch that we didn't get to. So, we can start with you.

DR. McLESKEY: Thank you. This is a question for the sponsor and I was just curious, when you say you are limiting the dose to six and a half milligrams per kilo on a per kilo weight basis but an individual less than 60 kilos would be dosed at the 60 kilogram dose, what was the logic for that?

DR. KLINE: The logic for the weight bounds that we have incorporated into the dosing recommendations are based on the pharmacology of the drug. I would like to ask Dr. Waters to speak to that information.

DR. WATERS: Yes. The weight-bound dosing regimen for fospropofol that we have used in our clinical studies is based on the known difference in propofol clearance

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across body weights. This is published in the literature and evident in our studies. Slide up, please.

The data presented here are propofol clearance versus the three different categories of the weight bounds within our dosing regimen. Shown on the left are the data propofol clearance for the patients below 60 kilos. You can see that the plasma propofol clearance is greater in those patients, relative to the heavier weight patients. That is, propofol is leaving the body more rapidly. In effect, what we have in those patients is, while they are dosed on a greater milligram per kilogram basis, the resulting propofol plasma levels are consistent across the weight population. Next slide, please.

These are data from a population PK evaluation. Shown on the left are the plasma propofol versus time concentration data for the patients below 60 kilos. In the

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middle, 60 to 90 kilos. And on the right, greater than 90 kilos. And as you can see, with this dosing regimen that we have employed within our clinical studies, we have achieved similar plasma propofol concentrations across these different weight bounds, by using the weight bounds we have incorporated.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: My question relates to the efficacy in different genders and I am wondering if you have data separating the pre-menopausal women versus men or postmenopausal women on the efficacy of the agent in producing your endpoints.

DR. KLINE: We looked at efficacy in subgroups. We did not look at the specific subgroup that you mentioned, postmenopausal women. When we look at differences in efficacy or look at the sub-populations based on gender, age, weight, ASA status, we see that in all cases, we still reach the efficacy endpoint.

DR. KIRSCH: I'm specifically interested in the low-weight people. I suspect that most of those people are women and wondering whether their rate of metabolism relates more to their gender than their size.

DR. KLINE: We, you know, the patients that were less than 60, we don't have the breakdown by other demographic factors by patients who were less than 60. I can't answer that question right now.

CHAIR FARRAR: Let me follow up, though. My understanding of propofol is that, unlike other very lipophilic agents, it is not metabolized so much as cleared by being transferred to other adipose predominant tissues. Is that true? I don't want to misspeak, if that is not true.

DR. KLINE: Dr. Waters?

DR. WATERS: There are several factors related to propofol clearance. One is distribution and also metabolism, conjugated metabolism and oxidative followed by

conjugated metabolism.

CHAIR FARRAR: So I guess my question is, if I give a single dose of propofol to a patient and, within a very short period of time, they go through a sedation and then a period where they wake up; what percentage of the propofol is actually metabolized as opposed to redistributed? The real question comes down to thinking about the smaller group and other subgroups. For instance, very cachectic patients who may need exams for a variety of reasons where their volume of distribution or their lipid available for distribution of the drug would be much smaller. And I think that gets to Dr. Kirsch's question. If the smaller patients are all women, women have a higher adipose tissue content, generally, than men and it may be that the need for the larger dose is related to them being women instead of just being small.

DR. WATERS: Well, I can ask

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another member of our group to speak to the demographics of our population, but I think the data that I showed relative the smaller body weight patients demonstrated that the plasma propofol concentrations are similar across the groups. So, we are not seeing the decreased body weight as impacting the plasma propofol concentrations, as you might have suggested.

CHAIR FARRAR: But to the specific question, is the short activity of propofol related to the redistribution into fat tissue?

DR. WATERS: The early aspect of propofol decrease is a redistribution phenomenon but also impacted by extensive metabolism.

CHAIR FARRAR: Thank you. Dr. Chang.

DR. CHANG: Yes, I had two questions just again about the applicability to the clinical practice.

So, when you do education and when

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you are planning on introducing this into clinical practice, are clinicians going to be told what to do if you don't have adequate sedation and that you are going to give, then, to tell them to supplement it with midazolam? And do you have enough information to know how these two interact and are there maximum doses? And also, are you going to have any guidelines on the limitation? If you have a patient that you think you are going to be scoping for a long period of time who has polyp disease, isn't there going to be some maximal dose? And is there going to be guidelines on maybe those aren't the correct patients to use this type of drug?

DR. KLINE: Your question gets to the idea of drug interactions and I would like to ask Dr. Sirek to address that.

DR. SIREK: We did do a pharmacokinetic drug interaction study, slide up please, that looked at the pharmacokinetic interaction with fentanyl, midazolam,

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meperidine, and morphine. And none of these drugs affected the pharmacokinetic parameters for fospropofol.

In addition, there is, of course, an additive affect of sedation. And that would be true also when you had a midazolam failure, for example, in clinical practice. And to that end, while we do have experience with the use of midazolam in our sedation failures, not unexpectedly, you know, when you do add sedation, they are more likely to become deeper-sedated. But within our clinical trials, the investigators were blinded. So when we had a sedation failure in our 6.5 milligram dose group, the investigator had no way of knowing whether or not the patient had gotten 2 milligrams or 6.5 milligrams and, therefore, we believe that they may have given a little bit more than they would if they really knew how much drug the individual had received.

To that end, we do not anticipate

giving a limit as to how much fospropofol can be given. We do have experience with substantially higher doses both as a bolus dose, as you have heard previously from our 400 series, as well as in a continuous infusion trial in the critical care unit over 12 hours. So, we have that range. We are not suggesting that this drug might be appropriate for very long procedures. We do not have experience in extended procedures and typically, moderate sedation is not used for procedures that are going to last several hours. But within the range of what is generally used for moderate sedation, the procedures that give moderate sedation with midazolam and fentanyl or other opioids, we do believe that our data is consistent with that use.

DR. CHANG: I mean, because some colonoscopies take a lot longer than the 11 minutes. You know? So I'm not taking about a two-hour colonoscopy; that would be bad.

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And then also, just for opioids, I mean, do patients really get out faster? I know their memory is a little bit better but it's not like they are not going to get opioids, which do sedate a patient as well. So, I am just wondering. Is it really going to be quicker for them to be more aware?

DR. KLINE: We, as I mentioned, didn't do comparative studies as far as looking at comparative claims. Our times to emergence, our time to a fully alert is approximately five minutes median time in the colonoscopy study, five and a half minutes in the bronchoscopy study.

CHAIR FARRAR: With regards to the interaction of the use of propofol with other medications, obviously it is used for a short period of time, but is there any data on -- in terms of its pathway metabolism effect on other drugs, Warfarin, Heparin, diabetes insulin, et cetera?

DR. KLINE: Dr. Waters can speak

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to that.

DR. WATERS: We don't have specific information but we wouldn't anticipate that to be an issue for this drug. Remembering this is a prodrug of propofol and the initial metabolic stent that is liberating propofol is a function of alkaline phosphatase mediated action. Thereafter, the drug is metabolized, as is propofol.

I wonder if I might clarify a couple of points that were made earlier on the PK assessment. Some of the data that was presented by outside speakers suggests that there are data published that are supporting a varied profile than the clinical pharmacology profile we have presented. That is not the case. Those studies that were studied early and referenced today are from early literature studies. Early in our clinical program, we determined that there were errors in the propofol methodology, the bioanalytical methodology, resulting in

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unreliable propofol concentration levels in some early published studies. As a result, PK and PK/PD conclusions made in those studies are incorrect. Slide up, please.

When we realized there were errors in the study, we optimized those assays and validated them and conducted further clinical pharmacology studies and used them in our Phase 3 program. We have demonstrated that fospropofol has very low intra-individual variability.

Secondly, we have demonstrated dose proportionality of both fospropofol and propofol. The statements made about metabolic inversion are incorrect. The compound is fully metabolized to propofol. This is based on metabolism and clearance studies. And furthermore, our pharmacokinetic, pharmacodynamic data demonstrate that propofol is propofol and produces the same pharmacologic effect, whether it is liberated from fospropofol or liberated from Diprivan,

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or provided as Diprivan.

I would also like to bring up the next slide. We recognized those problems, we fixed those problems, we have presented this data in a number of scientific forms. The first two presentations you see there were delivered at the ASA meeting last year, where we presented the PK/PD relationship.

The second study looked at the population pharmacokinetics. And then, in a variety of other settings, AEPS, we have demonstrated the dose proportionality data and PK/PD data presented at two subsequent meetings.

One final clarification. There was this comment made about the dose ratio, if you will, of a 1.8 to one. That is based on the molecular weights of fospropofol being a heavier compound to propofol. However, if we think about that, that ratio need not reflect what the dose ratio should be. What we have is a drug that's pharmacology and

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pharmacodynamic effect is driven by plasma propofol concentration. Yes, dose but more readily by concentration. That is, when you look to our PK/PD relationship, you see that we have a similar identical, if you will, profile of propofol from fospropofol or propofol from Diprivan.

So yes, the doses differ but that is not a function of variability within the drug. It is a function of the fact that our drug requires metabolic release of the active agent. Thereafter, plasma propofol concentrations behave, and the pharmacology behaves, as one would expect.

CHAIR FARRAR: You can stay there for one second. I don't want to press the issue too much. But as a pain physician, I am very comfortable with the concept of titration. And I think, actually, your strategy of starting at a relatively lower dose, meaning one that is only effective initially in 65 percent and then titrating up

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makes huge amounts of sense. However, if you could put up slide CP-4, I just would like to ask one clarification.

This is a logarithmic scale and if I read the logarithmic scale correctly, the difference between the lower levels and the upper levels there could be considered two-fold. You have got a level that goes up to around, it looks to be around two and you have levels that seem to level off around 0.8. That seems to me to be a two-fold difference.

Again, it doesn't bother me one way or the other because I think titration is the right way to deal with this drug. But, given that it is a logarithmic scale, I am not sure that a two-fold difference in terms of patient variability is not consistent with the data.

DR. WATERS: I'm sorry. Your question has to do with demonstrating dose proportionality?

CHAIR FARRAR: You made the

comment that one of the presenter's slide, which indicated a two-fold difference in plasma level of propofol based on with the same dose, was perhaps not correct. And I would simply like to point out that your slide indicates that there could be a two-fold difference between the lowest and the highest level here on this logarithmic scale.

DR. WATERS: Yes. Maybe it would be a little more clear if we were to show you this data in a little different format. Slide up, please.

What we showed you there were the individual plasma concentration versus time profiles and here we are looking at the mean data. And I think it is a little easier to --

CHAIR FARRAR: Just to be very clear. The individual data is the important data. This data takes into account averaging based on statistical probabilities. And I am not arguing the issue too much, but simply to say that individual variability is likely to

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be, on that previous graph, is clearly in the range of two-fold difference in plasma level. Again, not an issue. It simply means that we need to titrate this drug. But I would be careful about using the statistics to obviate the individual data.

DR. WATERS: We agree entirely and that is the reason we showed the individual patient data at the beginning. I thought that might be more clear. But just going back to the variability. We have low inter-patient variability. Less than a 30 percent coefficient of variation, which is considered low in clinical pharmacology standards.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: Although I don't recommend this practice, I have done colonoscopies unsedated. I have done double procedures unsedated in people who wanted to go back to work and nobody left claw marks in the ceiling.

So, therefore, my question comes

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up. Why was the initial dose of fentanyl part of the protocol? Were you afraid your drug wasn't going to work with a single dose?

And regardless of that question, which I want to have answered, how can we, therefore, ascribe the positive effects in terms of sedation only to fospropofol, when actually, it could be the combination with fentanyl or perhaps even the fentanyl alone?

My typical sedation for a colonoscopy is only 50 of fentanyl with two or three of Versed. I mean, it really has to do with how much scope you shove in and how much air you blow in as to whether the patient has discomfort. So, you know, I have some concerns with the efficacy as well. because of the completely uncontrolled nature of the study.

And further to that, my third part of the question is, why did you, and this question I asked before but it wasn't answered, why did you not see the need to do

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a controlled study between fospropofol alone versus a combination of fentanyl and Versed, which is the current standard of care?

DR. KLINE: We used fentanyl in our studies in combination with fospropofol because the combination of an analgesic and a sedative is the common practice for moderate sedation. We look at, for example, the combination of fentanyl and midazolam that is used in colonoscopy. So, we used it because colonoscopies are painful procedures. Fentanyl is provided to manage that pain. We provided the fospropofol to decrease anxiety and awareness, as you do with sedatives.

In response to your question about the controlled trial, again, we elected to do dose-controlled studies. We demonstrated that fospropofol sedates patients. Again, about a 90 percent rate of treatment success, which was completing the procedure without requiring an alternative sedative, without requiring manual or mechanical ventilation. In

addition, we did include the comparator in the colonoscopy study as an internal reference.

DR. BUCHMAN: But you specifically stated in your presentation that it was actually not there to be a comparator.

DR. KLINE: It was there as an internal reference. You are absolutely right. They were not designed as comparative studies. We did include -- slide up, please. I would like to ask our statistician to speak specifically to the results that we see here with fospropofol versus midazolam, but we did include midazolam in our study as an informal comparator.

DR. BLUMENSTEIN: Slide up, please.

CHAIR FARRAR: Could you identify yourself, please?

DR. BLUMENSTEIN: Yes. My name is Brent Blumenstein. I am a biostatistical consultant. Actually the slide, ST-12, please. Slide up.

The issue in the design was not to compare to Midazolam as a formal comparison. Midazolam was included as a internal reference. So, the issue about whether studies 0522 and 0524 were successful with respect to the primary pre-specified comparison is really not so important. The difference specified in order to compute the trial size and so forth was really a quite easy bar. That is, it was the comparison between two and 6.5 milligrams per kilogram was not a difficult thing. We observed, as you saw, very robust P values.

The real issue here is has sufficient sedation been observed? And if that is a matter of referring to external standards. That is, what people think of as sufficient sedation as measured by a validated instrument of assessing that and also by reference to the internal sedation reference that we had in the trial.

ST-11, please. Slide up. No, ST-

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10. No, the one that was there before the -- No --

DR. BUCHMAN: The one where all the confidence intervals across zero, I think, is the one. Is that the one you are referring to?

DR. BLUMENSTEIN: No. This one. Yes, please. Slide up.

What we have here is the -- are the estimates of these percent sedation success for all of the arms of studies of 0520, 0522, and 0524. Now they are arranged in a way that is not necessarily intuitive. But if you can see, the first one, two, three, four, of these are the arms out of 0520 in increasing dose. And as you can see, the sedation success has a monotonic relationship with dose.

The next two are 0522 and 0524. The two milligrams per kilogram dose. And as you can see, we have the sedation success in the 20 percent range. The next two are 0522

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and 0524 6.5 milligram doses. And as you can see, the level of success there are both consistent and approach 90 percent.

Now, the final two are the two Midazolam arms for 0520 and 0522. And excuse me. Yes, 0520 and 0522. And as you can see, that there is a good deal of success with Midazolam and you can, from this, you can see the informal comparison of the 6.5 dose to the Midazolam arms.

DR. BUCHMAN: So when I look at this slide, I see that Midazolam and Fentanyl were actually better than Fentanyl in your low dose group. But the question that I have is there a statistical difference between - from the 0520 study with Midazolam and Fentanyl alone versus the 0524 with the 6.5 milligram per kilogram dose?

Numerically, there is a difference there perhaps between what appears to be about 82 and 87 percent or so. Is that statistically different? Because if it is

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not, what that tells me is that your drug didn't add anything to the fentanyl and midazolam. And that is even given the fact that the midazolam is an extremely low dose, a dose that is lower than what we would typically use.

CHAIR FARRAR: I'd actually like to interrupt here, if I could, because, in fact the comparison between two active drugs is not, there is not a P value comparison. It is a comparison of equivalents and the issue is the difference that you are able to detect.

The presentation here is showing competence intervals that show that they overlap. The interpretation is that the midazolam and the 6.5 were -- both created the same range of results. In addition, using a dose response is a standard format for testing drugs in the pain world where it is unethical to not give -- to give a placebo of any kind.

So, I think actually the design is reasonable. There is no statistical test for

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what you are asking.

DR. KLINE: And if we may, Dr. Cohen could give his clinical perspective on the results as well.

DR. COHEN: Thank you, Dr. Kline. I would like to put some of this into clinical perspective. The first issue I would like to talk about is Dr. Buchman's discussion of unsedated endoscopy. And the fact is, we all see a very small percentage of patients that come into the clinics that are suitable for unsedated endoscopy. This has been looked at in a systematic fashion. And if you look at the published literature on sedated endoscopy, approximately five to seven percent of all patients are capable of undergoing an unsedated endoscopy. And no one disputes that. We are talking about sedation for the masses, for the rest of us.

The second issue relates to the use of fentanyl as an agent in addition to a sedative. I think it is important to first

bear in mind that this drug was being developed for moderate sedation. We all know what that means is that patients are awake and they are responsive. The fact of the matter is that the majority of patients having our procedures do not want to be uncomfortable. And if they are going to be awake and not analgesic, they are going to be uncomfortable. So, we provide them with a sedative for anxiolysis and amnesia. We provide them with an analgesic that helps to abate their pain and the combination tends to produce what we refer to as procedural or moderate sedation. And it keeps them awake, keeps them in a safe level of sedation but allows us to do our procedures in patients who can walk out. Either they are amnestic and they say gee that was great and when do we start or they are at least satisfied with the experience. And that is the reason that we use a combination of an analgesic and an amnestic or sedative drug.

The other comment I would like to

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make, which really takes us a little bit away from the issue of the combinations of drugs relates to this issue of sedation. There has been a lot of discussion this afternoon about the issue of education of providers, of proceduralists.

You made some comments. There was one of the public comment speakers talked about, cited a paper that I happened to be the senior author on that addressed the issue of education of proceduralist of gastroenterologists. And the paper was written in 2006, although it was published the following year. And we made then comment in the paper that there was some lack of educational process surrounding issues related to sedation. And I think at the time that that statement was made, it was absolutely true. And I think that that statement served a very useful purpose.

Since that statement was published, all three of the major GI

societies, the AGA, the ASGE, and the ACG have all developed training programs around the issue of sedation so that today there are many offerings related to education in the field of sedation that were not available.

In addition to the new training programs and conferences that are available, a tri-society task force has been formed, which I chair, called the tri-society sedation task force, which one of the strategic objectives is education in the field of endoscopic sedation. So that there are many initiatives that have been developed over the past several years to educate our societies in the field of sedation.

If I can just transfer and ask Dr. Joel Brill to sort of expand a little bit on the subject of education.

CHAIR FARRAR: Actually, if you don't mind, I would like Dr. Buchman to be able to continue with his question.

DR. COHEN: I'm sorry.

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DR. BUCHMAN: It just, essentially, I mean, my question again, which wasn't answered was why the study was designed the way it was. Why was the fentanyl dose given as part of the protocol to everybody? Why not just your drug? You are comparing it to midazolam with fentanyl. There is some comparisons, perhaps not some comparisons, perhaps some post-hoc analysis but it gets down to the crux of the issue.

And, obviously yes, we give analgetics. I mean, I only give an example in terms of the unsedated procedures. Obviously, it is not something I would want to have done on me but I only use that as an example because it doesn't really take all that much sedation for the average person. We also have people who require 400 of fentanyl and 30 of midazolam and they are still looking at us.

So, but my question goes back to the average individual and why you felt the need in the protocol design to administer

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fentanyl prior to your medication, which of course, again, corrupts the efficacy data evaluation, as well as the safety data evaluation.

DR. KLINE: Again, we administered fentanyl, as Dr. Cohen referred to, we are targeting moderate sedation. And to the extent that patients are awake and aware during moderate sedation, the use of an analgesic is appropriate and warranted in that case. And so we feel that is, we know that is the way moderate sedation is typically practiced and we wanted to use the drug in a situation that mimicked real life practice.

DR. BUCHMAN: Well then, that doesn't mimic ours. I mean, we do 100, 120 procedures a day and three or four times a year do we use propofol. And when propofol is administered, it is administered as a sole medication and, of course, by an anesthesiologist.

DR. KLINE: And of course when it

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is administered as a sole agent by an anesthesiologist, it is in the case of MAC sedation, where the patient is much more deeply sedated. They are not awake and aware. And that is the main difference.

CHAIR FARRAR: So, I think we can all agree that it wasn't done, whether it should be done or not, as a way of looking at a way of providing moderate sedation. I will leave it up for another time and that certainly can be a recommendation of yours, if you feel strongly about that.

Next is Dr. Epstein.

DR. EPSTEIN: Yes, thank you, Mr. Chairman.

Dr. Kline, can you or your colleagues expand a little bit on the -- after the procedure on what occurred during recovery? How quickly did these patients recover, on average? How did it compare to just using the current midazolam and fentanyl?

DR. KLINE: Right. The patients

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in our study, the recovery parameters that we looked at were time to alertness, which was measured as the time to three consecutive MOAA/S scores of five occurring after the scope was removed. And we also looked at time to reach an Aldrete score of nine or greater.

And what we saw in the colonoscopy study was that the time to reach that alertness, the time to a MOAA/S score of five was five minutes. In the bronchoscopy study, that was five and a half minutes. Those are median times I am providing. And the time to an Aldrete score of nine or greater occurred two or three minutes later in the studies. So a time of seven to eight minutes after the scope was removed.

As far as how that compares to typical practice and recovery times, I would like to ask Dr. Cohen to give his experience on the agents he typically sees.

DR. COHEN: Thank you. If you look at average recovery times, it obviously

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depends on what agents that we are talking about. If we are using benzo/opioid combinations, recovery times vary from 30 to 60 minutes. If we are talking about using propofol-based sedation, recovery times, again using the standardized sedation scales, such as the Aldrete, recovery times usually range from 15 to 30 minutes.

CHAIR FARRAR: We don't have anybody else on our list. Are there any other questions that people would like to ask before we move on to consideration of the questions?

Okay, Dr. Roca or -- do you have any preliminary information for us before we get to the questions or should we just proceed with that?

DR. ROCA: Go crazy.

CHAIR FARRAR: All right. The first question is not a voting question. We are, however, interested in everyone's opinion and would like to give everybody an opportunity to provide some advice and an

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answer to the question. What I would ask is that if you have information or an opinion that is very similar to something that has already been stated, that you concur with those opinions and that we not repeat ourselves too many times as we go around the table and -- but please do be complete. The whole purpose of this meeting is to garner our opinions to help to advise the FDA in terms of its process of moving forward.

So the first question is, "Do the clinical trials data support the adequacy of using purposeful responsiveness as a clinical sign to make appropriate and safe decisions regarding supplemental dosing of fospropofol disodium? If not, which other clinical responses should be incorporated in this assessment?"

And if we can keep our answers reasonably specific, that would be a great help. Ms. Aronson.

MS. ARONSON: Not being a

clinician, I would respond as I am not sure. I don't know but the questions that do come up for me are the incidence of the 25 percent deep sedation that the FDA pointed out in the bronchoscopy procedures, in small number, granted. But also the variable processing in the liver.

I also am not clear. I heard reference to some training but I don't hear the training that might be on the ground. I hear the benefit of 100,000 procedures and more and how, you know, the watching regarding multiple dosing might be possible. But for non-anesthesiologists, I have a question.

CHAIR FARRAR: Dr. McLeskey, you actually can participate in this particular question, if you have anything to add.

DR. McLESKEY: No comment for the moment, thank you.

DR. KLINE: Can I correct just one statement? The incidence of deep sedation in the bronchoscopy study was not 25 percent. We

saw 16 percent in the bronchoscopy study. We saw four percent in the colonoscopy study.

CHAIR FARRAR: Thank you.

Ms. Krivacic.

MS. KRIVACIC: Again, I am not a clinician either but one comment I would make regarding this issue is, you know, the purposeful responsiveness is a clinical sign. When you are dealing with maybe perhaps people with addictive behaviors that may say, yes, keep giving me this, that may kind of come into question. I just say this from a personal experience of somebody that I took to have a colonoscopy. And following the colonoscopy, this individual kept asking for more of the sedative product. So, that is kind of my concern. Whether it is a valid one or not, I don't know.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: Well, I have problems with the use of any one sign. I mean, the thumbs up is, you know, a good sign

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but nothing should be used in isolation. Certainly, we have seen that that does not absolutely guarantee the absence of hypoxia and I think that or any other purposeful responsiveness clinical sign can't be used in isolation but needs to be in conjunction with the vital signs, the EKG, the pulse oximetry, ideally, capnography, I would agree with Dr. Kirsch, as well as purposeful responsiveness assessments.

CHAIR FARRAR: Dr. Buchman?

DR. BUCHMAN: I would completely concur with all of those. In addition to hypercapnia, we have to keep in mind that with conventional sedation, you can get in the same trouble that you can get into with this medication as well. It just potentially might be a little bit easier with this medication. So the question is just a clinical sign. And in my opinion, you have to have a variety of clinical signs.

CHAIR FARRAR: Dr. Prough.

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DR. PROUGH: Yes, I think the important thing is that purposeful responsiveness is a limit and not an indication for more drug. It is used in conjunction with other findings to determine whether more might be tolerated, if it is necessary but it is not an indication for more drug.

CHAIR FARRAR: Just to be clear, in that setting, you think that the measures that the sponsor has used are adequate?

DR. BUCHMAN: My impression was that it was used an assessment of the depth of sedation and as a limit, not as an indication for further treatment. So yes, I think that was appropriate.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I remain unconvinced that the thumbs up sign has much of any value and strongly urge the sponsor to consider encouraging users of this product to use end tidal CO2 monitoring.

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I would also encourage the educational process that has been talked about. It would be helpful if the societies who strongly support this talk to the RRC and train those who are coming up through the system in appropriate sedation and airway management.

CHAIR FARRAR: Dr. Epstein.

DR. EPSTEIN: I concur with Dr. Prough.

CHAIR FARRAR: Dr. Chang.

DR. CHANG: Yes, the first question, I would say no. But I think it is probably applicable to other sedatives. I don't think it is necessarily just isolated to fospropofol.

My question would be, has there ever been any literature looking at all potentially a priori factors that can predict side effects or hypotension or hypoxia with sedatives. You know, looking at not just the oxygen saturation data, but the systemic

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disease age gender, how much dose was given prior to that supplemental dose. And if there was any review or literature on that, that would certainly be helpful because I just don't think that purposeful responsiveness, the way it was defined here, is adequate. But I don't think it is only with this drug.

CHAIR FARRAR: Dr. Sang.

DR. SANG: I completely agree with that. My answer is no. It should be a composite score. And what that -- what makes up that composite score isn't clear. Vital signs, capnometry, saturation. But then what else? I mean, there are some sedation studies that have used BIS. There are some sedation studies that have used BIS and the arm. And then there are softer more subjective signs and it is not clear at all to me. And the literature hasn't established this, to my knowledge, with other sedatives.

I think in terms of training, independent of what ends up happening with

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this particular drug, I think that operating rooms would welcome GI fellows to come and spend three months to learn some basics about airway management.

CHAIR FARRAR: My opinion is that the single measure is difficult. I agree that its use in limiting the addition of the decision to give additional drug makes it somewhat more useful but that a combined score is clearly going to be advantageous.

And I completely agree that looking at the CO2 levels is paramount and would offer only that in fact opioids are remarkably good at reducing the CO2 responsiveness and in what I do remains one of the biggest problems both in post-op and chronic pain management.

So, I thank you for that. If we move to question number two. Before considering the question, I would ask Teresa to give us repeat instructions for some of us and new instructions for others, in terms of

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the voting process.

DR. WATKINS: Hopefully it will go a little better than it did yesterday.

We do have an electronic voting system for the members of the panel. Before the first vote, you will first need to press the button on the left-hand side that says attend.

CHAIR FARRAR: Please don't do it now.

DR. WATKINS: Right. And then once everyone has done that and I get the signal, then I will ask you to go ahead and place your vote. Your choices are yes, no, or abstain. You will have 30 seconds or so to do that. And then once the vote is locked in, you cannot change your vote beyond that period of time.

CHAIR FARRAR: Okay. So, the question is, "Adverse events, particularly respiratory adverse events, were observed at a greater frequency among geriatric patients,

patients categorized as ASA III or IV, and patients weighing less than 60 kilograms." So the yes/no vote. And we will vote first and then provide our comments second.

The yes/no vote is the following. "Are additional data needed for these patient populations in order to provide appropriate dosing guidelines for these subpopulations? " And then the discussion will be, "If additional data are needed, what studies do you recommend?"

So the question is, do they need additional data? A yes vote means yes for additional. A no vote means no additional data is necessary.

If everybody can push their attend button please. Okay.

DR. WATKINS: Okay, everyone please make your selection. Oh, hold on. Okay, now please make your selection. Has everyone placed their vote? Yes, it will continue to blink once you have made your

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selection.

And here are the results.

CHAIR FARRAR: We would now like to go around the room and -- to get people -- so if you voted yes or no, what additional data are needed and what studies do you recommend?

And we will start at the other end. Dr. Sang.

DR. WATKINS: The results are yes - are nine votes for yes, one vote for no, and no abstentions. And the names are listed as to how each person voted on the screen.

DR. SANG: Yes, I answered yes. I think we have already discussed the need or at least my rationale for studies that look at both efficacy and safety in subpopulations. I think in addition to the ones listed in question two, there are several others. I think end stage renal disease. Actually, more commonly, let's just add those who are obese, those who are on a variety of concomitant

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medications, those with different levels of renal dysfunction and liver dysfunction, among others.

CHAIR FARRAR: Wrong button. Excuse me. Dr. Chang.

DR. CHANG: Yes, I would just state probably some dose ranging. It probably doesn't need to be a wide range and particularly in the young, I mean, not the young, the low weight or lower weight individuals in looking at efficacy and side effects.

DR. EPSTEIN: While I don't disagree with asking for more data, the fact is that we use midazolam and fentanyl currently in these special populations and also, we have an enormous experience with propofol. I have been using propofol personally for quite a long time and we have a lot of data and information already on those special populations.

And what it really comes down to

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is the skill, training, and expertise of the treating physician in identifying those patients who could be at risk and having them treat MAC, and there are so many different variables there, I think it would be extremely difficult to tease out every possible risk subgroup.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I agree with this additional subgroup information, particularly related to patients size and gender, that I have pointed out before.

And of course, I can't not talk about end tidal CO2. I would like to know at the therapeutic dose, whether the PCO2s or the end tidal CO2s are in the eighties or nineties or if they are at some more reasonable value.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: I think it would be useful to see dose ranging studies in patients less than 60 kilograms and patients who are relatively high SA classifications because of

cardiovascular disease, hepatic disease or renal disease.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: In particular, I would like to see an inpatient study, which would get at patients who have more concomitant co-illnesses.

Specifically, I want to point out in the slide that the sponsor showed on the limited number of patients who had end stage renal disease and hepatic disease, the vast vast majority of those patients, approaching 80 percent, had some AE that was possibly attributed to the medication. So, clearly, those may be aberrancies but they need more data to show that that is an aberrancy.

I would also, from a GI standpoint, I would add ERCPs. I am not sure about using this for colonoscopy. And quite frankly, I don't think it is necessary. But I think a procedure like an ERCP that is longer, patient is in an uncomfortable

position, these kinds of medications are probably where the standard of care should go. But, unfortunately, that was actually not the group studied.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: Yes. Well, even in the relatively healthy colonoscopy patients, at least four percent achieved sedation scores of zero to one. The other 96 percent were apparently at the desired level. But I am quite concerned about that four percent and I think it is likely that that percentage would be considerably higher if patients had been studied with comorbidities.

Certainly we have some data regarding pulmonary comorbidity in one of their studies but there is a real paucity of data in patients with any other comorbidities, as has been discussed by the other panelist, cardiovascular disease, renal insufficiency, marked obesity, or even again, the elderly population, those over the age of 70 or 75.

So, I think much more data is needed to know what the true incidence of low sedation scores, and for that matter, hypoxia would be.

CHAIR FARRAR: Ms. Krivacic.

MS. KRIVACIC: I think also doing a study in non-opioid tolerant patients as well with fospropofol versus versed alone.

CHAIR FARRAR: Ms. Aronson.

MS. ARONSON: I have nothing more to add.

CHAIR FARRAR: So, I agree with what has been said. I would summarize by saying that the reasons were, primarily, a need for additional data in a variety of comorbid groups, where there is some sense that the use of a propofol predrug in the setting of a non or less monitored environment might be at increased risk.

I agree with Dr. Epstein that there is a huge amount of data about the use of propofol. I think the issues that are

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being expressed by other committee members are concern about the use of a propofol-like agent in a setting where they are not so carefully monitored. And where certainly a hypercapnia has not been carefully studied.

There is also a concern about the less than 60 pound -- sorry less than 60 kilogram patient population. And I think that what I am hearing is that that needs to be addressed in terms of dose finding. I would also like to add to that my own perspective that this clearly will be used in children, at some point, and I would hope that some studies in children may be possible to understand, especially given their difference in metabolic rates.

And then since propofol is already used for long-term sedation in certain circumstances, although I understand it is falling out of favor, somewhat, it would be useful to have at least some experience with its use over 12 to 24 hours to understood

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whether there are any additional problems that might come up from that.

Did I summarize that? Anybody?

Okay. Question number three. Just to note, first, that there is a correction on the screen versus -- well, I will get to that in a minute. The question number three says, "Do the data from clinical trial indicate that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia? Please vote 'yes' or 'no.' If you vote 'no,'" and that is the correction over what is on your slide there, "what types of studies would best provide this data?"

Are we set? Okay. If I could ask everybody to push your attend button, please.

DR. KIRSCH: Can I ask for clarification?

CHAIR FARRAR: Oh, I'm sorry. Go ahead.

DR. KIRSCH: So, for

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clarification, I am having a little bit of trouble with the wording, "can be safely managed by health care providers without training in general anesthesia." Are we to assume that with appropriate monitoring or with the, as currently suggested by the sponsor, you can guess it without monitoring of end tidal CO2.

DR. ROSEBRAUGH: I would say as suggested by the sponsor.

DR. BUCHMAN: And Just as a further question on that, then. Is it can be or will be? Do we want to stick with that word can? Because anything is possible or should be.

DR. ROSEBRAUGH: I feel like I am back in the Bill Clinton era on what is is mean. But I would just rather try to intuitively say, look, they want to have this approved such that you don't need an anesthesia guy to give it, which is different than propofol's labeling, sort of. And it is

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a little different thing because propofol is MAC and stuff. So, we just want to know, do you guys agree with that, based on what you heard today.

DR. KIRSCH: But if you have the opinion that it could be provided by a non-anesthesia provider with appropriate monitoring, one should vote no currently because that is the -- what the current recommendation from the sponsor.

CHAIR FARRAR: Yes. And I would like to recommend that you take that approach and then in the presentation of the types of studies, indicate also what, you know, clarify what it is that you think would be necessary in order to achieve that. Did that make sense?

DR. ROSEBRAUGH: Absolutely.

CHAIR FARRAR: Dr. Prough?

DR. PROUGH: Another quibble with the wording. The "without training in general anesthesia" is different than non-anesthesia

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providers. And it is quite possible for somebody who has not done a residency in anesthesia or been trained as a nurse anesthetist to have sufficient training that they can manage an airway. So, I am a little uncomfortable with the wording.

DR. ROSEBRAUGH: How would you rather have it worded?

DR. PROUGH: I guess, I mean, it would probably be more straight forward if it said non-anesthesia health care providers. I mean, I don't know if that is perfect either.

DR. ROSEBRAUGH: Yes.

DR. PROUGH: But training is a different issue, I think.

DR. ROSEBRAUGH: Okay, let me just tell you why we are saying training in general anesthesia. That is what the propofol label says and we would like to stick with that, if we could. And I understand your discomfort but whether you vote yes or no then you can clarify your vote when we get to the dialogue

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session.

CHAIR FARRAR: Are we ready? Yes? Okay. If you could press your attend button.

DR. WATKINS: No.

CHAIR FARRAR: Okay. Hold on a second. There is no attend button. Simply indicate your answer yes or no.

DR. WATKINS: Has everybody voted? Yes. The result is two yes, eight no, and zero abstain.

CHAIR FARRAR: And then you want to show the next one?

DR. WATKINS: And this is how each individual voted.

CHAIR FARRAR: Okay. With regards to the no votes, we need a comment about the rationale for that. Ms. Aronson.

MS. ARONSON: I would like more information on what the training would be for the non-anesthesiology community. Just, more extensive information on what that training would be.

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CHAIR FARRAR: Ms. Krivacic.

MS. KRIVACIC: I voted no because I think if everything is done as was done in the clinical trial with rigorous monitoring and oversight and overall training, then this, you know, would be something to look into. And also, we need to look at some of those sub-areas a little bit more.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: Well, I am not completely convinced that there is an unmet medical need here. In other words, a benefit that justifies the risk of even a few deaths, if the drug is initially approved with labeling that differs from the labeling for propofol. I mean, there was and I think still is a reason for that labeling for propofol and fospropofol is the prodrug for propofol but it is still propofol.

I think we just need more experience in carefully monitored settings before we can change that labeling, even

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though this is a slightly different drug. I am still very concerned about dose stacking with respect to practitioner patients' issues and with respect to that need to wait four minutes between doses. And then when you add to that at least some degree of interpatient variability, I just don't think that it would be safe, at this point in time.

And perhaps even more importantly, unlike all of the currently available agents that are used for these thousands of procedures that are done every year, there is still no reversal agent for propofol or fospropofol. So, I think at this point in time, you still must have someone skilled in airway management for that four percent who is going to go into a much deeper plane.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: I don't think this is a good example of see one, do one, teach one. Not only do we need to see what the training program would entail but also the

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certification program and whether it just, perhaps even an added rigorousness to what many or most current hospitals do.

The other issue here is that I feel strongly that there should be a RiskMAP that is required and that the training and certification is actually just an integral part of that. And the RiskMAP would cover the entire spectrum of unanticipated uses, indications, appropriate monitoring, and also the issues that have been brought up with -- I think it is going to be more difficult to divert this medication but, because it won't be carried supposedly in outpatient pharmacies, for example, but that needs to be a written protocol on how to avoid that, as been the case with other controlled substances.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: Well, I'm not sure which question I answered. I was supposed to say that I think the -- that with appropriate

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training, non-anesthesia providers can safely give the drug. But the issue of training, obviously, is critical.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I have really nothing to add.

CHAIR FARRAR: Dr. Epstein.

DR. EPSTEIN: Yes, I agree with Dr. Prough regarding the training. In addition, and I think it can be given safely, I do question whether or not capnography would be a helpful adjunct in these patients.

CHAIR FARRAR: Question as in thinking yes or no? I'm sorry.

DR. EPSTEIN: Whether or not it could be added. But I believe the drug can be given safely.

CHAIR FARRAR: Okay. Dr. Chang.

DR. CHANG: I actually think there is an unmet need in endoscopic sedation and feel that this drug is very promising. And I think of all the people that spoke that are

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experienced endoscopists, I am sure they can give this safely without any problem.

My issue is even though Dr. Cohen said a lot of strides are being made with endoscopic sedation training, that is more of the younger trainees. And I do think that, if you look, if you survey in all different conditions about who follows guidelines in the community, I think you would find that a minority of practitioners follow guidelines.

So my main issue is about the limitations of this drug, knowing your limits. And so speaking from a maximized patient safety and minimized medical malpractice viewpoint, I just feel like I am just not quite sure if I look at the limits of how the duration, the dose, the patient population. That is the information I feel that I would need.

And my second point is as an endoscopist, if I was given the choice of using fospropofol and midazolam, I still would

ask myself, well what is the difference, how do they compare? What is the benefits and what is the risk? And I agree with Dr. Buchman. I really think it would be nice to do a comparative study and look at patient comfort, the dose of opioids. Maybe you need less with fospropofol. The recovery time, the side effects, the duration of the endoscopy. I think there is information that would really be helpful as an endoscopist who is going to choose the sedation drug.

CHAIR FARRAR: Dr. Sang.

DR. SANG: Yes, I voted no. I really don't have much more to add except that the context is different here from say over ten years ago when fosphenytoin was being developed. That was really developed for use in an uncontrolled setting, where it was critically important to get to the patient fast and get a safer drug onboard fast. We are talking about a controlled setting here.

And so, that is really all I have

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to add. CHAIR FARRAR: To try and summarize the comments, I think there was a great deal of concern about the level of training in specific, given the depth of the, or the intensity of the monitoring that goes on in a clinical trial, it is very hard to interpret how that will translate into the general population. Secondly, clearly, people in residencies and training programs now will get training on new medications. But there is concern about how that training will be extended to the general population of folks who would use this, not just for endoscopy but for other procedures that would be -- require some sort of sedation.

And Dr. Nussmeier continues to bring up the point, which seems valid, that there was a reason for limiting the use of propofol and that we would need to specifically address some of those reasons.

The other thing that I would add is simply that you have carefully abided by

the ASA guidelines. In listening to the ASA guidelines and not knowing anything more about them than what I hear today, I would suggest that in the world we are moving into, they would probably need to be revised. And I am sorry. I don't mean to be telling anybody what to do, necessarily but certainly the -- from my perspective, the lack of measurement, the ubiquitousness of measuring saturation, 02 saturation that happened with relatively inexpensive devices, suggests to me that we could do the same thing with hypercapnia and certainly in what I do in pain management, that is becoming a very big issue and certainly would need to be, from my perspective, part of the need before this could be used safely in an environment where there is not access to people who can manage an airway adequately.

And the last thing is simply that I think the exclusion criteria for the use, although it may be clear to some people what

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a person at higher risk, what their airway looks like, I think there needs to be some standardization of how that approach is taken. And certainly I would not judge myself capable of understanding whether somebody's airway was more or less likely to get them into trouble. And I would be concerned that certainly the majority of people in practice may not know exactly how to approach that.

So, that would be my additional comments. Any other, anything I left out from -- no?

Okay, moving on to question number four. So the new question is, "Do you recommend approval of fospropofol for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures? This is a yes/no vote. If yes, are there additional studies you would recommend to be post-approval? If no, what additional data would you recommend to be needed to gain approval?"

Is the question clear? So, just to be clear, this is not a question about use in offices and elsewhere. The question is, is the drug -- should it be approved for use in any medical circumstance. Are folks clear about the question? Okay.

DR. WATKINS: Are you ready to vote?

DR. KIRSCH: Again, I'm sorry. For clarification, as written by any type of provider, not isolated to providers who are specially trained in airway management like anesthesia providers.

DR. ROSEBRAUGH: Well again, one of the things we were trying to do a little bit with this question was the fact that they are -- have said that they didn't want it, that it didn't need to be given in people with training in general anesthesia or advanced training or whatever. That doesn't necessarily make it a package deal.

I mean, we could always say no,

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you have to, the way we write it, we could say you have to have training in general anesthesia or you have to have advanced training in airway management or something. And so we were trying to get to, well based on what they gave you on just the drug, does the drug look okay? That was where we were going.

And we also were trying to tie together with question two because we got a lot of recommendations on question two on other things that they needed to do but we were trying to find out do you want that pre or post approval. And this gives you an opportunity to say, well, I think the drug is okay and you can label it that somebody that is ASA III or IV shouldn't get it and they can do that stuff post-approval. Or now is your opportunity to say, you know, I think they really ought to have all that stuff sorted out before it goes on the market.

CHAIR FARRAR: Did that answer your question? The question is, given the

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right limitation -- if this drug were to be approved with the same provisions that are there for propofol currently, would this be an acceptable drug? Because the FDA can work with the sponsor to put as many limitations as they feel are appropriate, based on the recommendations of this committee and other scientific information.

Okay?

DR. KIRSCH: Yes that's --

DR. WATKINS: Are you ready to vote? Okay, go ahead and vote.

(Pause.)

DR. WATKINS: Has everybody finished?

DR. BUCHMAN: I want to change mine.

DR. WATKINS: Go ahead now. Do it before he -- everyone is finished? Okay.

DR. BUCHMAN: I'm from Chicago though, I can vote more than once.

CHAIR FARRAR: Okay, just hold on

a second, please. Fingers off the buttons. Thank you.

DR. WATKINS: We will reset the vote, for the benefit of Dr. Buchman, and do this all over again.

(Pause.)

DR. WATKINS: Everyone please revote. Has everyone cast a vote? Okay.

The result is six yes, three no, and one abstain. And the results are displayed on the screen for the individual votes.

CHAIR FARRAR: So let's start at the other end again, Dr. Sang.

DR. SANG: Yes, may answer was yes for use by anesthesiologists -- for use by those trained in general anesthesia. And by that I mean anesthesiologists and nurse anesthetists. You know, there is a steep learning curve still. There will be. This may be effectively giving propofol but anesthesiologists by now are fairly skilled in

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administering propofol using a pump or giving intermittent boluses and so on. But when you introduce metabolism, there will be a steep learning curve about the use of it. I think that that should take place in the context of anesthesia care.

We need many more PK/PD studies and PK/PD modeling studies. Any intraindividual variability is the opening for potential risk. So, I think it is going to be really quite important to establish that in a controlled setting.

And I am also concerned about the, I mean, we know that there is a steep concentration response relationship of propofol. And once again, this is a drug that, to some extent, we have quite a bit of experience with but we have to really respect the novelty of using a prodrug.

Moreover, there is no reversal agent. So, for that reason, I certainly think that it should be first used under anesthesia

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care.

CHAIR FARRAR: Dr. Chang.

DR. CHANG: Yes, I think this is a potentially good drug and I voted yes. But I think that there should be restrictions on who uses it, to train personnel, and that additional studies are needed, which I outlined in the answer to question three, before widespread use.

CHAIR FARRAR: Dr. Epstein.

DR. EPSTEIN: Yes, I generally agree with the other panelists. Midazolam and fentanyl were never developed for use in endoscopy primarily and they do not provide very good sedation or analgesia in a large percentage of our patients. We have not had a new agent in many many years. And it is never going to be perfectly safe but, with appropriate training, education, and the right skill set, the use of these type of new agents should be able to be used safely in the proper environment. And we are talking about those

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people who have a lot of experience in performing conscious sedation.

I would like to point out that gastroenterologists and pulmonologists probably deal with as much or more conscious sedation and evaluation of patients than do anesthesiologists. I do approximately 18 to 21 cases a day, day in and day out, for the last 20 some years. We do get ongoing training and education and we certainly should work closely with our anesthesia colleagues who are experts in airway management and design a simple but effective program to make certain that people can manage the airway appropriately.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I completely agree with Dr. Epstein. I think it has the potential of being really an important drug in medicine and am thankful that the company came up with it and look forward to being able to use it myself and working with my GI

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colleagues to get a safe protocol in place.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: I would like to see data in high-risk populations, particularly, the smaller, older patients, and patients with chronic comorbid conditions. And I also am concerned that if the -- that release of the agent for use by anesthesiologists would likely result in very little use because it would have no obvious advantages for trained anesthesia providers over the parent drug.

CHAIR FARRAR: Dr. Buchman.

DR. BUCHMAN: Well, being newer and more expensive isn't always equal to better. But that being said, I don't see any reason that the drug can't simply be a competitor to propofol with its current use.

I abstained, however, because that is not what the question asked. The question was a very all-inclusive question. And no, frankly, I don't believe, given all the discussion and recommendations made today that

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this drug is ready for primetime use by anyone for anything. But that is a separate question from whether it could be approved for any reason. And I think, clearly, if the question had been asked should this drug be approved, for example, under the same circumstances as propofol, it is basically the same thing. It is really no different from giving azithoprine or 6-MP, for example. So, I would certainly be in favor of that. But for the broader indication, absolutely not.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: Yes. I think it is likely that this drug will have a role in sedation for procedures. You know, it is going to be less painful to inject. It is going to deliver less lipid to the patient. It possibly may be less prone to having the patient develop an infection. Certainly, as my colleagues have stated, we need some data on certain populations, the very elderly, the very small. And you know, were I to use it

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tomorrow in somebody who is markedly obese, I would have no idea whether to use the lean body weight, the actual body weight or try to split the difference. And I'd also -- I think it might have a great role in pediatric patients. It needs to be studied.

So I think it could be used in the healthier patients sooner rather than later. And I think these other studies can be ongoing.

CHAIR FARRAR: Ms. Krivacic.

MS. KRIVACIC: I voted no for really the same reason Dr. Buchman voted but I know he voted for abstaining and it was kind of a, I guess, an understanding call.

The other reason I voted no, too, is I do think a lot of these other studies need to be done that we discussed today, especially in the elderly population and people under 60 kg weight -- kilogram weight.

And the area of post-marketing kind of concerns me because a lot of these,

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not to say that MGI won't do these, but a lot of post-marketing commitments aren't being done. And so, that is why I voted no.

CHAIR FARRAR: Ms. Aronson.

MS. ARONSON: I voted no because of the number of times I heard raised today the need for additional studies, comparative studies, and population studies.

CHAIR FARRAR: I voted yes, primarily because I think that we have huge amounts of data on the propofol and this is not really substantially different.

I also think, therefore, that the risk of using it in a less monitored situation has huge potential downsides and that that whole issue needs to be much better understood and studied and could be very effectively studied, I think, using for instance, a CO2 monitor on patients to understand how much hypoventilation really occurs, not just with this drug but also with the current combination. I don't think we understand that

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and certainly could do that.

The other thing is that I think there needs to be in place a very clear plan for studying what actually happens when this drug is used, with very clear consequences, based on the outcomes of those studies. And I am hopeful that the FDA either has or will shortly have the authority to do that.

In summarizing what other folks have said, the concerns were that it is a prodrug, that it is not really very different than propofol. There was concerns about the lack of a reversal agent and the implications for that in its use outside of an environment where airway control could be adequately taken care of. And that there was a division, I guess, about whether there needs to be additional studies in elderly populations and other populations that are not carefully studied so far in what the sponsor has produced.

Anything that I have missed? So I

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would ask, our FDA colleagues whether there were any other questions or concerns they would like from the Committee?

DR. ROSEBRAUGH: I don't think we have any other questions or concerns. What I would like to do, though, is express my gratitude to you folks for today. It has been very enlightening.

And I would particularly like to express my deep gratitude to those that had the cast iron endurance to do the last three days. You have no idea how helpful they have been to us. Thank you very much.

CHAIR FARRAR: I would like to add my thanks to the Committee for putting up with sometimes tyrannical chairing but I want to provide you with a gift of almost an hour and 15 minutes. Thank you very much.

DR. WATKINS: Have a safe trip home, everyone.

(Whereupon, at 3:10 p.m., the meeting was adjourned.)

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