UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH
(CDER)

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MEETING OF ANESTHETIC AND LIFE SUPPORT DRUGS
ADVISORY COMMITTEE

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OPEN SESSION

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WEDNESDAY,

MAY 7, 2008

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The meeting came to order at 8:00 a.m. in the Grand Ballroom at the Holiday Inn, Gaithersburg, 2 Montgomery Village Avenue,

Gaithersburg, Maryland, John T. Farrar, M.D., Chair, presiding.

PRESENT:

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY

COMMITTEE MEMBERS (Voting):

JOHN T. FARRAR, M.D., Chair

TERESA WATKINS, Pharm.D., Acting Designated Federal Officer

JEFFREY R. KIRSCH, M.D.

NANCY A. NUSSMEIER, M.D.

DONALD S. PROUGH, M.D.

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE TEMPORARY VOTING MEMBERS PRESENT:

DIANE ARONSON, B.S.,
Acting Consumer Representative

ALAN L. BUCHMAN, M.D.

LIN CHANG, M.D.

MICHAEL EPSTEIN, M.D., FACG, AGAF

SUSAN KRIVACIC, Patient Representative

CHRISTINE SANG, M.D., Ph.D.

SULPICIO de GUZMAN SORIANO, III, M.D.

ACTING INDUSTRY REPRESENTATIVE (Non-Voting):

CHARLES McLESKEY, M.D.

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH

PARTICIPANTS (Non-Voting):

CURTIS ROSEBRAUGH, M.D., Acting Director,
Office of Drug Evaluation II

RIGOBERTO ROCA, M.D., Deputy Director,
Division of Anesthesia, Analgesia, and
Rheumatology Products

LEX SCHULTHEIS, M.D., Ph.D., Medical Officer,
Division of Anesthesia, Analgesia, and

Rheumatology Products

SRIKANTH NALLANI, Ph.D., Clinical Pharmacology
Reviewer, Division of Anesthesia, Analgesia,
and Rheumatology Products

T A B L E O F C O N T E N T S

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T A B L E O F C O N T E N T S (Con't.)

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

(8:00 a.m.)

CHAIR FARRAR: I'd like to call this meeting to order for the Anesthetic and Life Support Drugs Advisory Committee.

For the topics this morning, such as those being discussed here at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for the discussion of these issues and that the individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting. Thank you.

I would like to start with introduction of the panel. Ms. Aronson?

MS. ARONSON: Diane Aronson, consumer representative.

MS. KRIVACIC: Susan Krivacic,

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patient representative, Austin, Texas.

DR. NUSSMEIER: Nancy Nussmeier, Chair of Anesthesiology at SUNY Upstate in Syracuse, New York.

DR. BUCHMAN: Alan Buchman, Professor of Medicine and Surgery, Northwestern University in Chicago.

DR. PROUGH: Don Prough, Chair of Anesthesiology at the University of Texas Medical Branch in Galveston.

DR. KIRSCH: Jeff Kirsch, Chair of the Department of Anesthesiology at Oregon Health Science University.

CHAIR FARRAR: John Farrar, neurologist and epidemiologist, University of Pennsylvania, interested in pain and symptom management.

DR. WATKINS: Teresa Watkins, the Acting Designated Federal Official for this Committee.

DR. EPSTEIN: Michael Epstein, gastroenterologist, Annapolis, Maryland.

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DR. CHANG: Lin Chang, gastroenterologist, UCLA.

DR. SORIANO: Sul Soriano, neuroanesthesiologist, Children's Hospital, Boston.

DR. NALLANI: Srikanth Nallani, Clinical Pharmacologist with the FDA.

DR. SCHULTHEIS: Lex Schultheis, Medical Officer, FDA.

DR. ROCA: Rigo Roca, Deputy Director, Division of Anesthesia, Analgesia and Rheumatology Products.

DR. ROSEBRAUGH: Curt Rosebraugh, Acting Director, Office of Drug Evaluation, II.

DR. McLESKEY: Charlie McLeskey, anesthesiologist by training. Currently employed by Baxter Labs and serving as the industry representative on ALSDAC.

DR. WATKINS: Good morning. I would first like to remind everyone to please silence their cell phones, pagers, and

BlackBerries if you haven't already done so.

I would like to identify the press contact for today. Her name is Ms. Cruzan. I'm not sure if she is yet in the room but if she is, stand please. Okay.

Now, I will read the conflict of interest statement. The Food and Drug Administration is convening today's meeting of the Anesthetic and Life Support Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees or regular Federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with Federal ethics and conflict of interest laws covered by but not limited to those found in 18 U.S.C. 208 and 712 of the Federal Food,

Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special and regular government employees who have potential financial conflicts of interest when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under 712 of the FD and C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise. Related to the discussion of today's meeting, members and temporary voting members of this Committee

have screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of new drug application NDA 22-244 fospropofol disodium injection 35 milligrams per mL, proposed trade name Aquavan, MGI Pharma, Incorporated, a subsidiary of E-I-S-A-I, Eisai Corporation -- am I saying that right -- for the proposed indication of sedation in adult patients undergoing diagnostic or therapeutic procedures or undergoing minor surgical procedures in conjunction with local anesthesia.

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Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

Charles McLeskey is serving as the industry representative, acting on behalf of regulated industry. Dr. McLeskey is an employee of Baxter Healthcare Corporation.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

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CHAIR FARRAR: Before the introduction, Dr. Sang, you want to just introduce yourself, please?

DR. SANG: Thank you. Christine Sang, anesthesiologist at the Brigham and Women's Hospital and Children's Hospital of Boston.

CHAIR FARRAR: Dr. Roca.

DR. ROCA: Good morning. I am Rigo Roca. I am Deputy Director of the Division of Anesthesia, Analgesia, and Rheumatology Products. Dr. Farrar, members of the Committee and invited guests, thank you for participating in the meeting of Anesthetic and Life Support Drugs Advisory Committee.

Today, we will be discussing the new drug application by MGI Pharma, Incorporated for fospropofol disodium, a prodrug that is metabolized into propofol phosphate and formate in a one-to-one ratio.

MGI Pharma is seeing approval for the indication of sedation in adult patients

undergoing diagnostic or therapeutic procedures. This morning, representatives from MGI Pharma will present an overview of their application. This will be followed by a presentation from the FDA where you will hear our preliminary findings, since the review of the application is still ongoing.

This afternoon, you will be asked to assess these findings and to discuss the apparent risks and benefits of fospropofol. Specifically, we will ask the Committee to address whether the Applicant has presented adequate data to support the safety of the administration of fospropofol by persons without training in the administration of general anesthesia.

As some of you may be aware, currently Diprivan, which is approved for a different indication, has language in it that indicates that it should only be administered by persons trained in administration of general anesthesia and not involved in the

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conduct of the surgical or diagnostic procedure.

In addition to the safety findings, factors that may be considered in this assessment will include the patient population, the procedures that were studied, and any differences between the way a product is administered in the setting of a clinical trial, and how it would be administered in the setting of clinical practice.

We will also ask the Committee to address whether the assessment of a patient's ability to respond purposefully to stimulation are useful in guiding supplemental dosing and whether the available data is sufficient to administer fospropofol safely to geriatric patients, patients with serious cardiopulmonary and comorbidity, and to patients weighing less than 60 kilograms.

In the event that the Committee recommends approval of this application, we would also like you to consider whether there

are any post-approval studies that should be required of the applicant.

The Division and Agency are grateful to members of the Committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Your clinical experience and expertise will be of significant assistance to us as we finalize our review of this potentially valuable anesthetic agent. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

CHAIR FARRAR: We will now proceed to the Sponsor's presentation for today's meeting. Before MGI's presentation, I would like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Chair.

And I will call on MGI Pharma to

present its information.

DR. KLINE: Good morning, Dr. Farrar, members of the Committee, FDA staff, ladies, and gentlemen. We are pleased to be here today to present fospropofol, a new molecular entity for the proposed indication of sedation in patients undergoing diagnostic and therapeutic procedures.

I am Dr. Jackie Kline, currently with Regulatory Affairs and previously the development team leader for this compound. I will present a brief introduction to fospropofol, also referred to as Aquavan.

Following my introduction, Dr. Cohen will discuss the medical need for fospropofol. He will be followed by Dr. Waters, who will present data that demonstrates that fospropofol results in a gradual onset and dose-related depth of sedation.

I will return to review efficacy data that show fospropofol provides

predictable and titratable sedation. Dr. Cohen will follow with a presentation of safety data that show a low rate of occurrence of sedation-related events at the proposed label dose. Dr. Leslie will then present a review of the benefits and risks of fospropofol.

Finally, I will return to present conclusions and moderate the question and answer session.

Fospropofol was developed for an indication of sedation in adult patients undergoing diagnostic or therapeutic procedures.

The proposed fospropofol dose regimen is an initial dose of 6.5 milligrams per kilogram, with supplemental doses provided as need to achieve the desired sedative effect. This type of dosing regimen is consistent with clinical practice and was designed to facilitate predictable sedation on an individual patient basis.

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In order to balance safety and efficacy parameters, the dosing regimen includes adjustments to 75 percent of the standard dose for persons 65 years and older, and those with ASA physical classification status of three or four.

Additional dosing considerations are applied for persons who weigh less than 60 kilograms or more than 90 kilograms to account for differences in clearance rates for patients in these weight groups.

In an effort to minimize dosing errors and to provide clear directions for use, the proposed package insert includes a table that provides the dose in milliliters for a given patient weight. A second table is also provided for patients who require the reduced dose.

In addition to the dosing instructions and dosing table, the proposed package insert calls for pre-procedure patient assessments, including evaluation of the

patient's airway. The package insert also instructs that a designated individual monitor the patient in accordance with the American Society of Anesthesiology Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. During this presentation, we will provide data to show that with appropriate pre-procedure evaluation and patient monitoring, this dose titration regimen results in safe and effective sedation for a range of patients, including healthy patients undergoing colonoscopy and those with relatively poor health who may need a bronchoscopy.

We recognize that education and training initiatives are vital for the safe use of fospropofol. We believe that the package insert is the most important tool in educating physicians. The slides I have just shown provide top line detail on the dosing, patient evaluation, and monitoring instructions that we have included in our

proposed package insert. We believe that fospropofol should be used in accordance with the principals outlined in the ASA Guidelines for Sedation and Analgesia by Non-Anesthesiologists. As a new sedation agent, it is important that fospropofol be included in the curriculum of existing training programs. We will provide comprehensive information on the pharmacology of fospropofol to societies who provide such training. We are committed to providing support for education and training programs provided by professional societies on the practice of moderate sedation.

The chemical structure of fospropofol is shown on the right. Fospropofol is a prodrug of propofol. It is formulated as a clear, colorless, aqueous solution that contains 35 milligrams per milliliter of fospropofol in a 30 milliliter vial. Fospropofol is rapidly converted to propofol upon intravenous injection.

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Fospropofol was developed based on the hypothesis that a prodrug of propofol would provide the beneficial effects of clear headed recovery associated with the activity of propofol but in a manner that could be safely administered by non-anesthesiologists.

Fospropofol was developed with ongoing input from the Food and Drug Administration. The IND for fospropofol was submitted in 2002. The Phase 3 studies were conducted in 2006 and the NDA was submitted in September of 2007.

A total of 21 clinical studies were conducted with fospropofol. Nine studies were conducted in healthy volunteers and two studies were conducted in intubated and mechanically ventilated patients.

Most relevant to our discussion today, ten studies were conducted to assess fospropofol's sedation in a variety of procedure types. Early studies were driven by the hypothesis that a single, relatively high

bolus injection could provide the majority of the patients with a sufficient depth and duration of sedation to complete a brief procedure. This dosing regimen resulted in a higher rate of sedation-related events than reported for other commonly available sedatives. These studies provide experience in over 500 patients, 240 of whom received initial bolus doses approximately two or more times our proposed initial dose.

Subsequently, we revised thinking and hypothesized that a lower initial dose administered on a milligram per kilogram basis and followed by a titration sequence would be adequate to sedate the majority of patients and would prevent those who are most sensitive from reaching deep sedation. This hypothesis was first tested in a dose response study.

A dose was selected for further study and was tested in randomized, double-blind dose controlled studies conducted in patients undergoing colonoscopy and flexible

bronchoscopy. In an effort to gain additional experience with the drug, an open label, single arm study was conducted in patients undergoing a variety of minor procedures.

Of note in our clinical program, with the exception of our initial proof of concept study, our protocols for sedation during diagnostic and therapeutic procedures, did not require the presence of an anesthesiologist or a nurse anesthetist. Further, while the protocols specified that patients were to be monitored during this study, MGI did not provide sedation training to the sites. Sites that participated in our studies included office-based practices, ambulatory surgicenters and hospitals.

Efficacy studies demonstrated that the recommended dose results in predictable and titratable sedation, while minimizing the likelihood of reaching deep levels of sedation.

We have tested fospropofol in the

hands of non-anesthesiologists at our proposed label dose and at doses more than twice our proposed label dose. We have convincing data that demonstrate that the proposed dosing regimen results in a low incidence of sedation-related events. Sedation-related events that did occur were easily managed by non-anesthesiology health care professionals providing sedation, in most cases, by increasing the flow of oxygen through the existing nasal cannula.

At this time, I would like to introduce Dr. Larry Cohen, who will present a review of the medical need for fospropofol. Dr. Cohen.

DR. COHEN: Good morning everyone and thank you, Dr. Kline, for that presentation.

My name is Dr. Larry Cohen. I am a gastroenterologist at the Mount Sinai School of Medicine and I have been asked by MGI to provide the perspective of a GI proceduralist

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on the unmet need in the area of sedation.

Let me begin by reviewing for you the spectrum of procedural sedation as it exists today in the United States. Approximately 40 million procedures are performed annually in the United States under moderate sedation given under the direction of non-anesthesiologist professional. These procedures are performed by gastroenterologists, pulmonologists, surgeons and other medical specialists. More than half of these procedures are endoscopic and they include both colonoscopies as well as upper GI endoscopies.

Currently approximately two out of every three endoscopic examinations is performed under moderate sedation that is directed by an endoscopist. My role today is to review for you the challenges and the opportunities of procedural sedation that are confronted by gastroenterologists such as myself.

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The number of endoscopic procedures that are performed annually by gastroenterologists has increased almost two to three-fold during the past 15 years. This is the result of considerable growth in the number of procedures being performed annually and this number continues to grow by about five percent per year. The primary reason for this growth is the recognition that colonoscopy is able to reduce the number of colorectal cancers by up to 90 percent.

In addition, there is heightened awareness in the public domain of the potential value of colonoscopy and its ability to reduce colorectal cancer frequency. Pairs have also acknowledged the role of colonoscopy in cancer screening and, based upon this, have shown their willingness to pay for routine screening examinations.

Despite these successes, barriers to colonoscopy continue to exist, as shown in this study. This study that was conducted by

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the center for disease control and prevention looked at the age-adjusted percentage of respondents who reported having undergone either fecal occult blood testing or colonoscopy. As you can see on this slide, fewer than 50 percent of the eligible U.S. population has undergone either of these diagnostic modalities for colorectal cancer screening.

When asked for the reasons and the barriers for patients not undergoing their examination at a reasonable time, it becomes clear that a fear of pain and discomfort is a major barrier to patients having an examination. And so therefore, sedation becomes an important element in the endoscopic procedures. Therefore, a successful sedation experience will include the ability to relieve patient anxiety and discomfort or at least to make patients amnestic for their experience. This will help to improve patient compliance with recommendations for their examinations.

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It will improve the quality of examination and will minimize the potential for patient injury from these examinations.

Now let's begin by looking at the current practice of sedation as it exists in the United States. The use of sedation during endoscopy is virtually universal. In 2005, this survey indicated that 75 percent of endoscopies performed in the United States were being performed with using a combination of a benzodiazepine and an opioid that was administered under the direction of a non-anesthesia professional. The remaining 25 percent were performed with propofol, generally given by an anesthesia professional.

Let's look at this in a little bit more detail. Currently, the standard of sedation in the United States is the use of a benzodiazepine and an opioid. And these drugs are effective in about 85 percent of individuals that receive these medications. In addition, the availability of reversal

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agents is believed to impart an added level of safety when using these drugs. However, there are certain challenges associated with these medications. There is considerable pharmacodynamic variability. They have the potential for significant drug-drug interactions. They have potential of producing respiratory depression.

In addition, these drugs are often accompanied by delayed recovery so that patients may be unable to recall their post-procedure instructions or their medical discussion with their physician. At times, patients may experience prolonged nausea and vomiting, and in some cases recovery may be delayed for 24 hours or more.

Now, these drugs are also not without certain risks, as shown in this slide. These data were collected retrospectively from the CORI database. CORI refers to the Clinical Outcomes Research Initiative, which is a large national endoscopic database that

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collects data from more than 200 endoscopists from 87 centers around the country.

In this study, more than 300,000 endoscopic procedures were performed under sedation using a benzodiazepine opioid combination. The observed rate of cardiopulmonary complication ranged from 0.6 to 2.1 percent, depending on the endoscopic procedure and it was 1.1 percent for patients undergoing colonoscopy.

Now, we shouldn't forget that all forms of sedation are potentially associated with complications. And let's look at the use of propofol sedation. At the current time, it is estimated that 38 percent of all endoscopic procedures performed in the United States are done using propofol. And so we might conclude that propofol has become, at least in certain markets within this country, the de facto standard of care for sedation. Propofol provides for rapid onset and offset, as well as clear headed recovery, which is a marked

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contrast to the recovery profile with benzodiazepine and opioids. Physicians and patients both prefer the experience of propofol over the use of midazolam for procedural sedation.

Some of the issues associated with propofol, however, include painful burning on bolus injection and the risks that accompany the lipid formulation. In most settings, an anesthesia professional is required to administer propofol. Now propofol, too, may be associated with certain cardiopulmonary risks, as we will see on the next slide.

These data were also collected from the CORI database and it looks at the incidence of cardiopulmonary complication in a series of 11,000 procedures that are performed using propofol. As you can see, the incidence of complication range from 0.86 to 1.66 percent. And therefore, I would again remind you that all endoscopic procedures and all methods of sedation are associated with

certain risks of complications.

Based upon all that we have said up to this point, I think it is fair to conclude that there are limitations that exist with all of our methods of sedation that are currently available. Benzodiazepine and opioids are a factor for many patients, although they are not suitable to meet the needs of all of our patients. The propofol experience is clearly preferred by many individuals, although here, too, there are certain constraints.

In closing, I would like to summarize by stating that alternative sedation choices for the non-anesthesia professional are needed in order to accommodate the growing demand for procedural sedation, as well as the needs and wishes of our patients. A sedation agent that provided the benefits of propofol in a formulation that was safe and effective when administered by a non-anesthesia professional would certainly fulfill this

unmet need.

Thank you. I would now like to introduce Dr. Stephen Waters, who will present the clinical pharmacology of fospropofol.

DR. WATERS: Good morning. My name is Steve Waters. I am the Vice President of Science and Technology for MGI Pharma and I will be presenting an overview of the clinical pharmacology of fospropofol.

To begin, I would like to highlight three key aspects of fospropofol clinical pharmacology. First, fospropofol is rapidly and completely metabolized to propofol. Secondly, we see both fospropofol and propofol dose proportional pharmacokinetics in our healthy subjects and in patient populations. Third and most importantly, the resulting pharmacodynamic profile of this drug is characterized by a gradual onset and dose-related depth of sedation.

Shown on the left in this figure

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is the chemical structure of fospropofol. It is a phosphonyl 0-methyl prodrug of propofol. It is rapidly and completely metabolized via the action of the alkaline phosphatase enzymes, which are widely distributed in the body, to form three metabolites, propofol, formaldehyde and phosphate. I will remind you that both formaldehyde and phosphate are also normal products of everyday cellular metabolism. And in vivo, formaldehyde is rapidly metabolized to formate. We see formate and phosphate levels, plasma levels, consistent with baseline endogenous levels, even after fospropofol doses that exceed our proposed clinical dose.

In our evaluation of the clinical pharmacokinetics of fospropofol and propofol, we optimized bioanalytical methodology and used that to evaluate plasma propofol concentrations. That is what you see in this slide. Plasma propofol concentration as logged concentration versus time for healthy

subjects receiving fospropofol doses of 6 and 18 milligram per kilogram.

First we see low intrasubject variability in these data. Second, we see that as fospropofol dose is increased, we see a proportional increase in plasma propofol concentration.

This table presents the pharmacokinetic parameters of the study I just described. On the left we see as fospropofol dose increases, we see a proportional increase in propofol Cmax. Focusing on the right side of the table, we see that as dose increases, we see a consistent propofol total body clearance. We see these total body clearance values for propofol derived from fospropofol are consistent with literature values of propofol clearance, further indicating complete metabolism of fospropofol to propofol.

In addition to studying the pharmacokinetics of this agent, we have also

examined its pharmacodynamics. This was a study conducted in healthy subjects where we examined fospropofol effects on EEG measuring sedation by examining EEG effects and measuring them by spectral index. A spectral index value of 100, is consistent with a subject who is fully conscious. And as BIS scores decrease, that represents a corresponding increased depth of sedation.

In this study, we examined fospropofol doses, IV bolus doses ranging from five to 30 milligram per kilogram and we see a dose dependent depth of sedation. Focusing on a time to maximal sedation, that is the time from dosing to the time of attainment of minimal BIS scores, we see that it is consistent across all doses.

If we just take a moment to focus on the two upper dose levels, the dose levels that bracket our proposed clinical dosing regimen, and I will remind you that is an initial dose of 6.5 milligrams per kilogram,

followed by supplemental doses of 1.6 milligrams per kilogram as needed. We see that these dose levels produce BIS scores consistent with those associated with minimal to moderate levels of sedation. Furthermore, we see that these dose levels produce a gradual onset and relatively duration of action.

These are results from another study, one in which we examine the pharmacokinetics and pharmacodynamics of propofol derived from fospropofol and propofol as DIPRIVAN. Focusing on the left, there are date that are the PK data from this study and on the right are PD data.

Let's focus first on the pharmacokinetic data. They are expressed as propofol concentration versus time. This was a two period study and in the first period, subjects received an IV bolus dose of fospropofol at 10 milligram per kilogram. We see the data in orange. A gradual increase in

plasma propofol concentration and a gradual decrease.

After a seven day washout, subjects then received the DIPRIVAN infusion at a rate of 50 milligram per minute for approximately three to four minutes. Focusing on the data in blue, we see a rapid attainment of a higher plasma propofol concentration and a rapid decrease.

The pharmacokinetic data are mirrored in the pharamacodynamic response. We see for fospropofol a gradual onset and gradual return from sedation. For DIPRIVAN, we see both a rapid onset and rapid recovery from sedation.

Now, in order to characterize the PK-PD profile of these agents, we took time-matched BIS plasma propofol concentration from these studies and performed PK-PD modeling. Those data are displayed on this graph of BIS versus plasma propofol concentration. Data in red are data derived from fospropofol dosing.

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Data in blue from DIPRIVAN dosing.

Superimposed on the observed data in the dark red and blue lines are the median PK-PD simulations for these datasets. We can see that these data are superimposed on one another, indicating that propofol from fospropofol and propofol liberated from DIPRIVAN are pharmacologically equivalent.

It is also important to note that this PK-PD relationship that we see in our study is very consistent with what we see in the published propofol literature.

In our Phase 3 clinical trials, we collected and analyzed plasma blood levels -- I'm sorry -- plasma samples to evaluate population pharmacokinetics. The results are shown in this graph of propofol concentration in time plots for 257 patients receiving our proposed dose regimen, that is 6.5 milligram per kilogram initial dose and from one to as many as seven supplemental doses. We see that there is a consistent plasma propofol

concentration-time relationship in our patients. Superimposed on these data are the mean and standard deviations for this dataset.

I would like to highlight that 95 percent of our observed propofol plasma concentrations are below two microgram per mL. As we look to the propofol literature, we find that propofol concentrations reported producing loss of consciousness typically range from 2.4 to 3.4 micrograms per mL. Therefore, the dosing regimen that we employ with fospropofol are producing plasma propofol concentrations consistent with those producing minimal to moderate levels of sedation.

In conclusion, we have demonstrated that IV bolus dosing of fospropofol produces a gradual increase in plasma propofol concentration.

We have demonstrated dose proportional pharmacokinetics over a wide range of doses and we have demonstrated that our proposed dosing regimen produces plasma

concentrations that are consistent with those producing minimal to moderate levels of sedation.

At this point, I would like to reintroduce Dr. Jackie Kline, who will review the study design and efficacy data from our clinical trials.

DR. KLINE: Thank you, Dr. Waters. In this portion of our presentation, I will present evidence that demonstrates that the recommended fospropofol dosage titration regimen provides predictable and titratable sedation while minimizing the likelihood of reaching deep levels of sedation.

I will briefly describe the use of the Modified Observer's Assessment of Alertness Sedation Scale, touch briefly on the overall clinical program, present the primary endpoint used throughout the program, and provide highlights of our dose response study. I will spend the majority of my time reviewing data from our Phase 3 studies.

Throughout the clinical development program, the Modified Observer's Assessment of Alertness and Sedation or MOAA/S Scale was used to assess a patient's level of sedation. The MOAA/S is a validated, widely used, accurate and reliable measure for the depth of sedation. MOAA/S scores of two to four correspond to minimal to moderate sedation, as defined by the ASA. And this was the target depth of sedation for our clinical program.

As I detailed in my introduction, ten studies were conducted to assess fospropofol's sedation in a variety of procedure types. Early studies used a single, relatively high bolus injection. This dosing regimen resulted in a higher rate of sedation related events than seen for other sedatives.

Subsequently, we went to a lower initial dose, followed by a titration sequence that was adequate to sedate the majority of patients while preventing those who are most

sensitive from reaching deep sedation. This hypothesis was tested in a dose response study and later Phase 3 studies shown on the right.

I will address the dose response study and the Phase 3 colonoscopy and bronchoscopy studies in my presentation.

The Phase 3 minor procedures study was an open label, single arm study and as such, did not include efficacy endpoints. Therefore, Dr. Cullen will cover this study in his safety presentation.

Sedation's success was the primary endpoint used throughout the clinical development program. It was a composite endpoint that included both efficacy and safety measures. It measured the ability of the drug to effectively sedate patients in a manner that did not require manual or mechanical ventilation.

A dose response study was conducted in patients undergoing colonoscopy. The goal of this study was to identify a dose

for further testing that provided predictable and titratable sedation while minimizing the likelihood of reaching deep levels of sedation and of developing sedation-related adverse events.

The study included five treatment groups. Four fospropofol groups of 2, 5, 6.5 and 8 milligrams per kilogram and one midazolam group. Midazolam was included as an internal reference and was not planned or intended for formal efficacy comparisons. Approximately 25 patients were randomized to each group for a total study enrollment of 125 patients. The primary endpoint was sedation success, a composite of efficacy and safety endpoints as described earlier. A highly significant dose dependent increase in sedation success was observed across the fospropofol dosing groups. The two largest fospropofol doses tested were both significantly different from the low dose control group. The midazolam group, our

internal reference, demonstrated a sedation success rate of 80.8 percent. As both 6.5 and 8 milligrams per kilogram meant the primary endpoint of sedation success, both were considered candidates for further study.

As shown in the second bullet, however, the 8 milligram per kilogram dose resulted in a higher percentage of patients reaching deep sedation as measured by MOAA/S. In contrast, only one of 26 patients in the 6.5 dose group reached deep sedation. Therefore, the 6.5 milligram per kilogram dose was selected for further evaluation in the Phase 3 studies because it provided the optimum balance between sedation success and depth of sedation of the four fospropofol doses tested.

Let me now present the results of the Phase 3 studies conducted in patients undergoing colonoscopy and flexible bronchoscopy. As you will see, these studies confirmed the primary efficacy findings of the

Phase 2 dose response study and clearly demonstrated the efficacy of the 6.5 milligram per kilogram dosage titration regimen.

The Phase 3 studies were conducted in patients undergoing colonoscopy and flexible bronchoscopy as they represent a broad demographic range of patients. Inclusion criteria for the studies were designed to allow entry of a diverse patient population with characteristics that would be representative of those who might receive the drug in clinical practice. Consistent with current practice of sedation by non-anesthesiologists, patients judged to have difficult airways were excluded from these studies.

These studies were similar in design and compared the 6.5 milligram per kilogram dose to a low dose control group. Randomization to the 6.5 and 2 milligram per kilogram arms was at a three to two ratio. A midazolam arm was included in the colonoscopy

study. Patients who were 65 years and older or who were ASA-4 received a dose that was 75 percent of the randomized dose. Patients who were ASA-3 also received this dose reduction at the discretion of the investigator.

The studies were designed to assess the efficacy of the 6.5 milligram per kilogram dose of fospropofol and compare it to a low dose control. A low dose control was selected over a placebo control or an active comparator because it provided a manner in which the blind could be maintained between the treatment arms, given the occurrence of paresthesia and pruritus in patients receiving fospropofol. Midazolam was included in the colonoscopy study for general information and was not intended for formal efficacy comparisons.

The colonoscopy study was not designed, nor was it our intent, to compare the efficacy of the 6.5 milligram per kilogram dose to midazolam. The colonoscopy and

bronchoscopy studies were similar in design. In the study design, three distinct phases were recognized. Sedation initiation, sedation maintenance, and recovery. Five minutes prior to the initial dose of study sedative, patients received 50 micrograms of fentanyl. From fentanyl administration until the time the patient reached fully alert, oxygen was administered via nasal cannula at four liters per minute.

Also starting with fentanyl administration and continuing to fully alert, purposeful response and MOAA/S scores were measured every two minutes. At time zero, the initial bolus dose of study sedative was administered. During the sedation initiation period, patients were allowed up to three supplemental doses to initiate sedation. Doses were to be given no sooner than four minutes apart and only to patients who were not sedated. That is, to those with a MOAA/S score of five.

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If the patient failed to become sedated after three supplemental doses, the patient was considered a sedation failure and was eligible to receive alternative sedative, per the site's standard of care.

Once the patient was sedated, the scope was inserted and the patient entered the sedation maintenance phase. During maintenance, patients could receive supplemental doses of study sedative, if needed. Doses were to be given no less than four minutes apart and only to patients who had a MOAA/S score of four or five and who could demonstrate a purposeful response. As in the initiation period, if a patient failed to remain adequately sedated during maintenance, the patient was considered a sedation failure and was eligible to receive alternative sedative for the site standard of care.

Upon completion of the procedure, the scope was removed and the patient entered

the recovery period. The recovery period ended when the patient was discharged from the facility.

The vast majority of patients who were randomized into the studies were included in the modified intent to treat or mITT population, which was the population included in the efficacy analysis. The six patients who were excluded from this analysis discontinued from the study prior to receiving sedative medication.

Most patients enrolled in the colonoscopy study were generally healthy, having an ASA status of one or two. In addition, approximately 13 percent of patients who received fospropofol in this study were over the age of 65.

Patients in the bronchoscopy study tended to have more underlying illness. And more than 35 percent of patients in this study were ASA III or IV. In addition, a higher percentage of elderly patients were enrolled

in this study with approximately 40 percent over the age of 65.

A side-by-side comparison of the two study populations further demonstrates that the bronchoscopy patient population is older and has more underlying disease. We elected to study patients undergoing bronchoscopy because we believe this population represents one end of the spectrum of patients undergoing sedation by non-anesthesiologists. In addition, these patients also differ in their position during sedation, the level of stimulation experience during the procedure, and the type of concomitant medications that are administered. During a bronchoscopy, the airway is also shared with the bronchoscope. All of these factors were expected to influence the sedation experience of these patients.

By including bronchoscopy patients, as well was the healthier patients in the colonoscopy study, we have studied

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fospropofol across the range of patients who might receive this drug upon approval. As a reminder, the primary endpoint in these studies was sedation success. It was a composite of efficacy and safety parameters measuring the ability of the drug to effectively sedate patients without the need for additional sedative medications and in a manner that did not require manual or mechanical ventilation.

The results of the colonoscopy and bronchoscopy studies clearly demonstrated the efficacy of the 6.5 milligram per kilogram dosage titration regimen. In describing this endpoint, as well as others in this presentation, it is important to note that the dose groups shown are the nominal group to which patients were randomized and as such, also include patients who receive dose reductions. Most of the patients who failed to reach sedation success did not reach MOAA/S scores of four or less and required an

alternative sedative.

As to the safety component of the endpoint, it is important to note that only one of the 308 patients who received the 6.5 milligram per kilogram dose in these two trials required mask ventilation. This patient was enrolled in the bronchoscopy study. No patient required intubation.

The midazolam group, our internal reference, demonstrated a sedation success rate of 69.2 percent.

Efficacy data was analyzed across age, sex, race, weight, and special disease populations as shown. The findings demonstrate that sedation success rate in each of the subpopulations tested was higher for patients in the 6.5 milligram per kilogram than in the low dose control in both the colonoscopy and bronchoscopy studies.

The figures shown represent the result of a Forest plot analysis for sedation success by demographic factors. The objective

of this graphic display of sedation success is descriptive. All confidence intervals are to the right of zero and support that sedation success for the 6.5 group was statistically significantly higher than for the two milligram per kilogram group, irrespective of subgroup. While in some cases the small number of patients in a demographic subgroup limited the ability to draw a definitive conclusion, the same overall trend that 6.5 milligrams per kilograms sedated more patients than 2 milligrams per kilogram is consistently seen in these patient subgroups.

Secondary endpoints were evaluated in a hierarchical order. All endpoints shown reached statistical significance in the bronchoscopy study. In the colonoscopy study, the first two endpoints reached statistical significance. In both studies, patients in the 6.5 milligram per kilogram group reached a higher proportion of treatment success, required less supplemental analgesic, had less

recall of the procedure, and were more willing to be treated with the same study sedative again.

In both studies, the results in the 2 milligram per kilogram group are confounded by the fact that most of these patients received an alternative sedative per the site standard of care; most often, midazolam.

Additional measures of efficacy included the number of supplemental doses of sedative, depth of sedation, and physician satisfaction. Data for these endpoints are provided in upcoming slides. As a reminder, the studies were not powered to demonstrate difference in these endpoints.

Starting first with the number of supplemental doses of sedative, in both studies fewer does of fospropofol required during the sedation initiation phase for patients who receives the 6.5 milligram per kilogram does compared to the low dose. In

addition, patients who received the 6.5 dose required fewer doses over all than the low dose group.

As I mentioned earlier, throughout the clinical development program, the MOAA/S scale was used to assess a patient's level of sedation. MOAA/S scores of 2 to 4 correspond to minimal to moderate sedation, as defined by the ASA, and this was the target sedation depth of our clinical program.

This is a graphical representation of the percentage of patients at each MOAA/S score over time. Data depicted are for patients randomized to the 6.5 milligram per kilogram dose in the colonoscopy study. At any given time, the majority of patients who had a MOAA/S score of 2, 3, or 5. In fact, 96 percent of these patients stayed in the target range of minimal to moderate sedation throughout the duration of their procedure and through recovery. Only a very small percentage of patients experienced MOAA/S

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scores of one or zero. And Dr. Cullen will provide more detail on patients who went to MOAA/S one or zero in his presentation.

Moving now to the bronchoscopy study, again, the percentage of patients at each MOAA/S score over time are depicted for patients randomized to receive the 6.5 milligram per kilogram dose. Similar to the colonoscopy study, at a given time the majority of patients were at MOAA/S scores of 2, 3, 4, or 5. Overall, 84 percent of these patients stayed in the target range of minimal to moderate sedation throughout the duration of their procedure and through recovery. Only a very small percentage of patients experience MOAA/S scores of one or zero and Dr. Cullen will provide more detail on these patients in his presentation.

The sedation continuum, as defined by the ASA uses purposeful response as one of several markers to characterize the depth of sedation. As shown, moderate sedation is

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associated with the ability to demonstrate purposeful response to verbal or tactile stimulation.

In our studies, we assess the patient's ability to respond to verbal commands which was defined as the ability of the patient to give a thumbs up sign when asked. Purposeful response, like MOAA/S score, was assessed every two minutes with sites instructed to assess for purposeful response prior to determining the MOAA/S score.

This slide shows the correlation between MOAA/S score and the ability to demonstrate a purposeful response. A yes response was recorded each time the patient was able to give a thumbs up sign in response to a verbal command. Data displayed are for all data points collected for all patients, regardless of treatment group in the dose response study and the Phase 3 colonoscopy and bronchoscopy studies.

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The ability to demonstrate a purposeful response correlates well with depth of sedation. As would be expected, over 99 percent of the time that the patients were able to demonstrate a purposeful response, they registered MOAA/S scores between 2 and 5.

At the end of the procedure, physicians were asked to rate on a scale of one to ten their level of satisfaction with the study's sedative medications administered. Physician satisfaction at the end of the procedure was dose dependent with the higher satisfaction rating associated with the 6.5 milligram per kilogram per dose over the low dose control. These results are as would be expected, given the higher rate of sedation success, decreased need for supplemental analgesic, and lower proportion of patients who recalled being awake during their procedure, as compared to the low dose control.

In summary, our efficacy

experience clearly demonstrates the fospropofol at the recommended dose provides predictable and titratable sedation, while minimizing the likelihood of reaching deep levels of sedation. Eighty-eight percent of patients undergoing colonoscopy and 91 percent undergoing bronchoscopy were able to complete their procedures without requiring an alternative sedative and the majority of patients remained in minimal to moderate sedation throughout the duration of the procedure through recovery.

Now, I would like to ask Dr. Michael Cullen to present the safety data.

DR. CULLEN: Thank you, Dr. Kline. I am Michael Cullen, Chief Medical Officer for MGI Pharma and I am delighted to be here to share safety data from the fospropofol clinical program with you.

The safety data demonstrates that fospropofol can be safely administered by non-anesthesia health care professionals, that

sedation-related adverse events were typical of sedation practice and managed by simple maneuvers such as increased oxygen flow and that all sedation-related adverse events resolved without sequelae.

Today I will cover exposure, demographics, adverse events, as well as subgroup analyses, experience in minor procedures and experience with higher fixed dose levels.

Dr. Kline presented this clinical program outline earlier. During my presentation, I will focus on the 0522 colonoscopy and 0524 bronchoscopy Phase 3 studies and the proposed dose of 6.5 milligrams per kilo. I will also provide a summary of safety data from the 0523 minor procedures study. The studies in the second column in orange include the fixed dose trials which will be presented later.

A total of 1611 subjects have been exposed to fospropofol and 455 patients

received the proposed dose of 6.5 milligrams per kilo. We are fortunate to have experience with 500 patients who received initial doses greater than 6.5 milligrams per kilo. In the fixed dose regimen, initial doses were approximately twice the proposed 6.5 milligram per kilo dose.

Patients in colonoscopy, minor procedures and bronchoscopy studies were exposed to fospropofol at the proposed dose and to initial doses approximately twice that proposed. Please note, for example, that over 300 colonoscopy patients were exposed to initial doses approximately twice the proposed 6.5 milligrams per kilogram.

In this slide and in others to follow, we displayed data from the 0522 Phase 3 colonoscopy trial on the left, the midazolam assay sensitivity arm of the 0522 trial in the center and the 0524 Phase 3 bronchoscopy trial on the right. Analysis of total study drug exposure shows that the colonoscopy patients

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required more fospropofol and more fentanyl than bronchoscopy patients. Also note that patients randomized to the midazolam arm of the colonoscopy study received a median total dose of 4.3 milligrams.

Patients who were not sedated with three supplements of study drug in the blinded Phase 3 trials were considered sedation failures by protocol and they received an alternative sedative agent. In nearly all cases, this was midazolam. Of the patients randomized to the 2 milligram per kilogram fospropofol arm, approximately 60 to 70 percent received midazolam as an alternative sedative. This is important to recall, as you consider the efficacy and safety of the 2 milligram per kilo fospropofol arm.

As presented by Dr. Kline in the efficacy section, patients in the Phase 3 bronchoscopy trial were older and had worse ASA status than those in the colonoscopy study. This is important because sedation-

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related adverse events, especially hypoxemia were more frequent in the 0524 bronchoscopy trial. A higher frequency of these events would be expected in older patients with pulmonary disease.

The patient characteristics are not evenly distributed across study type. Therefore, today's presentation will present results by study and procedure.

In the 0522 colonoscopy study -- excuse me. In the 0524 bronchoscopy study, over 90 percent of the patients in the 6.5 milligram per kilo group had a history that coded to the cardiac or respiratory system organ class. This slide shows the most frequent cardiac and respiratory medical history for these patients.

Most patients did experience treatment emergent adverse events, primarily paresthesia and pruritus, which I will discuss on the next slide. Severe events were relatively uncommon but, as expected, more

common in the bronchoscopy patients. As a reminder, severity of adverse events is a measure of their intensity, while seriousness denotes a regulatory definition including, for example, whether an event required an initial or prolonged hospitalization. Only a single serious adverse event was considered drug-related. In addition, there were five deaths in the bronchoscopy trial but no death was considered drug related and all occurred at least four days after exposure.

The treatment emergent adverse events of paresthesia and pruritus were common in patients receiving fospropofol. The paresthesia and pruritus reported with fospropofol is commonly seen with other drugs containing phosphate, such as dexamethasone and fosphenytoin, and was not dose-related. These events were mild to moderate in intensity for 98 percent of those reporting and only a single patient discontinued treatment. Note also that 95 percent of

patients were willing to receive fospropofol again.

Paresthesia and pruritus were the most common treatment emergent adverse events in the Phase 3 trials. Adverse events likely related to study procedure included procedural pain for colonoscopy and cough for bronchoscopy. Events possibly related to both procedure and study drug were hypoxemia and hypotension. Both were more common in the bronchoscopy trial. This was expected, given the differences in study populations and the impact of the bronchoscope on the airway.

3.6 percent of the 1611 subjects in the fospropofol clinical program experienced serious adverse events. These were fairly rare in the colonoscopy trials for both fospropofol and midazolam patients. Serious adverse events were more common in the bronchoscopy population. Note that this effect was not dose-related. This suggests that the observed serious adverse events were

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more an indication of the health status of the populations and not drug-related. Serious adverse events were collected for 30 days following the procedure. Of the serious adverse events occurring within 24 hours in the bronchoscopy trial, only hypoxemia was considered related to study drug. All others were considered by the investigator to be related to underlying conditions.

There were ten deaths in the clinical program. However, no deaths were related to study drug. Note that five deaths occurred in an early study of ventilator-dependent intensive care unit patients. Fospropofol infusions up to 12 hours were studied in these critically ill patients, who each died of causes related to their underlying disease and all deaths were at least one day post-exposure. There were also five deaths in the Phase 3 program, all in the bronchoscopy study. All occurred at least four days post-exposure and all were

considered related to underlying disease.

In the far right-hand column we see the initial onset of events which led to death in the bronchoscopy study. The patient with the anoxic encephalopathy in the top line had HIV and cryptococcal meningitis. The second patient had metastatic lung cancer with a respiratory arrest 11 days after bronchoscopy. The other deaths in patients with septic shock, lung cancer and pneumonia were also unrelated to study drug.

Before I present the sedation-related adverse events from our Phase 3 trials, it is useful to review the definitions of the terms we use shown here. Hypoxemia was defined as an oxygen saturation of less than 90 for at least 30 seconds. Note that the definition hypotension required both a systolic pressure below 90 and medical intervention.

Using these definitions, we identified patients who experienced at least

one sedation-related adverse event in the Phase 3 trials. The frequency of sedation-related adverse events in the colonoscopy study was low. Less than one percent of colonoscopy patients experienced hypoxemia. No Phase 3 colonoscopy patient experienced apnea or bradycardia.

In the bronchoscopy study, there was a higher incidence of sedation-related adverse events. The primary event experienced by these patients was hypoxemia, as would be expected, given that this population has underlying lung disease and the airway is shared with the bronchoscope. The actual airway assistance provided to patients in these trials for sedation-related adverse events is summarized here. Please note that patients may have required more than one type of airway assistance. A single patient in the colonoscopy study required verbal stimulation for hypoxemia. In the bronchoscopy study, most patients who required airway assistance

were managed by increasing the flow rate of inspired oxygen through the existing nasal cannula. Other common forms of assistance were tactile stimulation, jaw thrust and chin lift. A single bronchoscopy patient did require manually assisted ventilation by bag-valve-mask and was effectively managed by the pulmonologist performing the study. No patient in the Phase 3 trials required intubation. All patients were managed effectively by the physician performing the study. All sedation-related adverse events resolved successfully, and all patients recovered without sequelae.

Let's now look at sedation-related events by subgroup. There were few sedation-related adverse events in the colonoscopy study. Given the low frequency of events, subgroup analyses were not revealing. All sedation-related adverse events in colonoscopy patients occurred in patients less than 65 years of age. Looking at sedation-related

events by ASA status and weight, the small event rate precluded meaningful conclusions.

For the Phase 3 bronchoscopy study, subgroup of sedation-related adverse experiences shows increasing incidents with increasing age. There was more hypoxemia but not more hypotension in older patients. The incidents of sedation-related adverse events did appear to be evenly distributed across ASA status in this trial. By weight, we see a slight increase of sedation-related adverse events in patients weighing either less than 60 kilos or more than 90 kilograms compared to those in the middle weight range.

We turn now to depth of sedation where we analyze the patients who went to a MOAA/S score of one or zero. The number of patients who went to a MOAA/S of one or zero at any time during the Phase 3 colonoscopy and bronchoscopy trials is shown here. Patients were counted twice if they were observed at any time to be at both one and zero.

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In the colonoscopy study, 3.2 percent of the 6.5 milligram per kilo fospropofol patients went to a MOAA/S of zero, and four of these five after both midazolam and fospropofol, and 3.8 percent went to either or both one or zero at any time.

In the bronchoscopy study, two percent of the 6.5 milligram per kilo patients went to a MOAA/S of zero and 16 percent went to either or both MOAA/S of one or zero at any time. We also looked closely at sedation-related adverse events and airway assistance in these same patients. Eleven of 34 and three of eight, two are 6.5 milligram per kilo patients who went to a MOAA/S of one or zero experienced a sedation-related event. Hypoxemia was the most common sedation-related event. And it is important to note that each of these events was managed by the physician performing the study and all events resolved without sequelae.

Turning now to the minor procedure

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study, this study included upper GI endoscopy, urologic and gynecologic procedures and a variety of other diagnostic and therapeutic procedures in a wide range of community and academic settings. Adverse events reported in the minor procedure study are summarized here. As expected, most patients experienced treatment emergent adverse events, primarily paresthesia and pruritus. Serious adverse events were not common and none were considered related to study drug. Sedation-related adverse events occurred at a low frequency. A single case of hypoxemia required airway assistance.

Here is a summary of sedation-related adverse events for colonoscopy, minor procedures, and bronchoscopy patients treated at 6.5 milligrams per kilo and also the airway assistance that was provided. No patient experienced apnea or hypotension requiring airway assistance in a colonoscopy or minor procedure study. A single patient in each of

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these two trials did experience hypoxemia that resolved with verbal and tactile stimulation and chin lift. Most sedation-related adverse events occurred in the bronchoscopy patients. This was expected with their underlying pulmonary disease, worse ASA status and increased age compared to the patients in colonoscopy and minor procedure studies. All but one of these events resolved with simple maneuvers and all were managed by the physician performing the study. All sedation-related events resolved without sequelae.

I mentioned earlier that fixed dose studies provide us experience with fospropofol in procedural sedation at higher than the recommended dose. In these studies, 241 patients received an initial bolus dose of at least 11 milligrams per kilogram. Another 249 patients received initial bolus doses between eight and 11 milligrams per kilo. The 11 milligram per kilo dose is roughly equivalent to an initial bolus dose of 6.5

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milligrams per kilo, plus the immediate follow-up of three supplemental doses of fospropofol. Thus, this fixed dose experience can be instructive for the scenario of fospropofol supplement dosing at far less than the recommended four minute intervals.

The 556 patients in these fixed dose studies experienced a higher incidence of apnea and hypoxemia that required airway assistance than did patients treated with the proposed 6.5 milligram per kilo dose. Compared to those patients in the Phase 3 trials, these patients required more manual ventilation. However, as with those receiving the proposed dose, most patients, even in the fixed dose studies, were managed with simple airway maneuvers and all were managed by the physician performing the study. All the sedation-related adverse events in these higher dose patients resolved without sequelae.

In summary, fospropofol provides

safe sedation to patients with a wide range of age, ASA physical status, and weight. Safe sedation was provided by non-anesthesia professionals for patients undergoing diagnostic and therapeutic procedures, including colonoscopy, minor procedures such as urologic and gynecologic procedures and bronchoscopy in a variety of community and academic settings.

Sedation-related adverse events were managed by non-anesthesia professionals. The typical maneuvers included increased oxygen flow, verbal and tactile stimulation, and chin lift. All sedation-related adverse events resulted in benign outcomes and no patient experienced sequelae from sedation with fospropofol.

Our clinical data support the safe use of fospropofol by non-anesthesia professionals when combined with pre-procedure evaluation, appropriate dosing, and monitoring by a designated health care professional. The

proposed label is consistent with current sedation guidelines. Physicians will be encouraged to follow ASA guidelines for non-anesthesiologists for procedural sedation and their own specialty society guidelines, when providing procedural sedation with fospropofol or any other sedative agent. Physicians should evaluate patients to determine their suitability for procedural sedation and to determine which patients might require the services of an anesthesia professional.

The initial fospropofol dose should be selected as described in the proposed label. For example, elderly and ASA III and IV class patients are to receive 75 percent of the standard dose. In addition, a health care professional should be designated for patient monitoring, paying particular attention to patient responsiveness, ventilatory effort, oxygen saturation and hemodynamics. Compliance with the proposed label and current

guidelines will ensure safe sedation by non-anesthesia professionals.

It is now my pleasure to introduce Dr. John Leslie of the Mayo Clinic, who will discuss the benefit and risk considerations with fospropofol.

DR. LESLIE: Thank you, Dr. Cullen. Mr. Chairman, members of the Committee, fellow anesthesia colleagues and people in the public forum, I want to thank you for the opportunity to speak today on a drug possibility for sedation that I think is extremely important. I am Dr. John Leslie and I am an anesthesiologist, and I work at the Mayo Clinic. I have been invited by MGI Pharma as an outside consultant, an advisor, to provide my overview as an anesthesiologist of the benefits and risks that will be associated with fospropofol use.

The company is seeking an indication for use in adult patients undergoing diagnostic or therapeutic

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procedures. In assessing this request, we really must consider the risks and benefits associated with fospropofol not only as it has been studied but as Dr. Roca points out, as it will also be used in the real world. When real clinicians get their opportunity to administer this drug, what risks and benefits with that administration?

What are the benefits of fospropofol? You have heard quite a few already listed. Fospropofol development was really based on the need for a drug that produced what we will call this propofol recovery experience. And it was also designed to be administered safely by non-anesthesia professionals.

The prodrug was the approach that the company chose to meet this specific need. Fospropofol results, as you have seen, in a very gradual increase in plasma propofol concentration and an gradual onset in sedation. In addition to these benefits, this

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prodrug approach also does avoid some of the downfalls of propofol as we use it today and its associated lipid emulsion. Specifically, the pain on injection and the risk of contamination.

As you have heard, patients undergoing a variety of procedures were tested in the Phase 3 studies. Eighty-eight to 91 percent of the colonoscopy or bronchoscopy patients were successfully and safely sedated. Ninety-five percent of the patients in the minor procedure studies were able to complete the procedure without requiring alternative sedative medications. Very few patients discontinued the procedure or asked for the fospropofol technique to be stopped. The rate of sedation-related adverse events seem to be in line with the experience and expectations of the clinicians performing the sedation and the procedures.

As it has been described, fospropofol is metabolized molecule for

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molecule to propofol. Propofol, a drug we know can provide a superior sedation recovery from the sedation drug itself. And consistent with this active metabolite propofol, the time to fully alert was quite rapid and the time to discharge readiness, as measured by the Aldrete score was quite excellent. This rapid recovery profile certainly can provide for good patient comfort and may actually reduce the burden of monitoring, for example, of the patient care team who has to take care of the patient, once the procedure is done and we wait for the drugs to disappear.

Additional benefits of fospropofol are also notable. Consistent with what we are describing as this propofol experience is the data that shows that the majority of these patients did not remember being awake during the procedure, despite the fact that they were asked to demonstrate purposeful responses. Very few remembered any of the pain, the discomfort, or the disagreeable aspects of the

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procedure, despite the fact they were asked numerous times before they received repeated doses to provide a purposeful response. Ninety-five percent of the patients stated they would like to receive the drug again. The physicians rated it nine out of 10, as far as their satisfaction with this technique.

I do think the data show that fospropofol can provide safe and effective sedation for this proposed indication, certainly as studied in these patient groups.

The risks of fospropofol fall into two main categories. Not to ignore the paresthesia and pruritus, as well as the clinically insignificant laboratory changes, but I do think the first major concern for any sedative agent is that short or long-term sequelae, specifically from the sedation-related adverse side effects as you have seen reported in detail in the previous presentations. Specific issues relating to development of apnea, hypoxia, hypotension or

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bradycardia. And second, there is a need for pre-procedure patient evaluation. And as has been stated repeatedly, very specific dosing recommendations and very specific monitoring maintaining patient interaction that increases the safety of fospropofol administration, if it is to be given by non-anesthesia professionals.

It is appropriate to always target the sedation level. It is a continuum. It is a target that we have to try and achieve. Drugs designed for minimal to moderate sedation really should have a therapeutic safe dose margin so that patients can always be kept on the left side of this particular line, distinguishing mild and moderate from deep sedation or general anesthesia.

Data does show that the proposed fospropofol dosing regimen, guided by the patient's ability to provide this purposeful response, as was described a thumbs up during the procedure, did result in minimal to

moderate sedation in the majority of situations. And rarely did the patient enter into deep sedation and rarely experience issues that related to loss of the airway where an intervention might be required or their ventilation might be judged inadequate either by MOAA/S or by the incidence of hypoxemia.

The Phase 3 protocols, as done, did not require the presence of anesthesia professionals. The majority of patients were treated in what is best described as real world clinical settings done by clinicians doing routine cases on a daily basis.

What are the risks of fospropofol sedation? The company has provided a fospropofol dose regimen and provided guidelines to help minimize the sedation-related adverse events. Specific dosing modifications have been proposed, based upon the patient's weight, their ASA status and their age. These proposed dosing

recommendations and modifications, as opposed to the original fixed dose, have been studied in the Phase 3 clinical trials. The sedation-related adverse events that we are seeing following fospropofol were certainly minimized by adherence to these tested dosing recommendations. Individual patient measurements of the MOAA/S or the purposeful response, again that thumbs up as has been described, were always used to determine the need for supplemental dosing following the initial 6.5 milligram bolus dose.

Now, certainly we have to be concerned about patients with severely compromised and medically unstable conditions. I think they did study patients with multiple medical problems but I really think we need to be cautious in suggesting that they study even more of these patients. The reason is quite simple because I believe that MAC sedation techniques are always going to be more appropriate as the patient develops or

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presents with more significant diseases or risks for developing the side effects of hypoxia, airway abnormalities and as such. I think that is the important part of this.

I would also point out that these patients did receive a single dose of fentanyl. A small dose of fentanyl. And that interaction has already been examined and is an important part of looking at the possible risks of drugs that are used in combination for sedation.

There are other risks of sedation with fospropofol I do think it is a risk that there is no reversal agent available and the caregivers are going to have to rely on propofol metabolism and their own management skills to support the patient if a patient undergoes or develops sedation-related events.

Notably, less than five percent of the measured propofol levels were higher than two micrograms per mL. Even then, only a small percentage of these patients did reach

deep levels of sedation or had significant sedation-related adverse events. Other risks do come with this prodrug pharmacology and proposed dosing. Unlike propofol, the onset is not rapid. There is a four minute re-dosing interval that will require specific attention to this detail to prevent dose stacking and over-sedation. This may require proceduralists to readjust their routines, if they want the benefits of a propofol wake-up routine.

I think sedation-related adverse events can be minimized by emphasizing pre-procedure evaluation and appropriate selection of patients who might receive fospropofol. This should be done, of course, for any sedative agent and is always good clinical practice. Patients with difficult airways, as well as those with life threatening underlying medical conditions should be identified and probably directed toward MAC sedation management, rather than simply say perhaps

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they are a great candidate for fospropofol but they may be at the limits of what is safe and reasonable.

Since we can expect some hypoxia, particularly in patients as studied in the bronchoscopy group here, a certain level of expertise should be expected of physicians who manage sedation of their own patients without anesthesia professionals present. The study data does not show that the physicians who use the fospropofol needed to be anesthesiologists but I do believe that they should have proven airway skills. They should be privileged and adept at minimal to moderate sedation techniques in the population that they treat and someone should be immediately available with ACLS certification.

Additional, I think misdosing can be minimized by compliance with the package insert, by education of clinicians along ASA guidelines for acceptable minimal to moderate sedation. Education programs, simplified

dosing charts, and continued reinforcement of the dosing regimen are needed as this drug is commercialized. It is a new drug that will also require specific instructions on how to give this drug. That dosing interval, the four minute wait are all an important part of minimizing adverse events and potential risks with this medication.

I hope that early promotional efforts will be in patient populations with the widest safety margin and the greatest clinical experience already described. After approval, additional trials in specific procedure settings, such as office-based practices, can be done to further establish and teach safe and effective procedural routines.

The company has stated, as you head, that they are committed to financial support of training programs provided by professional associations. Hospitals and ASCs certainly credential and offer training for

all sedation agents available for minimal to moderate sedation by non-anesthesia professionals and I hope these associations will participate in this important opportunity to help optimize their clinical pathways for sedation in their patient populations.

Regulatory approval of fospropofol should come with the acknowledgment that this is not a substitute for MAC anesthesia management when that is needed. As per ASA guidelines, patients who are severely compromised and medically unstable should undergo MAC sedation, management by an anesthesia professional. In addition, patients who desire the services of anesthesia professionals should still be allowed to receive this care.

We should also recognize that physicians in different specialties routinely see and treat patients who differ in their risks for procedural adverse events. A pulmonologist may feel more comfortable

providing sedation to a patient with significant pulmonary disease than would a gastroenterologist. Therefore, the idea of limitations of ASA III versus IV for certain practices becomes a very difficult challenge. However, fospropofol should be utilized by physicians privileged and skilled at providing minimal to moderate sedation to the patient populations they treat normally.

To conclude, in the end, I think the balance of the data show that fospropofol is an effective, predictable, titratable sedation agent that can be given by non-anesthesia professionals. And it can provide safe procedural sedation to allow completion of the procedures. I think the dosing regimen, as it has been proposed, really optimizes the safety margin and that the adverse events and sedation-related adverse events are certainly easily understood and they were easily monitored for and, as has been stated, they were effectively managed by

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the non-anesthesia professionals doing these studies.

I do believe fospropofol can be a valuable addition to our armament. I think it is a needed addition to the drugs currently available to help provide minimal to moderate sedation, certainly by non-anesthesia professionals. Thank you.

And now I would like to invite Dr. Kline back to the podium to present the conclusion.

DR. KLINE: Thank you, Dr. Leslie.

In conclusion, we have demonstrated that fospropofol results in a gradual onset and overall dose-related depth of sedation. We have demonstrated that fospropofol can successfully sedate patients so that they can complete diagnostic and therapeutic procedures. We presented convincing data that demonstrate that the proposed dose regimen results in a low incidence of sedation-related events.

Sedation-related events that did occur were easily managed by non-anesthesiology health care professionals providing sedation.

We believe that the benefit to risk ratio for fospropofol is clearly positive and that fospropofol would be an important addition to the moderate sedation armamentarium. In preparation for your discussions this afternoon, the FDA has requested feedback in three key areas. The first involves the use of purposeful response as a measure of sedation level and the associated risks. Our data are clear. Purposeful response are an ability to give a thumbs up in response to verbal or light tactile stimulation is highly correlated with minimal to moderate sedation. This is expected because the definitions of MOAA/S levels of two to five are consistent with the ability to demonstrate a purposeful response.

We have recommended that our dosing instruction indicate that supplemental

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doses be administered as needed to achieve the desired effect but no sooner than four minutes apart and only to patients who can demonstrate a purposeful response. Of course, the decision to provide supplemental dosing should be made in the overall context of the patient's status as determined through monitoring ventilatory function, oxygenation, and hemodynamics.

Turning now to the populations of special interest and starting with the geriatric population, we have dosed 157 patients aged 65 or older at or above a recommended dose. Most of our geriatric patient experience occurred in the bronchoscopy study, a patient population that is more susceptible to sedation-related events due to comorbidities and to the fact that the airway is shared with a bronchoscope during the procedure. Geriatric patients in this study experienced only slightly greater rates of hypoxemia as compared to those who are less

than 65 years of age.

Moving to patients with cardiopulmonary disease, all 149 of the patients who received the proposed dose in the bronchoscopy study had cardiopulmonary comorbidities. The sedation-related events in this population are consistent with what is observed for other sedative agents.

Finally, patients who weigh less than 60 kilograms. We have dosed 145 low-weight patients at or above the recommended dosage across a variety of procedures. Fifty-four of these patients received our proposed dose regimen. While the frequency of hypoxemia was slightly higher in these patients, as compared to those who weigh more than 60 kilograms, the results are confounded by the comorbidities in these patients.

It is important to note that all sedation-related events that occurred in all patients, in all subgroups, in all studies, were easily managed by the health care

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professional providing sedation most often with simple maneuvers, such as increasing the oxygen flow or verbal stimulation.

Our data are clear. Fospropofol can be safely managed by health care providers without training in general anesthesia. The safety of fospropofol in the hands of non-anesthesia personnel is a testable proposition and we have tested it throughout our clinical program. The data are convincing. We have tested fospropofol at our proposed label dose and at doses more than twice our proposed label dose. Our data demonstrate that the proposed dosing regimen results in a low incidence of sedation-related events which were easily managed by non-anesthesiology personnel, most often using simple maneuvers, such as increasing the oxygen flow or by verbal stimulation.

In summary, our data clearly support approval of fospropofol for the indication of sedation for diagnostic and

therapeutic procedures. We would be pleased to address any questions you may have and, in addition to our MGI and Eisai colleagues, we have several experts in addition to Doctors Cohen and Leslie available to assist us with answering your questions. Dr. Brill, a gastroenterologist, Dr. Candiotti, an anesthesiologist and investigator in our study of fospropofol's sedation in intubated and mechanically ventilated patients, and Dr. Silvestri, a pulmonologist and investigator in our Phase 3 bronchoscopy study. Thank you.

CHAIR FARRAR: Thank you very much. We now have a period of time to begin asking questions. You will notice that we have a number of periods like that today and we will, therefore, cut this one off at 10:15, in time for our break but that is a good 35 minutes from now.

I think it would be useful to begin with clarification and questions about the presentation and perhaps to leave the more

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comparative questions or the more complicated questions until after the presentation from the FDA. Panel members, if you could indicate your interest in asking a question, we will take note of your name and try and call you in order.

Dr. Nussmeier?

DR. NUSSMEIER: Thank you. The colonoscopy studies were apparently done in fairly healthy patients and I understand the need for exclusion of severely compromised or medically unstable patients. But these study patients, it seems, are not necessarily representative of modern day Americans seeking colonoscopy. I am particularly interested in how much data you may have on obese patients, not just greater than 90 kilos, but certainly we see many patients greater than 120 kilos, greater than 150 kilos. How much data do you have in patients who are older than 75, patients who specifically have cardiovascular disease, patients who use tobacco, patients

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with renal insufficiency? I would be very interested in another summary of the data as it currently exists with respect to fairly marked comorbidity.

DR. KLINE: First let me start by clarifying that in our colonoscopy study, we did not exclude patients who were at risk of higher comorbidities. We did allow enrollment of ASA status one to four. So the population that we enrolled is reflective of the all comers there.

To your specific questions about the experience in the subgroups, I would like to ask Dr. Sirek to speak more directly to those populations.

DR. SIREK: Could I please have the slide of demographics? Oh, I'm sorry.

My name is Dr. Ivana Sirek. I am the Executive Director, International Pharmaco Vigilance from Eisai. Slide up, please.

This demographic slide is for both colonoscopy and bronchoscopy. As you can see,

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