

BRIEFING MATERIALS

FOR

**THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE
TO THE DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY
PRODUCTS (DAARP)/CDER/FDA**

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Fospropofol Disodium Injection

NDA 22-244

MGI PHARMA, Inc

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AANA	American Association of Nurse Anesthetists
AE	Adverse Event
AGA	American Gastroenterological Association
ASA	American Society of Anesthesiologists
ASC	Ambulatory Surgical Center
AST	Aspartate Aminotransferase
AUC	area under the concentration-time curve
AUC _(0-∞)	AUC from time 0 to infinity
BIS	Bispectral index
BP	Blood pressure
BPM	Beats per minute
CI	Confidence interval
CAD	Coronary artery disease
CHF	Congestive heart failure
C _{max}	Maximal plasma concentration
Cl ⁻	Chloride ion
CL _F	fospropofol total body clearance
CLL	Chronic lymphocytic leukemia
CL _P	propofol total body clearance
CL _{P/F}	Apparent total body clearance
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSA	Controlled Substance Act
CYP450	Cytochrome P450 enzyme
DIPRIVAN	Propofol lipid emulsion
dL	Deciliter
eg	Exempli gratia
EC ₅₀	Plasma concentration producing 50% change in the baseline PD response
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration
g	Grams

GABA	Gamma-aminobutyric acid
HOPD	Hospital Outpatient Departments
h	Hour
HVLT-R	Hopkins Verbal Learning Test – Revised
ICU	Intensive care unit
IND	Investigational New Drug
IV	Intravenous
kg	Kilogram
L	Liter
m ²	Meters squared
MAC	Monitored Anesthesia Care
MAP	Mean Arterial Pressure
max	Maximum
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	Modified intent-to-treat
mL	Milliliter
mm Hg	Millimeters of mercury
mmole	Millimole
MOAA/S	Modified Observer’s Assessment of Alertness/Sedation
MRI	Magnetic resonance imaging
ms	millisecond
NA	Not applicable
NDA	New Drug Application
O ₂	Oxygen
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
QT interval	time necessary for cardiac repolarization
QTc	QT interval corrected for heart rate
QTcB	Length of the QT interval corrected for heart rate by Bazett’s formula

QTcF	Length of the QT interval corrected for heart rate by Fridericia's formula
QTcI	Individually corrected QT interval
QTcS	Length of the QT interval corrected for heart rate by Studywise formula
RBC	Red blood cell
RN	Registered Nurse
SAE	Serious adverse event
Sec	Second
SD	Standard deviation
SOC	System Organ Class
SpO ₂	Saturation of hemoglobin with oxygen in peripheral blood
SRAE	Sedation-related adverse event
t _{1/2}	Terminal elimination half-life
T _{max}	Time to achieve C _{max}
TEAE	Treatment emergent adverse event
WT	Weight
Yrs	Years

1. EXECUTIVE SUMMARY AND OVERVIEW

1.1 Introduction

This briefing package has been prepared for a meeting with the Advisory Committee of Anesthetic and Life Support Drugs of the United States Food and Drug Administration (FDA) for the public meeting scheduled on May 7, 2008. During this meeting the committee will discuss the safety and efficacy of MGI PHARMA, Inc.'s new drug application (NDA) 22-244, fospropofol disodium injection (AQUAVAN[®]), a sedative-hypnotic agent intended for use during therapeutic and diagnostic procedures.

Included in this briefing package is a summary of the work performed during the development of fospropofol disodium injection and includes a review of nonclinical and clinical data from the development program. These data support the following conclusions:

- Fospropofol disodium is a phosphate prodrug of the sedative agent, propofol. The pharmacologic activity of fospropofol disodium results from the liberation of propofol by alkaline phosphatase enzymes.
- Bolus intravenous (IV) administration of fospropofol disodium produces a smooth and gradual rise and fall in therapeutic plasma propofol concentrations that is mirrored by a moderate increase in the depth of sedation. In contrast, bolus or rapid infusion of propofol produces a spike in plasma propofol concentration and a rapid increase in the depth of sedation.
- Administration of fospropofol disodium via the proposed dosing regimen sedates patients to a level that is appropriate for therapeutic and diagnostic procedures.
- The risks associated with administration of fospropofol disodium are predictable, are known to and understood by physicians who perform procedural sedation, and include apnea, hypoxemia, hypotension and bradycardia.

1.2 Proposed Indication and Dosing

Fospropofol disodium, is an IV sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures.

The safety and efficacy of the proposed dosing regimen (including the modified regimen) was confirmed in 2 randomized, double-blind, controlled phase 3 studies performed in patients undergoing colonoscopy (3000-0522) and flexible bronchoscopy (3000-0524) and in 1 open label study in patients undergoing minor surgical procedures (3000-0523).

The fospropofol disodium dose titration regimen includes:

- Administration of an initial IV bolus dose of 6.5 milligrams/kilogram (mg/kg) followed by supplemental doses of 1.6 mg/kg IV provided as needed, but no more frequently than at 4 minute (min) intervals, to achieve and maintain minimal to moderate sedation.
- A modified dosing regimen, 75% of the standard dosing regimen, for patients ≥ 65 years (yrs) of age or who have severe systemic disease according to the American Society of Anesthesiologists (ASA P3/P4). A single reduction is applied for patients with multiple reduction criteria (e.g. those who are ≥ 65 years of age and have severe systemic disease).
- Lower and upper weight (wt) bounds of 60 kg and 90 kg, so that adults who weigh >90 kg are dosed as if they are 90 kg; adults who weigh <60 kg are dosed as if they are 60 kg.

1.3 Medical Need for Sedation by Non-anesthesiologists

In 2002 the U.S. Preventative Services Task Force, sponsored by the Agency for Healthcare Research and Quality, updated routine screening recommendations for colorectal cancer. Since that time the number of colonoscopies performed in the United States has continued to rise so that today, approximately 16 million endoscopic colonoscopies are performed each year. In spite of this, almost 60% of eligible adults have not undergone a colorectal cancer screening procedure (*American Cancer Society, Facts & Figures, 2007*). Reasons cited by patients include fear of the procedure and its associated discomfort.

The American Society of Anesthesiologists (ASA) has determined that sedation provides benefit to patients undergoing therapeutic and diagnostic procedures. According to the American Gastroenterological Association (AGA) Institute, sedation is intended primarily to reduce a patient's anxiety and discomfort, consequently improving their tolerance and satisfaction for the procedure (*AGA Institute Review of Endoscopic Sedation, 2007*).

The demand for procedural sedation continues to increase as more emphasis is placed on cancer screening. With a growing population and the continuing shortage of anesthesiologists (*Grogono, 2005*), there is a need for alternative sedative agents that can be safely administered to patients by non-anesthesiologists. In response to the results of a nationwide survey of large-hospital administrators, an ASA spokesperson stated:

"The survey shows that a nationwide shortage of anesthesiologists is beginning to have a profound effect in larger hospitals, delaying elective procedures, and in extreme cases, closing down surgical suites." (*ASA News Release: PR Newswire, July 2002*).

In recognition that sedative-hypnotic agents can be safely administered by non-anesthesiologists, the ASA has established patient care and monitoring guidelines to better enable proceduralists to safely provide minimal to moderate sedation for patients during diagnostic and therapeutic procedures. For the proceduralist, the choice of sedative agent depends on patient and practice needs, state and local regulations, and other factors.

The most widely used regimens for procedural sedation include administration of either an opioid plus a benzodiazepine or propofol lipid emulsion. Disadvantages associated with the use of midazolam, the most commonly used benzodiazepine, include respiratory depression, apnea and a prolonged time to clear headed recovery.

The disadvantages of propofol lipid emulsion include pain on injection, risk of bacterial contamination, allergic reaction, and hyperlipidemia-related side effects. Additionally, administration of propofol can result in a rapid and marked increase in depth of sedation that enhances the risk of respiratory depression, apnea, airway obstruction, oxygen desaturation, and cardiovascular effects including hypotension and bradycardia. A practical limitation of propofol lipid emulsion is that labeled use requires monitored anesthesia care (MAC) and therefore the presence of an anesthesiologist. Despite these

limitations, the desire of physicians and patients for the “propofol experience”, including the associated clear headed recovery, is driving the growth in propofol use by non-anesthesiologists.

In a survey of 1,353 gastroenterologists, over 25% report using propofol lipid emulsion for endoscopic procedures. For these practitioners and their patients, as well as for others who would prefer the benefits of propofol, an alternative to propofol lipid emulsion is needed.

Development of fospropofol disodium was based on the hypothesis that the pharmacokinetic profile of a prodrug (gradual liberation and lower maximum concentration (C_{max}) of the active moiety) would provide a mechanism by which safety concerns associated with an IV bolus injection of propofol could be reduced with modest effects on time to sedation and awakening. Furthermore, administration of an aqueous solution rather than a lipid emulsion reduces the risks for lipid formulation-related side effects.

1.4 Mechanism of Action

The primary effect of injectable sedative-hypnotic agents is a dose-dependent depression of the central nervous system (CNS). The widely-accepted mechanism for this neurodepression is associated with enhancement of inhibitory synaptic transmission. One of the most abundant inhibitory transmitters in the brain is gamma-aminobutyric acid (GABA), a prime target for the sedative-hypnotic class of drugs. For example, propofol activates the GABAA receptor complex to result in increased chloride ion (Cl⁻) conductance and hyperpolarization of the postsynaptic cell membrane, functionally inhibiting the postsynaptic neuron.

Fospropofol disodium is a pharmacologically inactive phosphate prodrug of propofol, the activity of which results from the enzymatic liberation of propofol by alkaline phosphatase enzymes. In comparison to the rapid rise and fall in plasma propofol concentrations observed after IV administration of propofol lipid emulsion, IV bolus administration of fospropofol disodium produces a smooth and gradual increase and decrease in therapeutic plasma propofol concentrations resulting in a lower C_{max}. The pharmacologic activity of fospropofol is dependent on the liberation of propofol; the activity of which is indistinguishable from that of propofol delivered directly as propofol lipid emulsion.

1.5 Non-Clinical Studies

In nonclinical studies, fospropofol disodium was well tolerated in multiple species (mice, rats, rabbits, dogs, monkeys) under various conditions of study. The primary pharmacodynamic effect of fospropofol disodium in animals was dose-dependent sedation-hypnosis that was pharmacologically indistinguishable from that of propofol lipid emulsion except for a more gradual onset and longer duration of sedation, effects characteristic of a prodrug. Plasma exposures were dose related, and there was no accumulation over time. The toxicology studies did not identify any findings that would preclude the safe use of fospropofol disodium for sedation-hypnosis for inpatient and outpatient diagnostic and therapeutic procedures in adult humans.

1.6 Clinical Program

The clinical development program for fospropofol disodium was undertaken to study the safety and efficacy of the propofol prodrug, fospropofol disodium. The program includes 21 clinical studies, 12 studies in patients and 9 studies in healthy subjects (Table 3). A total of 1611 individuals, including 1,338 patients and 273 healthy subjects were treated with fospropofol disodium in these studies. Of the 12 studies conducted in patients, 10 studies examined the use of fospropofol disodium for sedation in procedures such as colonoscopy (5 studies), flexible bronchoscopy (2 studies), and minor surgical procedures (3 studies). Two studies examined the use of fospropofol disodium for prolonged sedation in intubated and mechanically ventilated patients. Two randomized, double-blind, controlled, phase 3 studies were performed, 1 each in the colonoscopy and bronchoscopy settings.

1.6.1 Clinical Pharmacology

Following intravenous injection, fospropofol disodium is rapidly and completely metabolized by alkaline phosphatase enzymes to yield propofol, the active metabolite, phosphate and formaldehyde. The subsequent metabolism of propofol is consistent with metabolic profiles reported in the clinical literature for propofol from lipid-based emulsion. Formaldehyde is rapidly metabolized to formate by several enzyme systems present in various tissues. Formate is metabolized to carbon dioxide and water by an enzymatic reaction: formate that is not utilized metabolically is excreted in the urine. Phosphate is primarily distributed in extracellular water and is excreted in the urine.

Fospropofol and its active metabolite, propofol, are highly protein bound (98%) primarily to albumin.

The pharmacokinetics (PK) of fospropofol and propofol liberated from fospropofol disodium were found to be approximately dose-proportional in healthy subjects and patients. Population PK evaluations performed in the pivotal clinical trials determined that there were no evident influences of race, age, or gender (after accounting for body weight differences), on fospropofol or propofol PK. Data from the population PK model indicates that patients weighing <60 kg have a higher propofol clearance than patients in the 60 to 90 kg weight range (0.057 and 0.044 /min/kg, respectively). Therefore, a weight bound dosing regimen normalizes C_{max} values consistent with those observed in the 60 to 90 kg patient group. Likewise, use of the modified dosing regimen takes into consideration the changes in fospropofol and propofol clearances, estimated to be 22% and 12% higher for patients with ASA P3 or P4 status, respectively, compared to those with ASA P1/P2 status.

Population PK evaluation performed in the pivotal clinical trials determined there were no influences of alkaline phosphatase concentration, total bilirubin concentration, and calculated normalized creatinine clearance on fospropofol and propofol PK. No influence of fentanyl dose or exposure on fospropofol or propofol PK was detected.

Bolus dosing with fospropofol disodium produced dose-dependent depth and duration of sedation as measured by bispectral index (BIS) scores over a range of doses (5 to 30 mg/kg). No dose dependency in time to minimal BIS scores was observed. The pharmacologic activity of propofol was found to be independent of whether it is liberated from fospropofol disodium or is delivered directly from propofol lipid emulsion.

1.6.2 Clinical Efficacy

Two randomized, controlled, double-blind phase 3 studies, colonoscopy (study 3000-0522) and bronchoscopy (study 3000-0524), and a single arm open label study in patients undergoing minor surgical procedures (study 3000-0523) were performed as part of the clinical development program. Study of fospropofol disodium in these distinct clinical settings and in patients with a broad demographic background provides data representative of the patient experience for those who might be administered fospropofol disodium injection upon regulatory approval.

The goal of these studies was to provide predictable and titratable sedation with fospropofol disodium, while minimizing the need for alternative sedatives, such as midazolam, and the need for advanced airway maneuvers including manual and mechanical ventilation. The studies were performed without the requirement for an anesthesiologist; rather, patients were monitored by a health care professional not performing the procedure, paying particular attention to the adequacy of spontaneous respirations, lack of response to stimuli, movement, hypoxemia, hypotension, and cardiac arrhythmia,

An active control (low dose, 2.0 mg/kg fospropofol disodium) was included in the phase 3 studies and this served 2 purposes: 1) provided a manner in which a blind could be established between the treatment arms given that paresthesia and/or pruritus in patients receiving fospropofol disodium is frequent and not dose related, 2) provided dose response data for further analysis and confirmation of the efficacy of the proposed fospropofol disodium dosing regimen.

Inclusion of midazolam provided a sensitivity measure of the tools used to determine sedation, including the Modified Observers Assessment of Alertness/Sedation (MOAA/S) scale (Table 5) and clinical benefit of sedation (e.g., patient and physician questionnaires). Following discussions with the FDA, midazolam was included in a single phase 3 study (study 3000-0522).

The primary efficacy endpoint, Sedation Success, was a composite endpoint that included both efficacy and safety parameters. It measured the ability of the drug to effectively sedate patients, in a manner that did not require advanced airway maneuvers, including manual (bag valve mask) or mechanical ventilation. Specifically, the endpoint was defined as a patient: (1) having 3 consecutive MOAA/S scores of ≤ 4 after administration of sedative medication, (2) completing the procedure, (3) without requiring the use of alternative sedative medication (such as midazolam) and, (4) without requiring manual or mechanical ventilation.

Analysis of patient data from the midazolam arm, (study 3000-0522), showed a Sedation Success rate of 69.2%, indicating the appropriateness of the MOAA/S scale to measure sedation in this setting. Sedation Success was significantly higher in the fospropofol disodium 6.5 mg/kg group compared with the 2.0 mg/kg group ($p < 0.001$) in both of the randomized phase 3 studies: 86.7% vs. 25.5 % (study 3000-0522) and 88.7% vs. 27.5% (study 3000-0524), respectively (Table 12).

Patients who did not meet the criteria for Sedation Success failed for 1 of 2 reasons. First, 58.8% (study 3000-0524) and 71.6% (study 3000-0522) of patients who received a low dose (2.0 mg/kg) of fospropofol disodium were not effectively sedated and received alternative sedative medications to achieve sedation and complete the procedure. Second, a single patient in these 2 studies required manual ventilation without intubation.

Analyses also demonstrated that Sedation Success in several subpopulations (race, gender, age, weight, sex, ASA P3/P4, renal impairment) for both randomized, double-blind, controlled studies was significantly greater in the fospropofol disodium 6.5 mg/kg group than in the 2.0 mg/kg group (Table 18).

The number of patients randomized to the 6.5 mg/kg dose group who reached a MOAA/S of 0 was 5/158 (3.2%) in study 3000-0522 (colonoscopy) and 3/150 (2.0%) in study 3000-0524 (bronchoscopy) (Table 17).

In summary, treatment of patients with the proposed fospropofol disodium dose titration regimen results in effective and safe sedation, as defined by the primary endpoint, in adult patients undergoing diagnostic and therapeutic procedures. The majority of patients treated with the proposed dosing regimen did not require the use of a rescue agent such as midazolam, and avoided the need for advanced airway assistance.

1.6.3 Clinical Safety

1.6.3.1 Safety Overview

Originally, the goal of the fospropofol disodium development program was to identify a single bolus dose of drug which would sedate the majority of patients (studies: 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415). This objective was reconsidered when several of the patients receiving fospropofol disodium in this manner reached deeper levels of sedation than desired. However, the data from these early clinical studies provide information related to safety outcomes that can be expected following bolus administration of at least twice the amount of fospropofol disodium than is provided by the proposed dose titration regimen tested in a phase 2 dose ranging study (study 3000-0520) and the phase 3 clinical program (studies 3000-0522, 3000-0523, 3000-0524).

An overview of the adverse event profile generated during the conduct of the phase 3 clinical studies demonstrates that the observed safety profile was no different than expected for the class and type of drug represented by fospropofol disodium (Table 23). Most patients experienced treatment emergent adverse events (TEAE) of paresthesia (reported as burning, stinging, tingling, prickling) or pruritus (itching) characteristic of phosphate prodrugs. There was a low incidence of serious adverse events (SAE) that were considered to be at least possibly related to study drug (6 of 1611 individuals) and no drug related deaths occurred in any study. Patients experienced sedation related adverse events (SRAE) such as apnea, hypoxemia, hypotension and bradycardia. The frequency was higher in the bronchoscopy study, which is likely a reflection of the demographics of this patient population. The most common types of airway assistance used to treat SRAEs included increased oxygen flow through the existing nasal cannula, verbal stimulation and chin lift, the most common of these being increased oxygen flow. Hypotension was most commonly treated with IV fluids, repositioning, or concomitant medication. Sedation related adverse events (SRAEs) were generally transient, rarely treatment limiting, and manageable in the clinical setting for which the drug is intended.

Data from the development program supports the following conclusions related to the proposed fospropofol disodium dose titration regimen:

- Administration results in a manageable safety profile in patients with a wide range of baseline physical conditions, age, and ASA status
- Administration by a non-anesthesiologist results in safe and effective sedation when patients are concomitantly monitored by a health care professional not performing the procedure, paying particular attention to the adequacy of spontaneous respirations, lack of response to stimuli, movement, hypoxemia, hypotension, and cardiac arrhythmias
- Adverse events were generally mild to moderate, those most frequently experienced included paresthesia, pruritus and procedural pain
- The incidence of SRAEs, including apnea, hypoxemia, hypotension and bradycardia is consistent with the experience of physicians providing sedation for diagnostic and therapeutic procedures

- Hypoxemia (O_2 saturation $<90\%$ for >30 seconds) is the most prevalent SRAE and occurs predominantly in patients undergoing bronchoscopy. In the majority of cases it is managed with increased oxygen flow through the nasal cannula
- No patient deaths were considered related to fospropofol disodium

1.6.3.2 Safety Analyses

Based on the metabolism of fospropofol disodium, the known incidence of paresthesias and pruritus associated with the metabolism of other phosphate prodrugs, the safety profile of other sedative/hypnotic agents, and a review of the fospropofol disodium safety profile, specific focus was placed on: 1) phosphate and formate; 2) paresthesia and pruritus; 3) sedation related adverse events (e.g. apnea, hypoxemia, hypotension, bradycardia) and 4) the nature and frequency of airway assistance.

Treatment Emergent AEs: The most common AEs in fospropofol disodium treated patients and healthy subjects were events of paresthesia (including: burning, tingling, stinging, prickling) and pruritus (itching) that occurred primarily in the lower abdominal and perineal regions (Table 24, Table 25, Table 26). These events occurred in the majority of individuals, were generally mild to moderate in intensity, self limited and lasted a few minutes. A single patient was discontinued from treatment with fospropofol disodium due to severe paresthesia.

Deaths: There were no deaths in the clinical program that were considered by the Investigator to be related to treatment with fospropofol disodium. There were a total of 10 patient deaths; at intervals from 1 to 31 days post fospropofol disodium exposure and all were considered to be related to the underlying disease state of patients. The 10 deaths occurred in the prolonged exposure ICU study (3000-0413) and the phase 3 bronchoscopy study (3000-0524) (Table 30). Detailed patient narratives for these 10 patients are found in Appendix C.

Serious Adverse Events: Six of 1611 individuals experienced SAEs that were considered probably or possibly related to treatment with fospropofol disodium. Of the 6 patients who experienced fospropofol disodium related SAEs, 4 patients experienced SAEs that were considered to be sedation-related and which required airway assistance; one of these 4 patients received fospropofol disodium with the proposed dose titration regimen.

Discontinuations due to AEs: Six of 1611 individuals experienced a TEAE that led to discontinuation of the study drug and/or procedure. Three patients discontinued due to events considered by the Investigator to be related to study drug ([Table 35](#)).

Sedation Related AEs: SRAEs in the described phase 3 studies were defined as apnea (absence of spontaneous breathing >30 seconds [sec]), hypoxemia (oxygen saturation <90% for >30 sec), hypotension (systolic blood pressure [BP] of < 90 mm Hg requiring medical intervention) bradycardia (heart rate of <50 beats per minute [bpm] and requiring medical intervention).

In the colonoscopy study (3000-0522), the incidence of SRAE experienced by patients in the 6.5 mg/kg fospropofol disodium group was 1/158 (0.6%) hypoxemia and 2/158 (1.3%) hypotension. In the fospropofol disodium control arm (2.0 mg/kg); 0/102 (0%), and 2/102 patients experienced hypoxemia and hypotension, respectively. In the midazolam arm, 1/52 (1.9%) patients experienced hypotension ([Table 37](#)). No apnea or bradycardia was reported in this study.

In the bronchoscopy study (3000-0524), the incidence of SRAE experienced by patients in the 6.5 mg/kg fospropofol disodium group was 23/149 (15.4%) hypoxemia, 8/149 hypotension (5.4%), and 1/149 (0.7%) patients with apnea. In the fospropofol control arm (2.0 mg/kg), 13/103 (12.6%) patients experienced hypoxemia ([Table 37](#)). No bradycardia was reported in this study. The increased incidence of SRAE in the bronchoscopy compared to colonoscopy study is likely a reflection of the baseline characteristics of this population including: increased age, a greater incidence of ASA P3/P4 patients, and an increased incidence of underlying disease related to respiratory conditions.

Importantly, the frequency of observed SRAE in the randomized, double-blind, controlled phase 3 studies did not appear greater than anticipated for sedation provided during these procedures based on the experiences of proceduralists as reported in the medical literature ([Section 8.6.1](#)).

In the phase 3 studies, there were no findings of clinical concern in the results of clinical laboratory tests, including those of phosphate and formate.

There were no shifts from normal to clinically significant abnormal in the electrocardiogram (ECG) results for any patient in any of the clinical trials. A thorough

QT study (3000-0521) was performed including doses approximately 3 times the proposed dosing regimen and no subject had a QT interval corrected for heart rate (QTc) >480 milliseconds (ms) throughout the study, regardless of the QT correction formula used. No subject had a individually corrected QT interval (QTcI), length of the QT interval corrected for heart rate by Fridericia's formula (QTcF), or length of the QT interval corrected for heart rate by Studywise formula (QTcS) interval change from Baseline that was >60 ms (3000-0521).

1.6.3.3 Safety in Subpopulations

Subpopulations selected for analysis include age, race, weight, sex, ASA status ([Table 9](#)), renal impairment and hepatic impairment.

There was a low frequency of SRAEs in the colonoscopy study, and no specific statements regarding subpopulation related trends can be made. For all of the groups analyzed, and all of the subpopulations, hypoxemia was the most commonly reported SRAE.

The frequency of Sedation-Related Adverse Events (SRAEs) in the phase 3 studies was determined in a subgroup analysis by age, race, weight, sex, ASA status and renal or hepatic insufficiency. SRAEs were too rare in the pivotal colonoscopy study (3000-0522) to draw conclusions, and none required manual or mechanical ventilatory assistance. In the pivotal bronchoscopy study (3000-0524), hypoxemia was the only SRAE of sufficient frequency to support any conclusions. In study 3000-0524, only advanced age (>65, >75) seemed to be associated with the frequency of hypoxemia.

Fifty-seven patients with moderate (creatinine clearance values of ≤ 50 mL/min) to severe (creatinine clearance values ≤ 30 mL/min) renal impairment were enrolled in the clinical studies. The majority of patients studied with renal impairment were enrolled in the bronchoscopy studies. All 7 of the patients with severe renal impairment were treated with the modified dose regimen (75% of the standard dose titration regimen). The profile of SRAEs reported for patients with renal impairment was similar to the general population in each of the study populations: colonoscopy, minor surgical procedures and bronchoscopy ([Table 49](#)).

Patients were considered to have had impaired hepatic function based on the Child-Pugh score and a complete review of their medical history. For 5 of the 8 cases of hepatic impairment, the Investigator chose to treat the patient with the modified dosing regimen. Sedation related AEs were experienced by 1 of these patients. The number of patients is

too small to make any conclusions about the influence of hepatic impairment on the potential occurrence of SRAEs.

1.7 Summary of Benefit-Risk

Sedation occurs in a continuum that ranges from minimal and moderate sedation to deep sedation and general anesthesia. For patients undergoing diagnostic and therapeutic procedures, the desired risk benefit ratio can be achieved if patients are maintained in the range of minimal to moderate sedation. Agents that are currently available for this purpose include benzodiazepines, midazolam being the most common, opioids including fentanyl, which is typically used in combination with midazolam, and propofol. The midazolam/fentanyl combination has advantages that include amnestic and analgesic effects and that monitored anesthesia care is not required for its administration. Disadvantages include patient variability in response, respiratory depression and a relatively slow time to clear headed recovery often reported by patients. Propofol provides for rapid onset and clear headed recovery; but limitations include a monitored anesthesia care label, and disadvantages include produce pain on injection, risk of bacterial contamination, allergic reaction, and hyperlipidemia-related side effects.

Preference for propofol and the rapid increase in colorectal screening in the US has led to a growing use of propofol by non-anesthesiologists in the setting of diagnostic and therapeutic procedures.

Fospropofol disodium, is a prodrug of propofol. The pharmacological activity of fospropofol results from the liberation of propofol by alkaline phosphatase enzymes. The pharmacokinetic-pharmacodynamic (PK-PD) profile of fospropofol demonstrates a more gradual onset of sedation than occurs with an IV bolus administration of propofol; while enabling a patient to experience the pharmacologic benefits associated with propofol.

The efficacy of the proposed dose titration regimen for fospropofol disodium injection has been demonstrated in 2 randomized double-blind controlled clinical studies of diagnostic/therapeutic procedures that provided for study of a wide range of patient populations (elderly, ASA P1 to P4). The safety of the dose titration regimen for fospropofol disodium injection, when administered by non-anesthesiologists following well-established guidelines for patient care and monitoring, has been demonstrated in the setting of bronchoscopy, colonoscopy and a broad array of minor surgical procedures. The sedation related risks associated with fospropofol disodium use are predictable, are

understood by, and are familiar to practitioners who routinely use sedative agents in a clinical setting of therapeutic and diagnostic procedures.

2. INTRODUCTION

2.1 Proposed Indication and Dosing

AQUAVAN[®] (fospropofol disodium) Injection is an IV sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures.

AQUAVAN is provided as an aqueous, sterile, nonpyrogenic, clear, colorless, isoosmotic solution containing 35 mg/mL of fospropofol disodium for IV administration (1,050 mg of fospropofol disodium per 30 mL single-use vial). A simplified dosing chart for determination of the correct dose was provided in the proposed package insert ([Table 1](#) and [Table 2](#)). The clinician is instructed to use [Table 1](#) if the patient is <65 years of age or ASA P1 or P2; otherwise [Table 2](#) provides instructions for the modified dose (75% reduction) to be used if a patient is ≥65 years of age and/or ASA P3 or ASA P4. A single reduction is applied for patients with multiple reduction criteria (e.g. those who are ≥65 years of age and have severe systemic disease).

The proposed fospropofol disodium dose titration regimen originated from a PK-PD modeling exercise that incorporated observed data from clinical studies. The dosing regimen includes weight bounds (60 kg and 90 kg) and a dosing regimen (75% of the standard dose) for those ≥65 years of age and those with severe systemic disease (ASA P3 or P4). The regimen was tested in a dose ranging phase 2 study performed in the colonoscopy setting and data from this study was used to identify the proposed fospropofol disodium dose titration regimen. The safety and efficacy of the regimen (including the weight bounds and modified dosing regimen) were confirmed in 2 randomized, double-blind, controlled phase 3 studies in patients undergoing colonoscopy (3000-0522) and flexible bronchoscopy (3000-0524) procedures, and in 1 open label study in patients undergoing minor surgical procedures (3000-0523).

The proposed standard dose titration regimen as tested in these studies includes administration of an initial IV bolus dose of 6.5 mg/kg fospropofol disodium followed by supplemental doses of 1.6 mg/kg IV, provided at 4 minute intervals, as needed to achieve and maintain the desired level of sedation ([Table 1](#)). In addition,

- A modified dosing regimen, 75% of the standard dose (both initial dose and supplements), is recommended for patients who are ≥ 65 years of age or who have severe systemic disease (ASA P3 or P4). A single reduction is applied for patients with multiple reduction criteria (e.g. those who are ≥ 65 years of age and have severe systemic disease) (Table 2).
- The dose of fospropofol disodium is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg (Table 1 and Table 2).

In the phase 2 and the phase 3 studies, patients with severe renal impairment (n=7 with creatinine clearance <30 mL/min); and 5 of 8 patients with moderate to severe hepatic impairment (based on Child-Pugh score and medical history) were treated with the modified dosing regimen.

As part of the dosing information supplied in the proposed package insert, it is also recommended that:

- Supplemental doses of fospropofol disodium be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.
- Supplemental oxygen should be administered to all patients.
- Patients should be continuously monitored with pulse oximetry, ECG, and frequent blood pressure measurements.
- A health care professional not performing the procedure should monitor patients during sedation, paying particular attention to the adequacy of spontaneous respirations, lack of response to verbal stimuli, lack of purposeful movement, hypoxemia, hypotension, bradycardia, or other cardiac arrhythmias.
- Patients should be managed during sedation and through the recovery process until clinical discharge criteria are met in facilities appropriately staffed and equipped for detection and management of apnea, hypoxemia, hypotension, hypoventilation, and/or airway obstruction.

The proposed package insert advises that, in keeping with current treatment standards, sedative-hypnotic agents should be used with caution in patients in whom management of

the airway is judged to be difficult due to obesity, short thyro-mental distance (“short neck”), or Mallampati score.

In nearly all of the clinical studies with fospropofol disodium, sedative use was preceded by the administration of an analgesic (fentanyl). The analgesic use was to relieve pain while the sedative reduced awareness and anxiety so as to provide patients with clinical benefit as defined by ASA.

Table 1 Standard Dosing Regimen, Adults 18 to <65 Years of Age Who are Healthy or Have Mild Systemic Disease (ASA P1 or P2)

Weight (kg)	Initial Dose		Supplemental Dose (No more frequently than every 4 min)	
	mg	mL	mg	mL
≤60	385.0	11.0	105.0	3.0
61 to 63	402.5	11.5	105.0	3.0
64 to 65	420.0	12.0	105.0	3.0
66 to 68	437.5	12.5	105.0	3.0
69 to 71	455.0	13.0	105.0	3.0
72 to 74	472.5	13.5	122.5	3.5
75 to 76	490.0	14.0	122.5	3.5
77 to 79	507.5	14.5	122.5	3.5
80 to 82	525.0	15.0	140.0	4.0
83 to 84	542.5	15.5	140.0	4.0
85 to 87	560.0	16.0	140.0	4.0
88 to 89	577.5	16.5	140.0	4.0
≥90	577.5	16.5	140.0	4.0

Source: Draft label for fospropofol disodium, NDA 22-244

Note: Doses are rounded to the nearest half-milliliter volume. Actual mg/kg may vary slightly due to the rounding effect.

Table 2 Modified Dosing Regimen, Ages ≥ 65 Years Or Those with Severe Systemic Disease (ASA P3 or P4)

Weight (kg)	Initial Dose		Supplemental Dose (No more frequently than every 4 min)	
	mg	mL	mg	mL
≤60	297.5	8.5	70.0	2.0
61 to 62	297.5	8.5	70.0	2.0
63 to 64	315.0	9.0	87.5	2.5
65 to 66	315.0	9.0	87.5	2.5
67 to 69	332.5	9.5	87.5	2.5
70 to 73	350.0	10.0	87.5	2.5
74 to 77	367.5	10.5	87.5	2.5
78 to 80	385.0	11.0	105.0	3.0
81 to 84	402.5	11.5	105.0	3.0
85 to 87	420.0	12.0	105.0	3.0
88 to 89	437.5	12.5	105.0	3.0
≥90	437.5	12.5	105.0	3.0

Source: Draft label for fospropofol disodium, NDA 22-244

Note: Doses are rounded to the nearest half-milliliter volume. Actual mg/kg may vary slightly due to the rounding effect.

2.2 Medical Need for Sedation by Non-anesthesiologists

The number of colonoscopies performed in the United States continues to rise so that today, approximately 16 million endoscopic colonoscopies are performed each year. In spite of this, almost 60% of eligible adults have not undergone a colorectal cancer screening procedure (*American Cancer Society, Facts & Figures, 2007*). Reasons cited by patients include fear of the procedure and its associated discomfort.

The ASA has determined that sedation provides benefit to patients undergoing therapeutic and diagnostic procedures. According to the AGA Institute, sedation is intended primarily to reduce a patient's anxiety and discomfort, consequently improving their tolerance and satisfaction for the procedure (*AGA Institute Review of Endoscopic Sedation, 2007*).

As defined by the American Society of Anesthesiologists (ASA) in its “Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists”, sedation/analgesia provides 2 types of benefit: (1) allows patients to tolerate unpleasant procedures by relieving anxiety, discomfort, and pain and (2) expedites the conduct of procedures that are uncomfortable and require no movement in children and uncooperative adults (*ASA*

Task Force on Sedation & Analgesia, 2002). These benefits result in the best possible operating conditions and satisfaction for both the provider and patient.

The most widely used regimen for procedural sedation combines an opioid for analgesia and a benzodiazepine for sedation (*Cohen, 2006*). Midazolam is the most commonly used benzodiazepine because of its amnestic, anxiolytic and sedative properties, as well as shorter elimination half-life when compared to other benzodiazepines (*Reves, 1985*). The disadvantages of using midazolam include the potential for apnea, respiratory depression and respiratory arrest in non-critical care settings; and a prolonged time to clear headed recovery (*Forster, 1979; Morel, 1982; Forster, 1982; Pratilla, 1993; Michalodimitrakis, 1999; Vicari, 2002; Sipe, 2002*).

Propofol lipid emulsion was introduced in the U.S. in 1989 for induction and maintenance of general anesthesia and was labeled for this purpose (*Thompson, 2000*). The advantages include rapid onset of sedation and clear headed recovery. However, IV bolus injection of propofol lipid emulsion produces a rapidly occurring spike in plasma propofol concentration, that can produce a rapid and marked increase in the depth of sedation, enhancing the risk of respiratory depression, apnea, airway obstruction, and oxygen desaturation, as well as cardiovascular effects including hypotension and bradycardia. Further disadvantages of propofol emulsion include pain on injection, risk of bacterial contamination, allergic reaction, and drawbacks inherent to a lipid emulsion formulation including emulsion instability and hyperlipidemia-related side effects (*Baker, 2005*).

Despite these drawbacks and a package insert indicating the requirement for monitored anesthesia care (e.g. the presence of an anesthesiologist), an increasing number of non-anesthesiologists are utilizing propofol in the setting of procedural sedation, in part because of the pharmacologic advantages of propofol over midazolam, including clear headed recovery (*Rex, 2005*).

In a survey of 1,353 gastroenterologists, over 25% report using propofol lipid emulsion for endoscopic procedures (*Cohen, 2006*).

Development of fospropofol disodium was based on the hypothesis that the pharmacokinetic profile of a prodrug (gradual liberation and lower C_{max} of the active moiety) would provide a mechanism by which safety concerns associated with an IV bolus injection of propofol could be reduced with modest effects on time to sedation and awakening. Furthermore, administration of an aqueous solution rather than a lipid emulsion reduces the risks associated with bacterial contamination and eliminates the concern of lipid-related side effects. The clinical development program for fospropofol disodium was undertaken to test these assumptions and to study the safety and efficacy of this propofol prodrug.

2.3 Regulatory History

The Investigational New Drug (IND) application for fospropofol disodium was submitted to the FDA in April 2002. Subsequent to completing a study of fospropofol for sedation in patients undergoing colonoscopy, an End-of-Phase 2 meeting was held on March 31, 2004. Phase 3 studies of sedation in patients undergoing colonoscopy, flexible bronchoscopy, and minor surgical procedures were completed by early 2007, and a pre-NDA meeting was held on January 29, 2007. The NDA was submitted on September 26, 2007.

3. MECHANISM OF ACTION

The primary pharmacodynamic (PD) effect of injectable sedative-hypnotic agents is a dose-dependent depression of the CNS. The widely-accepted mechanism of action for this effect is direct activation of the inhibitory gamma-aminobutyric acid (GABA) neurotransmitter system in the absence of endogenous ligand. For example, propofol interacts principally with targets on the GABA type A (GABA_A) receptor complex. Activation of the GABA_A receptor complex results in increased Cl⁻ conductance and hyperpolarization of the postsynaptic cell membrane, functionally inhibiting the postsynaptic neuron (*Hales TG, 1991*). Propofol also enhances Cl⁻ conduction coupled to central GABAergic synapses and shifts the GABA dose-response curve to the left (*Patten D, 2001*). Importantly, propofol does not bind to the GABA agonist site but at specific sites on the α and β subunits of the GABA receptor complex (*Bali M, 2004*).

4. NON-CLINICAL PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOLOGY

4.1 Toxicology

The potential for toxicity of fospropofol disodium was evaluated in multiple species and in in vitro assays. Specifically, single-dose studies were conducted in mice, rats, dogs and monkeys. Repeated-dose studies including continuous infusion (>24h) and intermittent infusion, were conducted in the rat, dog and monkey. In these studies propofol emulsion was included as a comparator.

Administration of fospropofol disodium was not associated with any specific organ toxicity, and there were no toxicologically-meaningful differences observed between fospropofol disodium and propofol lipid emulsion. Plasma formate concentrations were assayed in several studies in monkeys and dogs. Animals treated with fospropofol

disodium showed no increases in plasma formate concentrations over endogenous levels in these studies. Likewise, measurement of serum phosphate concentrations in rat, dog and monkey toxicity studies did not show any dose-related changes.

Fospropofol disodium was considered non-genotoxic on the basis of an in vitro and in vivo testing battery and was not associated with fertility changes in rats or reproductive developmental toxicity in rats or rabbits. In a multi-generation rat study, treatment of dams through gestation and lactation with fospropofol disodium had no adverse effects on pups, including learning, memory, and reproductive performance.

Safety margins estimated from the ratios of the administered cumulative dosages from single- and repeated-dose animal studies and the anticipated human dosages or exposures support the use of fospropofol disodium as a sedative-hypnotic agent for diagnostic and therapeutic procedures in adult patients.

4.1.1 Nonclinical Pharmacology

The pharmacological profile of fospropofol disodium was evaluated in vitro and in vivo in mice, rats, rabbits, dogs, and monkeys. Where fospropofol disodium and propofol emulsion were evaluated concurrently, either equimolar or equipotent (based on PD) dosages were compared.

In all species, fospropofol disodium produced dose-dependent sedation-hypnosis that was pharmacologically indistinguishable from that of propofol lipid emulsion. Consistent with the expected pharmacodynamic behavior of a prodrug, fospropofol disodium pharmacologic activity was characterized by a more gradual onset and longer duration of sedation than propofol. There were no secondary pharmacodynamic effects of fospropofol disodium and no adverse safety pharmacology findings, including no epileptiform or myoclonic activities, no arrhythmias, and no potential for QT prolongation.

No formal drug interaction studies were conducted with fospropofol disodium. It was demonstrated in a study in dogs that fospropofol disodium did not induce cytochrome P450 (CYP450) enzyme activity. The most significant drug interactions expected to occur following administration of fospropofol disodium are the same as those observed for propofol and these have been well described in the literature.

4.1.2 Nonclinical Pharmacokinetics

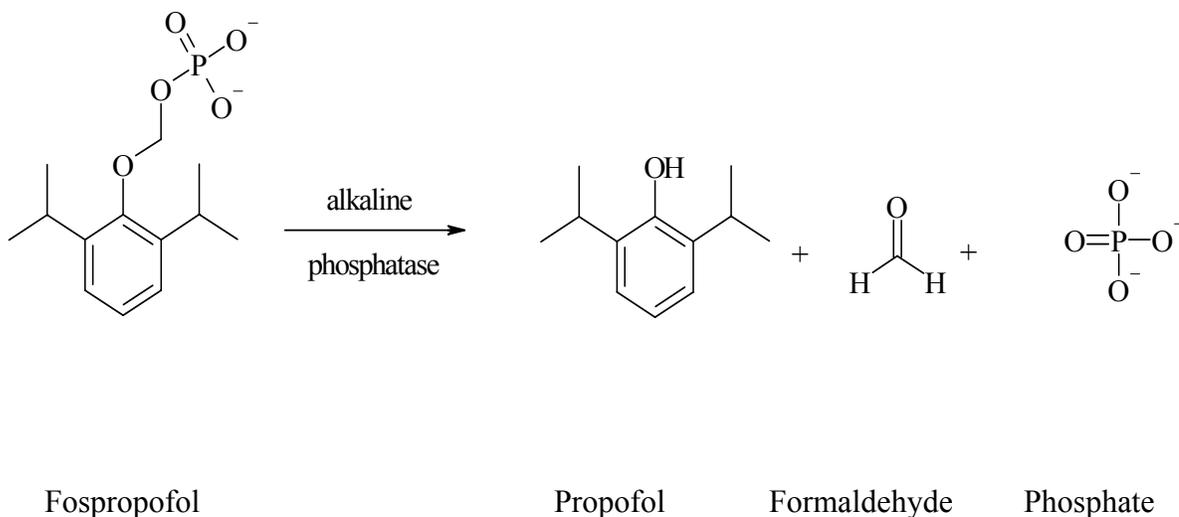
Fospropofol disodium is the water soluble phosphono-O-methyl prodrug of propofol that is enzymatically metabolized by alkaline phosphatases to liberate propofol, phosphate and formaldehyde (Figure 1). In vitro studies demonstrate this metabolism is concentration-independent and is complete. Since these enzymes are widely distributed in the body and are high capacity enzymes, rapid and complete fospropofol metabolism is anticipated in vivo. Formaldehyde is rapidly metabolized to formate by several enzyme systems, including formaldehyde dehydrogenase which is present in various tissues (Pandey, 2000). For every millimole of fospropofol disodium administered, one millimole of propofol is produced (1.86 mg of fospropofol disodium is the molar equivalent of 1 mg propofol). Formate is metabolized to carbon dioxide and water by an enzymatic reaction which is folate dependent (Pandey, 2000) and excess formate that is not utilized metabolically is excreted in the urine (Boeniger, 1987). Phosphate is primarily distributed in extracellular water and is excreted in the urine (Pollak, 2004). Propofol is mainly excreted in the urine after glucuro-conjugation of the parent drug (to form propofol-glucuronide) and sulfo- and glucuro- conjugation of the hydroxylated metabolite to form 4-(2,6-diisopropyl-1,4-quinol)-sulphate, 1-, or 4-(2,6-diisopropyl-1,4-quinol)-glucuronide (Simons, 1988. Favetta. 2002). The subsequent metabolism of propofol after fospropofol disodium administration in humans was characterized through isolation and identification of radiolabeled urinary metabolites and is consistent with metabolic profiles reported in the clinical literature.

In vitro studies with animal and human liver microsomes indicated that CYP450 does not appear to play a significant role in the metabolism of fospropofol.

Radiolabeled distribution studies in the rat demonstrated that fospropofol-derived radioactivity was widely distributed throughout the body including the brain. Total recovery of the administered dose was high (91% in rats, 88% in dogs) and excretion of radioactivity was predominantly via the urinary route. Both fospropofol and propofol are highly protein bound.

Pharmacokinetic studies in rats, rabbits, dogs and monkeys demonstrated that exposure (area under the curve (AUC) and C_{max}) increased with dose and that fospropofol is rapidly eliminated with a short elimination half-life. No evidence of systemic accumulation of fospropofol was observed during multiple dose administrations.

Figure 1 Metabolism of Fospropofol Disodium



5. CLINICAL PHARMACOLOGY

5.1 Clinical Pharmacokinetics

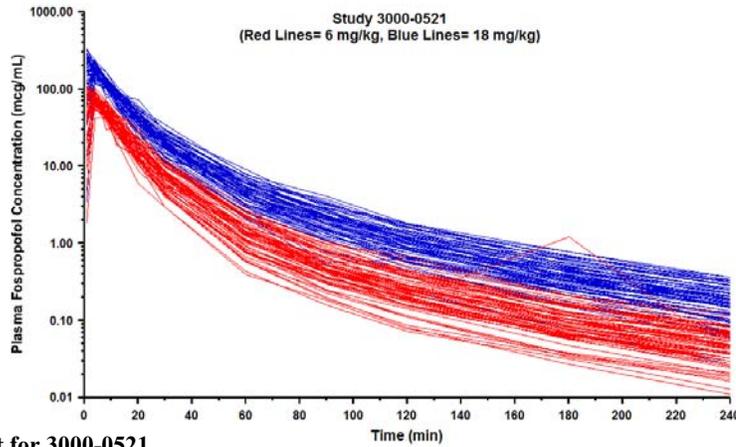
5.1.1 Dose Proportionality

The pharmacokinetics of 6 mg/kg and 18 mg/kg doses of fospropofol were examined in a crossover study in healthy subjects (3000-0521) (Figure 2).

Following bolus injection, mean fospropofol C_{max} values were 78.7 mcg/mL and 211 mcg/mL and mean predicted area under the concentration-time curve from time 0 to infinity (AUC_{0-∞}) values were 19.2 mcg ·h/mL and 50.3 mcg ·h/mL, respectively. The mean ratios of dose-normalized C_{max} and AUC_{0-∞} values for these doses indicated the dose proportional pharmacokinetics of fospropofol. The terminal elimination half-life (T_{1/2}) for fospropofol, 0.81 h, was identical following the 6 mg/kg and 18 mg/kg doses. The plasma concentration of propofol liberated from fospropofol was also examined in this study (Figure 3). The median time to propofol C_{max} was 12.0 min and 8.0 min following the 6 mg/kg and 18 mg/kg fospropofol doses, respectively. Propofol mean C_{max} values were 1.08 mcg/mL and 3.90 mcg/mL, and mean AUC_{0-∞} values were 1.70 mcg ·h/mL and 5.67 mcg ·h/mL, following the 6 mg/kg and 18 mg/kg fospropofol doses, respectively. The apparent mean clearances of propofol liberated from fospropofol

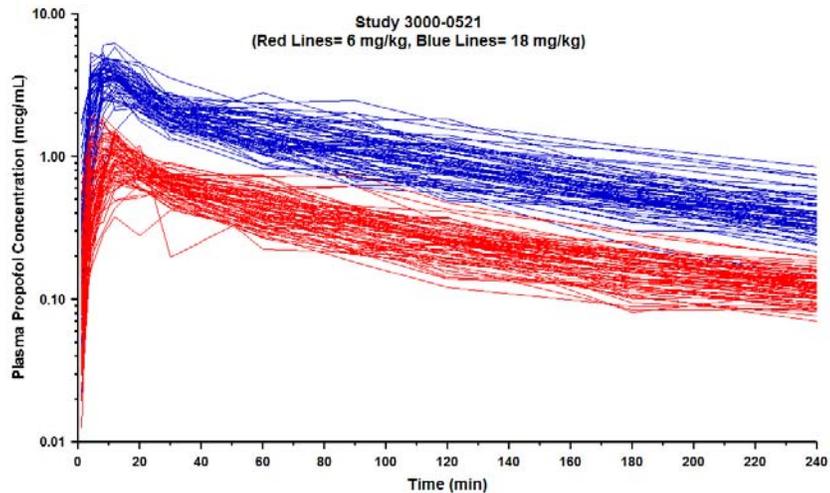
at these doses were similar indicating that the pharmacokinetics of propofol are dose proportional. Propofol terminal elimination half life was similar after the 6 mg/kg and 18 mg/kg fospropofol doses (2.06 h and 1.76 h, respectively).

Figure 2 Plasma Concentrations of Fospropofol for Subjects at 6 mg/kg (N=69) and Subjects at 18 mg/kg (N=68) of Fospropofol Disodium



Source: Study report for 3000-0521

Figure 3 Plasma Concentrations of Propofol Liberated from Fospropofol for Subjects at 6 mg/kg (N=69) and Subjects at 18 mg/kg (N=68) of Fospropofol Disodium



5.1.2 Population PK Characterization in Patients

Population PK modeling for fospropofol (N=667) utilized data from the following studies: 3000-0207, 3000-0415, 3000-0520, 3000-0522, 3000-0523, and 3000-0524; PK modeling for propofol (N=401) liberated from fospropofol utilized data from studies 3000-0522, 3000-0523, and 3000-0524. Findings from this model are described below.

5.1.2.1 Pharmacokinetics

Both fospropofol and propofol PK were found to be approximately dose-proportional and no difference was observed in the PK between patients and healthy subjects. No influences of race, age, or gender (after accounting for body weight) on fospropofol and propofol PK were detected.

No influence of fentanyl dose or exposure on fospropofol and propofol PK was detected. No influences of alkaline phosphatase concentration, total bilirubin concentration, and calculated normalized creatinine clearance on fospropofol and propofol PK were detected.

Fospropofol and propofol clearances were estimated to be 22% and 12% higher for patients with ASA P3 or P4 status compared to those with ASA P1 or P2 status, respectively. Additionally, fospropofol and propofol clearances were estimated to be higher for patients with low albumin concentrations (<3.0 g/dL). The overall effect was faster fospropofol-to-propofol metabolism and a corresponding increase of 25% in propofol C_{max}. The effect of low albumin resulted in a decreased plasma concentration producing a 50% change in the baseline PD response (EC₅₀) value for PK-PD modeling of MOAA/S for fospropofol; however, the observed data from studies 3000-0522 and 3000-0524 indicated that sedation depth based on MOAA/S was not consistently influenced by albumin levels, even when examining results based on age, ASA status, and weight.

5.1.2.2 Weight Bound Dosing

The proposed dose titration regimen was limited by lower and upper weight bounds of 60 kg and 90 kg based on PK modeling. Adults who weigh >90 kg are dosed as if they are 90 kg; and adults who weigh <60 kg are dosed as if they were 60 kg. Upon completion of the clinical program, a post hoc analysis was performed using the

population PK model to estimate maximum plasma propofol concentrations of patients when dosed with fospropofol disodium as if:

- Regimen 1: all patients received a bolus dose of 6.5 mg/kg, regardless of weight
- Regimen 2: the proposed weight boundaries were employed and patients weighing 60 to 90 kg were administered a 6.5 mg/kg bolus dose; patients weighing less than 60 kg were administered a 390 mg bolus dose; patients weighing more than 90 kg were administered a 585 mg bolus dose

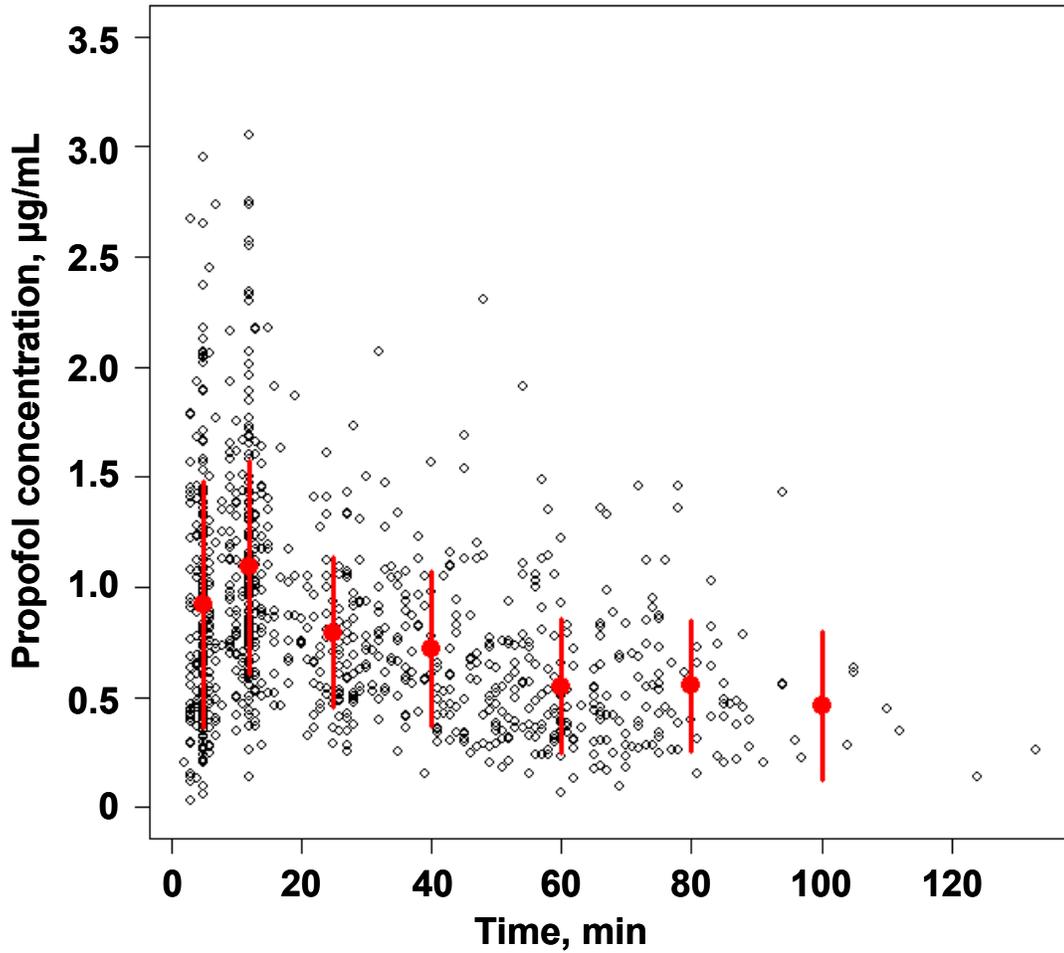
In patients weighing <60 kg, dosing without a weight boundary results in a 8.5% lower C_{max}; while, dosing with the weight boundary results in a 5.1% higher C_{max} than what was observed in patients weighing between 60 to 90 kg. These minimal differences in calculated C_{max} are not considered to be clinically meaningful.

Further supporting the weight bound dosing regimen is the observation from the population PK model that patients weighing <60 kg have higher propofol clearance than patients in the 60 to 90 kg weight range (0.057 and 0.044 L/min/kg, respectively). Therefore, a weight bound dosing regimen normalizes C_{max} values consistent with those observed in the 60 to 90 kg patient group.

Further support for the weight boundary based dosing comes from comparison of the observed and predicted propofol concentrations in patients in the population PK model. The observed propofol concentrations for patients that received the initial 6.5 mg/kg and all supplemental 1.6 mg/kg doses in the 3000-0522, 3000-0523, 3000-0524 studies are presented in Figure 4. Superimposed on these data is a mean and standard deviation (SD) plasma propofol concentration time profiles for these data.

Measured propofol plasma concentrations were less than 2 mcg/mL for 95% of patients in the 3000-0522, 3000-0523, and 3000-0524 studies. The proportion of patients weighing <60 kg (9.3%) was similar to the proportion of patients weighing 60-90 kg (7.2%) who had propofol plasma concentrations greater than 2 mcg/mL. These data demonstrate the proposed dose titration regimen predictably produces plasma propofol concentrations associated with minimal to moderate levels of sedation ([Appendix A](#), [Table 12-A](#), and [Figure 1-A](#)).

Figure 4 Observed Plasma Propofol Concentration (mean (•) ± SD) from Patients in Studies 3000-522, 3000-523, 3000-524 (N = 401)



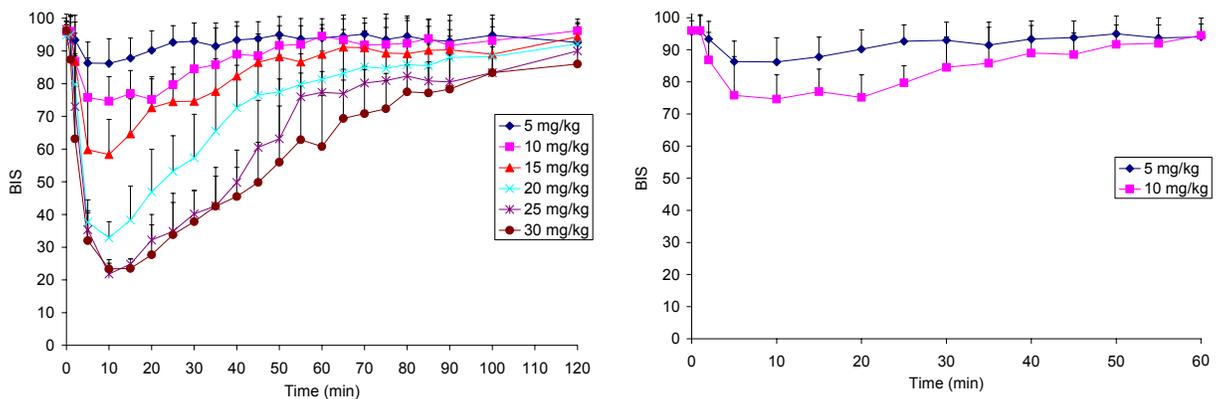
Source: Module 5.3.3.5 in PR-AQUA-02-02, NDA, mean and SD added post hoc

5.2 Clinical Pharmacodynamics

Fospropofol bolus dosing in healthy subjects produced dose-dependent depth and duration of sedation as measured by bispectral (BIS) index scores.

Healthy subjects (n=36, 6/dose group) received a bolus injection of 1 of 6 dose levels of fospropofol disodium, (5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg and 30 mg/kg) and BIS scores were measured (study 3000-0103). Fospropofol disodium dosing at 5 mg/kg and 10 mg/kg produced minimum BIS scores that were consistent with minimal to moderate sedation, while doses of 25 mg/kg and 30 mg/kg induced minimum BIS scores indicative of general anesthesia. Regardless of dose, all patients reached a minimal BIS score at similar times. Subjects sedated by the 5 and 10 mg/kg doses recover rapidly (Figure 5 5, right panel) compared to sedation produced by the higher doses (Figure 5, left panel).

Figure 5 Dose Related PD for Fospropofol Dosing (Mean \pm SD)



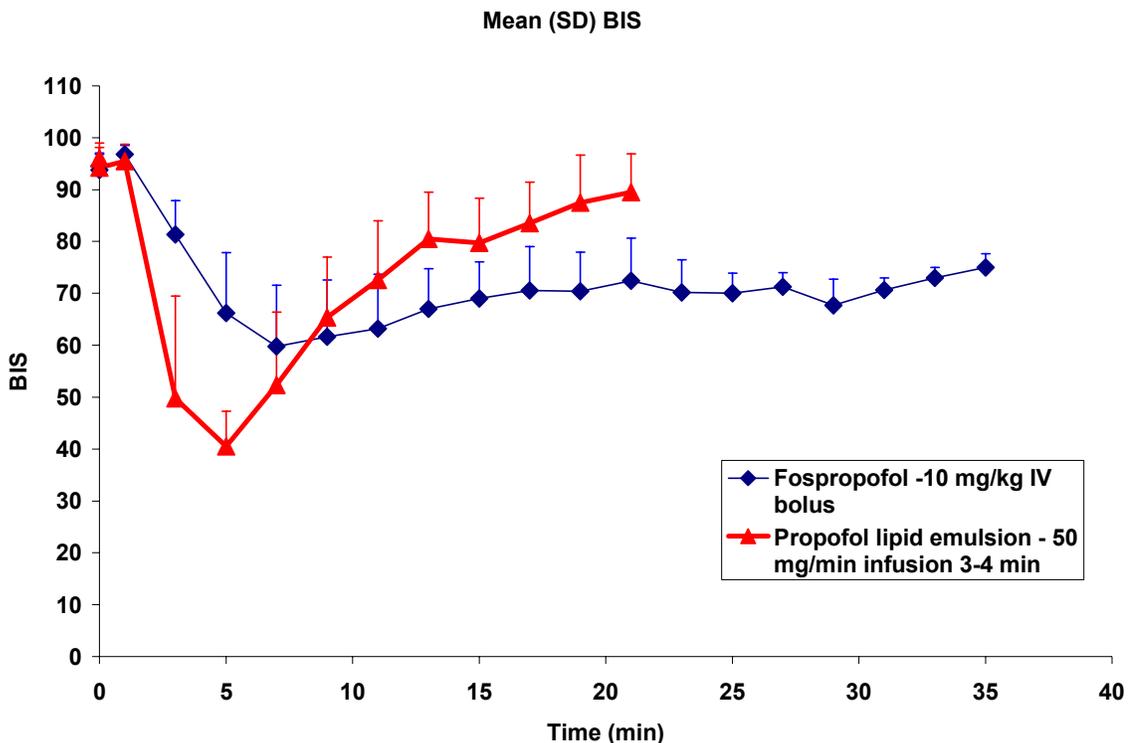
Source: Study 3000-0103

A second study compared the PD of fospropofol disodium and propofol emulsion in 12 healthy subjects (study 3000-0625). Subjects received a 10 mg/kg bolus IV dose of fospropofol disodium and the minimal BIS score was recorded. After a 7-day washout period, subjects received a 50 mg/min infusion of propofol lipid emulsion targeted to produce the same peak electroencephalogram (EEG) effect that was observed in that subject after administration of the fospropofol disodium. Subjects treated with fospropofol disodium reached a mean minimum BIS score of 54.0 (range: 40-69) at a mean of 8.2 min (range: 5-17) following study drug administration. Subjects treated with propofol lipid emulsion reached a mean minimum BIS score of 37.7 (range: 25-51) at a mean of 4.7 min (range: 3-7) after the start of the infusion (Figure 6). While the study

was intended to match sedation levels in both study periods, the deeper level of sedation achieved in the propofol lipid emulsion treated group highlights the technical expertise required to manage depth of sedation when propofol is delivered directly as an emulsion by rapid infusion.

Sedation levels were sustained for longer times following dosing with fospropofol disodium versus propofol lipid emulsion. The longer sedative effect can be explained by the observation that this treatment delivered a greater mean dose of propofol than the infusion of propofol lipid emulsion (2.102 millimoles [mmoles] [propofol mean dose delivered from fospropofol disodium: 5.36 mg/kg]) versus 0.906 mmoles [propofol mean dose administered from propofol lipid emulsion, 2.3 mg/kg]).

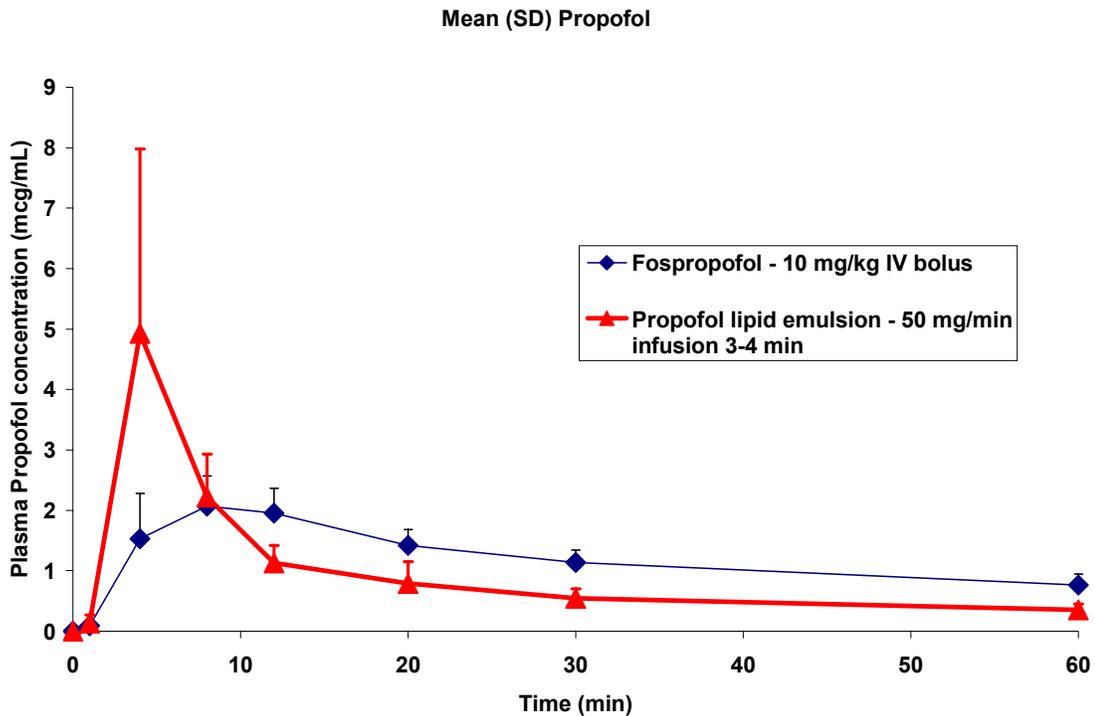
Figure 6 BIS Index Following Treatment of Healthy Subjects with Fospropofol IV Bolus vs Infusion of Propofol Lipid Emulsion (N = 12)



Source: Study 3000-0625

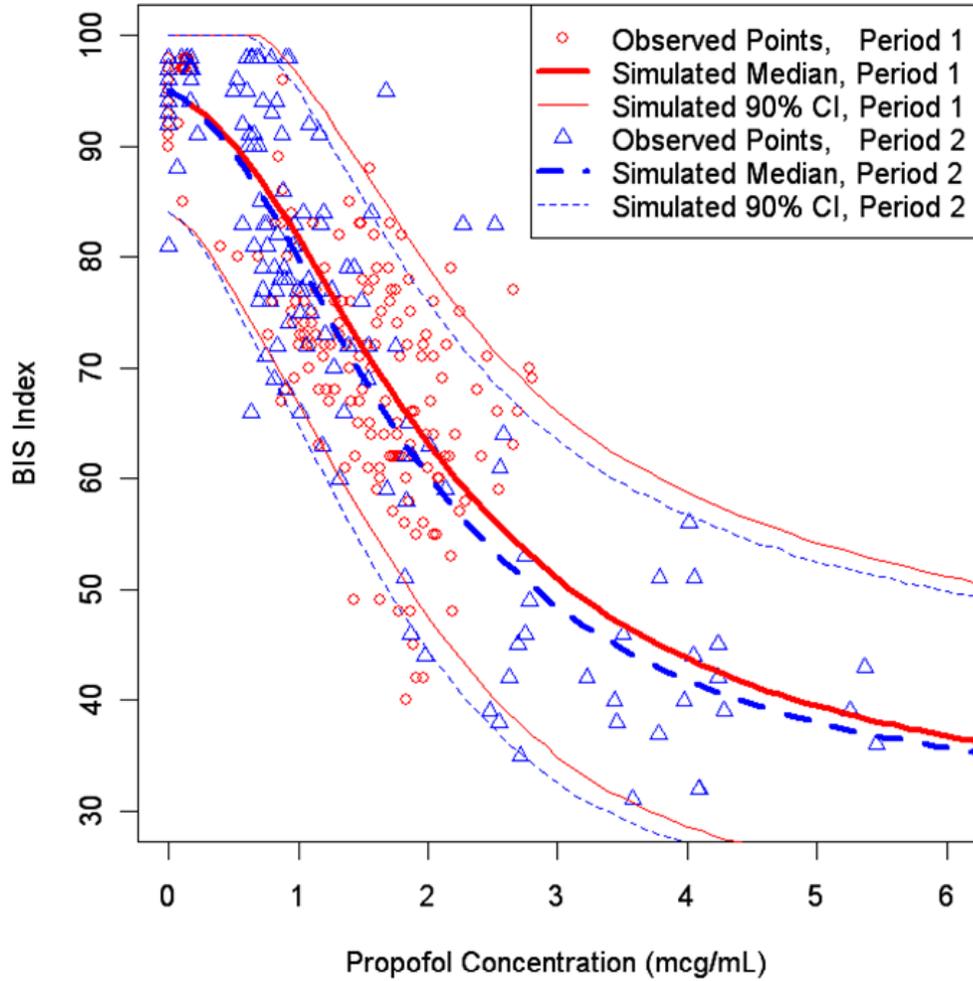
The propofol median time to maximum concentration (T_{max}) was reached at a later time following administration of a single bolus dose of fospropofol disodium (8 min, range: 4-13 min) than following administration of propofol lipid emulsion (4 min, range: 4-8 min). In addition, the mean propofol C_{max} (2.20 mcg/mL) was lower and mean AUC (3.07 mcg ·h/mL) was higher following administration of fospropofol disodium compared to propofol lipid emulsion (5.16 mcg/mL and 1.72 mcg ·h/mL, respectively) (Figure 7). The higher propofol AUC following fospropofol disodium dosing is due to the greater propofol dose derived from fospropofol disodium treatment as compared to the propofol lipid emulsion treatment. Apparent total body clearance (CL_{p/F}) for propofol was slightly higher following fospropofol disodium treatment (1.79 L/h/kg) than total body clearance following administration of propofol lipid emulsion (1.38 L/h/kg), which suggests that the conversion of fospropofol was almost complete.

Figure 7 Mean (±SD) Propofol Plasma Concentration Profiles for Fospropofol disodium 10 mg/kg and Propofol Lipid Emulsion 50 mg/minute



The time-matched, BIS index –propofol concentration pairs derived from both fospropofol disodium and propofol lipid emulsion dosing in study 3000-0625 were used in PK-PD modeling evaluations. The simulated median curves for both treatments are superimposable, indicating that the pharmacologic activity of propofol is independent of whether it is liberated from fospropofol or delivered from propofol emulsion (Figure 8).

Figure 8 PK-PD Modeling of BIS Index versus Propofol Concentration: Comparison of Model Simulations and Observed Data, Period 1 (Fospropofol disodium) and Period 2 (Propofol Lipid Emulsion)



Source: Module 5.3.3.5 in PR-AQUA-02-01, Figure 34, NDA

6. CLINICAL DEVELOPMENT PROGRAM

The clinical program for fospropofol disodium includes 21 studies ([Table 3](#)): 12 studies in patients and 9 studies in healthy subjects. A total of 1611 patients were exposed to fospropofol disodium. A total of ten studies examined the use of fospropofol disodium for sedation in procedures, such as colonoscopy (N = 750 patients), flexible bronchoscopy (N = 292 patients), and minor surgical procedures (N = 250 patients). Two studies examined the use of fospropofol disodium for prolonged sedation in intubated and mechanically ventilated patients (N = 46 patients; [Appendix B, Table 1-B](#)).

The original goal in the early development stages of fospropofol disodium (studies 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415) was to identify a dose at which a single IV bolus administration could achieve and maintain the desired level of sedation for the majority of patients. Thus, studies conducted in the initial clinical development used a relatively high, fixed dose regimen in which the same dose, in milligrams (mg) was administered to all patients who fell within a broad weight range and the data showed that a single IV dose of between 10 and 12.5 mg/kg sedated the majority of patients (study 3000-0207). However, results of subsequent series of studies (3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415) indicated that this regimen led several patients to inappropriate levels of sedation. This observation led to the development of a revised dose titration regimen that would sedate the majority of patients while minimizing the number of patients reaching deep sedation. The individualization was based on weight, age and health status and titration to the desired effect, a practice currently used by proceduralists with commercially available sedative agents.

In the phase 2 study (3000-0520) and in the phase 3 pivotal studies (3000-0522 and 3000-524), as well as an open-label safety study (3000-0523), the goal was to provide predictable and titratable sedation, avoid the use of alternative sedative agents, such as midazolam, and minimize the likelihood of reaching deep levels of sedation thought to be associated with an increased risk for requiring advanced airway assistance.

Two populations (colonoscopy and flexible bronchoscopy) were chosen for the randomized, double blind, controlled studies. A large number of relatively healthy patients undergo colonoscopies each year; whereas, patients undergoing bronchoscopy are generally less healthy and are usually receiving a diagnostic procedure for conditions such as chronic obstructive pulmonary disease (COPD), lung masses, infections, and cancer. The bronchoscopy patients are typically older than those undergoing colonoscopy, have more underlying illnesses, and are taking multiple concomitant medications. Patients undergoing bronchoscopy differ in their position during sedation

and the level of stimulation experienced during the procedure. During the procedure the airway is shared with the bronchoscope. All of these factors were expected to influence the observed AE and SRAE profiles.

In summary, study of fospropofol disodium in these 2 populations provided an opportunity to examine safety and efficacy in patient populations with a broad spectrum of baseline characteristics. The program was therefore expected to provide data representative of the patient population expected to receive the drug upon regulatory approval.

6.1 Clinical Studies

A list of the studies included in the development program for fospropofol is included in [Table 3](#).

Table 3 Fospropofol Disodium Clinical Development Program

Study Number / (No. of Fospropofol- Treated Subjects)	Colonoscopy, Bronchoscopy or Minor Procedure	Adequate and Well- Controlled	Double- Blind	Randomized	Dose- or Active- Controlled
Studies Conducted in Patients					
Pivotal, Adequate, Well-controlled, Double-Blind, studies					
3000-0520 (101)	Colonoscopy	X	X	X	X
3000-0522 (260)	Colonoscopy	X	X	X	X
3000-0524 (252)	Bronchoscopy	X	X	X	X
Open-label Supportive Studies					
3000-0207 (164)	Colonoscopy			X	
3000-0523 (123)	Minor procedure				
Open-label Fixed-dose, Supportive Studies					
3000-0409 (40)	Bronchoscopy			X	X
3000-0410 (210)	Colonoscopy			X	X
3000-0411 (6)	Minor procedure			X	X
3000-0412 (121)	Minor procedure			X	X
3000-0415 (15)	Colonoscopy			X	X
Prolonged Treatment Duration Studies in Intubated and Mechanically Ventilated Patients					
3000-0104 (8)	Other			X	X
3000-0413 (38)	Other			X	X
Studies Conducted in Healthy Subjects					
Clinical Pharmacology Studies					
3000-0001 (12)	NA				
3000-0102 (12)	NA				
3000-0103 (36)	NA				
3000-0205 (8)	NA				
3000-0206 (54)	NA			X	
3000-0308 (10)	NA				
3000-0414 (60)	NA		X	X	
3000-0521 (69)	NA			X	
3000-0625 (12)	NA			X	X
Total N = 1611					

Source: Module 5.3.5.3, Table 70

6.1.1 Study Design for Phase 2 and Phase 3 Studies

The 3 controlled studies evaluating the fospropofol disodium proposed dose titration regimen include the phase 2 dose ranging study, 3000-0520, in patients undergoing colonoscopy and the phase 3 pivotal studies, 3000-0522 (colonoscopy) and 3000-0524 (flexible bronchoscopy). An open label study was conducted in patients undergoing minor surgical procedures (study 3000-0523).

6.1.1.1 Randomization and Dosing with Study Sedative

Patients in study 3000-0520 were randomized to one of the following 5 groups in a 1:1:1:1:1 ratio including 4 dose levels of fospropofol disodium (8.0 mg/kg, 6.5 mg/kg, 5.0 mg/kg, 2.0 mg/kg) and midazolam 0.02 mg/kg. Patients in study 3000-0522 were randomized to one of the following 3 groups in a 3:2:1 ratio: fospropofol disodium 6.5 mg/kg; fospropofol disodium 2.0 mg/kg; and midazolam 0.02 mg/kg, respectively. Patients in study 3000-0524 were randomized to one of the following 2 groups in a 3:2 ratio: fospropofol disodium 6.5 mg/kg and 2.0 mg/kg, respectively (Table 4).

6.1.1.2 Blinding

All patients and study site personnel, except the study pharmacist or designee preparing the study medications, were blinded to study treatments in the randomized, double-blind, controlled studies. The occurrence of paresthesias and/or pruritus in fospropofol treated patients is not dose-related. Therefore, inclusion of a low dose fospropofol disodium control group was essential for maintaining the blind between the treatment groups. The frequency of paresthesias and/or pruritus differs between populations treated with midazolam and fospropofol disodium so the blind may not have been maintained between these groups.

6.1.1.3 Treatments Administered

Oxygen

All patients in studies 3000-0520, 3000-0522, 3000-0523, and 3000-0524 received supplemental oxygen, nasally (4 L/min), throughout the dosing period and until the patient met the criteria for Ready for Discharge.

Analgesic Pretreatment

All patients in studies 3000-0520, 3000-0522, 3000-0523, and 3000-0524, received fentanyl at an initial dose of 50 mcg as analgesic pretreatment 5 minutes prior to administration of the initial dose of study sedative medication. If the patient was experiencing pain during the procedure, 1 additional dose of 25 mcg of fentanyl was allowed per protocol. At least 10 minutes were to have elapsed between the initial fentanyl dose and the single additional fentanyl dose allowed per protocol. Sites were instructed that if additional analgesic medication was required, only fentanyl 0.5 mcg/kg (not to exceed 50 mcg) was to be administered.

In study 3000-0524, lidocaine was administered as a topical anesthetic for suppression of cough upon the introduction of the flexible bronchoscope. The recommended dose for this study was ≤ 300 mg, or ≤ 4.5 mg/kg (whichever was less on a per patient basis), per procedure. Lidocaine was not administered to patients in the colonoscopy or minor surgical procedures studies.

Study Drug

Table 4 Dosing Regimen in Phase 3 Pivotal Studies (3000-0522 and 3000-0524)

Dosing Group ²	Sedation Initiation ¹		Sedation Maintenance
	Initial Bolus ³	Supplemental Dose ^{3, 4}	Dose
Fospropofol disodium 2.0 mg/kg	2.0 mg/kg No less than 120 mg. No more than 180 mg.	0.5 mg/kg No less than 30 mg. No more than 45 mg.	0.5 mg/kg No less than 30 mg. No more than 45 mg.
Fospropofol disodium 6.5 mg/kg	6.5 mg/kg No less than 390 mg. No more than 585 mg.	1.6 mg/kg No less than 97.5 mg. No more than 146 mg.	1.6 mg/kg No less than 97.5 mg. No more than 146 mg.
Midazolam ⁵	0.02 mg/kg Not to exceed 2.5 mg.	1.0 mg	1.0 mg

¹ Initial dose of study sedative administered 5 minutes after fentanyl administration

² The lower and upper dosing limits were based on a weight boundary of <60 kg or >90 kg.

³ Patients who were ≥ 65 years of age or ASA P4 (or P3 at the discretion of the Investigator) received doses that were 75% of the proposed standar dose.

⁴ In the Sedation Initiation phase, supplemental doses were administered only as required to reach a Modified OAA/S score of ≤ 4 and to start the procedure.

⁵ Midazolam was included only in the 3000-0522 study.

Source: Study 3000-0522, Protocol, Section 6, page 420

In the Sedation Initiation phase, an initial bolus dose and up to 3 supplemental doses were available to initiate sedation. Supplemental doses were to be administered no more

frequently than every 4 min and only as required to reach a MOAA/S scale score of ≤ 4 and to allow the Investigator to start the procedure (Table 5). If more than 3 supplemental doses were necessary to start the procedure, an alternative sedative medication could be administered per the site's standard of care and the patient was considered a sedation failure. Alternate sedative/analgesic medications were not to be administered unless sedation failure had been reached.

Supplemental doses of study sedative could be administered no more frequently than every 4 minutes. Supplemental doses were only to be administered in the Sedation Initiation phase if the patient's MOAA/S score (Table 5) was 5 and the patient could demonstrate a purposeful response. After the procedure was initiated, supplemental doses were only to be administered in the Sedation Maintenance phase if the patient's MOAA/S score was 4 or 5 and the patient could demonstrate a purposeful response.

Control Treatment

An active control (low dose, 2.0 mg/kg fospropofol disodium) was included in the phase 3 studies and this served 2 purposes: 1) provided a manner in which a blind could be established between the treatment arms given that the incidence of paresthesia and/or pruritus in patients receiving fospropofol disodium is frequent and not dose related, 2) provided dose response data for further analysis and confirmation of the efficacy of the proposed fospropofol disodium dosing regimen

A midazolam arm was included in studies 3000-0520 and 3000-0522 to provide a measure of the sensitivity of the tools used to determine sedation (MOAA/S scale) and clinical benefit (e.g., patient and physician questionnaires). Discussions with the FDA led to the inclusion of a midazolam arm in a single pivotal study (3000-0522).

6.1.1.4 Patient Population

Inclusion and exclusion criteria for the studies were designed to allow entry of a diverse patient population. Patients ≥ 18 years of age and an ASA status of P1 through P4 were eligible for the study. Patients were excluded from these studies if they had a Mallampati Classification Score of 4; or a Mallampati Classification Score of 3 and a thyromental distance ≤ 4 cm; or for any other reason had a difficult airway or at-risk airway based upon the opinion of the Investigator; if they had clinically significant abnormal electrocardiogram results at screening; or if they had known allergies to anesthetic agents, narcotics, or benzodiazepines.

6.1.1.5 Depth of Sedation

Throughout the clinical program, sedation was evaluated using the MOAA/S scale, a widely used, accurate, and reliable measure for the depth of sedation (Table 5). MOAA/S score was measured every 2 minutes, beginning one minute prior to fentanyl administration and continuing until the patient was Fully Alert (defined as 3 consecutive MOAA/S scores of 5) beginning at or after the end of the procedure.

Table 5 Responsiveness Scores of the MOAA/S Scale

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Source: *Chernik, 1990; Degoute, 2001*

The primary efficacy endpoint, Sedation Success, was a composite endpoint that included both efficacy and safety parameters. It measured the ability of the drug to effectively sedate patients, in a manner that did not require advanced airway maneuvers, including manual (bag valve mask) or mechanical ventilation. Specifically, the endpoint was defined as a patient meeting all of the following criteria:

- (1) having 3 consecutive MOAA/S scores of ≤ 4 after administration of sedative medication,
- (2) completing the procedure,
- (3) without requiring the use of alternative sedative medication (such as midazolam) and,
- (4) without requiring manual or mechanical ventilation.

Patients who have less discomfort with a procedure are more likely to return for necessary screening procedures in the future. Sedation improves patient tolerance during the procedure itself and compliance with screening and follow-up procedures (*Kuznets, 2002; Weston, 2003*). Therefore, secondary endpoints represented measures of clinical benefit including:

- (1) Proportion of patients who experienced Treatment Success, defined as a patient:
 - a) completing the procedure,
 - b) without requiring alternative sedative medications and
 - c) without requiring manual or mechanical ventilation.
- (2) Proportion of patients requiring Supplemental Analgesic medication.
- (3) Proportion of patients who did Not Recall Being Awake during the procedure as determined by patient survey questionnaire.
- (4) Proportion of patients Willing to be Treated Again with the same study sedative agent as determined by patient survey questionnaire.

The endpoint, “proportion of patients requiring Supplemental Analgesic medication,” was a tertiary endpoint in study 3000-0524 because minimal pain is associated with bronchoscopy.

Other endpoints included: (1) Number of analgesic doses administered; (2) Number of supplemental doses of study sedative medication administered; (3) Time to Fully Alert, defined as 3 consecutive responses to their name spoken in a normal tone, measured every 2 minutes, beginning at or after the end of the procedure; (4) Time to Ready for Discharge, defined as an Aldrete Discharge Criteria score of 9 or greater; and (5) Percent retention score on the Hopkins Verbal Learning Test-RevisedTM (HVLTR) (*Aldrete, 1970; Benedict, 1998*).

6.1.1.6 Prespecified Plans for Analysis

For the primary endpoint, the number and proportion of patients who met the criteria for Sedation Success were calculated by treatment group. A 95% confidence interval for the Sedation Success rate was calculated for each treatment group and a 95% confidence interval for the between-group difference was provided. The p-values for the between-group differences were calculated using the Fisher’s exact test. Secondary efficacy endpoints were also analyzed using the Fisher’s exact test. The statistical tests were performed in a hierarchical order, i.e., the test proceeded only if all the endpoints in the top hierarchy were statistically significant at $\alpha=0.05$ level. In addition, 95% confidence interval (CI) for the proportion of patients reaching the endpoint by treatment group and for the difference in proportions between treatment groups were calculated for each endpoint.

Analysis Populations

For analyses of efficacy endpoints, the primary analyses were based on the modified Intent-to-treat (mITT) population ie, defined as all patients who received at least one dose of study sedative medication and had at least 1 post-dose observation recorded. Patients were analyzed according to the study drug to which they were randomized.

The safety population included all randomized patients who received at least 1 dose of study sedative medication. Patients were analyzed according to the study drug they received. If a patient received both fospropofol disodium and midazolam, this patient was analyzed as if s/he was in the fospropofol disodium arm.

7. CLINICAL EFFICACY

Collectively, the results of the phase 2 dose ranging and the phase 3 pivotal studies present the most relevant data set for demonstrating the effectiveness of the proposed fospropofol disodium dose titration regimen in providing effective sedation for patients (e.g. avoids the use of rescue with alternative sedatives such as midazolam) while avoiding more advanced airway manipulations such as manual and mechanical ventilation. Overall, the data demonstrate that patients treated with the proposed fospropofol dose titration regimen experienced effective sedation and measures of clinical benefit were achieved with fewer supplemental doses of fospropofol disodium and decreased need for alternative sedative medication.

7.1 Efficacy Results

7.1.1 Phase 2 Dose-Response Study 3000-0520

Study 3000-0520 was a dose-response study designed to assess the efficacy and safety of the proposed dose titration regimen and to identify the initial dose of fospropofol disodium that provided for the optimal safety/efficacy ratio. The primary efficacy endpoint for this study was Sedation Success. A highly significant dose-dependent trend in Sedation Success was observed across fospropofol disodium dosing groups in the mITT population (Table 6; $p < 0.001$ by Cochran-Armitage trend test).

Table 6 Sedation Success For All Dose Groups (Study 3000-0520)

	Sedation Success n (%)	95% Confidence Interval¹ of Sedation Success Rate (%)	p- value²
Fospropofol 2 mg/kg (N=25)	6 (24.0)	(9.4, 45.1)	
Fospropofol 5 mg/kg (N=26)	9 (34.6)	(17.2, 55.7)	
Fospropofol 6.5mg/kg (N=26)	18 (69.2)	(48.2, 85.7)	
Fospropofol 8 mg/kg (N=24)	23 (95.8)	(78.9, 99.9)	
Midazolam 0.02 mg/kg (N=26)	21 (80.8)	(60.6, 93.4)	
Test for dose-dependent trend over fospropofol dosing groups.			<0.001
Comparisons of Sedation Success rates	Difference in Sedation Success Rates (%)	95% Confidence Interval of Difference (%)	p- value³
Fospropofol 8 mg/kg – 2 mg/kg	71.8	(53.3, 90.4)	<0.001
Fospropofol 6.5 mg/kg – 2 mg/kg	45.2	(20.8, 69.6)	0.002
Fospropofol 5 mg/kg – 2 mg/kg	10.6	(-14.2, 35.4)	0.541

¹The 95% confidence interval is an exact computation.

²p-value from exact Cochran-Armitage test for trend in Sedation Success rate across the 4 different fospropofol dosing groups.

³p-value from Fisher's exact test for pairwise comparisons between groups

Source data: Study 3000-0520 Table 2.1.1 (Section 14.2)

Twenty-five percent of patients in the 8 mg/kg group reached a deep level of sedation. In contrast, only a single patient (3.8%) in the 6.5 mg/kg group had a MOAA/S score of ≤ 1 (Table 7).

On balance, the strong efficacy data coupled with a low incidence of SRAEs and deep sedation events indicated that an initial dose of 6.5 mg/kg of fospropofol disodium was the optimal treatment regimen of the 4 doses tested.

Table 7 Patients Who Had MOAA/S of 0 or 1 (3000-0520)

	Fospropofol 2 mg/kg N=25	Fospropofol 5 mg/kg N=26	Fospropofol 6.5 mg/kg N=26	Fospropofol 8 mg/kg N=24	Midazolam 0.02 mg/kg N=26
	Number and Percent (%) of Patients				
At any time	2 (8.0)	1 (3.8)	1 (3.8)	6 (25.0)	1 (3.8)
For ≥5 minutes	0	1 (3.8)	0	2 (8.3)	0

Source data: Study 3000-0520 Table 2.13.4 (Section 14.2)

7.1.2 Phase 3 Pivotal Studies 3000-0522 and 3000-0524

7.1.2.1 Populations Analyzed

The number of patients in the mITT and safety populations by treatment group for studies 3000-0522 and 3000-0524 are summarized in [Table 8](#) below.

Table 8 Populations Analyzed (3000-0522, 3000-0524)

	Fospropofol 2.0 mg/kg	Fospropofol 6.5 mg/kg	Midazolam 0.02 mg/kg	All
3000-0522 Colonoscopy	Number of Patients			
Patients randomized	102	160	52	314
mITT population ¹	102	158	52	312
Safety population	102	158	52	312
3000-0524 Bronchoscopy	Number of Patients			
Patients randomized	103	153	—	253
mITT population ²	102	150	—	252
Safety population ³	103	149	—	252

¹In study 3000-0522, two patients randomized to the 6.5 mg/kg fospropofol disodium group did not receive study drug. One discontinued after experiencing AEs of facial rash, pruritus, and warmth and another discontinued due to inadequate bowel preparation.

²In study 3000-0524, one patient randomized to 2.0 mg/kg fospropofol disodium group and 3 patients randomized to the 6.5 mg/kg fospropofol disodium group did not receive study drug. Reasons for discontinuation were procedure canceled due to abnormal laboratory test results in the 2.0 mg/kg group; and patient not dosed, invalid consent, and bronchoscopy cancellation due to symptom resolution in the 6.5 mg/kg group.

³In study 3000-0524, of the 252 who received study drug, one patient who was randomized to the fospropofol disodium 6.5 mg/kg group actually received 2.0 mg/kg. Based on the population definitions, this patient was included in the fospropofol 6.5 mg/kg group for mITT analyses and was included in the 2.0 mg/kg group for safety analyses.

Source data: Study 3000-0522 Table 1.4 (Section 14.1) and Study 3000-0524 Table 1.4 (Section 14.1)

7.1.2.2 Demographics

Demographics and baseline characteristics by treatment group in the mITT population for studies 3000-0522 and 3000-0524, are summarized in [Table 10](#) and [Table 11](#), respectively. Overall, the percentage of patients ≥ 65 years of age and the percentage of ASA P3 or P4 patients was higher in the bronchoscopy study ([Table 10](#) and [Table 11](#)). The ASA status for a patient was assigned by the Investigator according to the ASA criteria ([Table 9](#)).

Table 9 Criteria for ASA Disease Classification

ASA P1	No known systemic disease-no physical or psychological disturbances
ASA P2	Mild systemic disease - asthma, obesity, diabetes mellitus
ASA P3	Severe systemic disease - cardiovascular disease that limits activity; severe diabetes with systemic complications
ASA P4	Systemic disease that is a constant threat to life - myocardial infarction or cerebrovascular accident within the last 6 mo; severe congestive heart failure or chronic obstructive pulmonary disease, diabetes

Source: American Society of Anesthesiologists, [ASA Relative Value Guide, 1999](#)

As per the protocol, a modified dose (75% of the standard dose) was to be administered to ASA P4 patients ≥ 65 years of age. Per protocol, Investigators were permitted to administer the modified dosing regimen (75% of the standard dose) to ASA P3 patients at their own discretion. Of the 106 ASA P3 patients in the randomized, double-blind, controlled studies (3000-0520, 3000-0522, and 3000-0524), 61 (57.5%) patients received a reduced dose of fospropofol disodium based on Investigator discretion.

Table 10 Demographics and Baseline Characteristics (Study 3000-0522, Colonoscopy [mITT Population])

	Fospropofol 2.0 mg/kg N=102	Fospropofol 6.5 mg/kg N=158	Midazolam 0.02 mg/kg N=52	All N=312
Age (years)				
Mean	52.4	52.9	54.0	52.9
Standard deviation	11.1	11.8	10.9	11.4
Range (min, max)	19, 76	18, 85	25, 79	18, 85
Age group¹, n (%)				
18-64 years	88 (86.3)	137 (86.7)	42 (80.8)	267 (85.6)
≥65 years	14 (13.7)	21 (13.3)	10 (19.2)	45 (14.4)
≥75 years	1 (1.0)	4 (2.5)	1 (1.9)	6 (1.9)
Sex, n (%)				
Male	46 (45.1)	76 (48.1)	34 (65.4)	156 (50.0)
Female	56 (54.9)	82 (51.9)	18 (34.6)	156 (50.0)
Race, n (%)				
White	69 (67.6)	133 (84.2)	43 (82.7)	245 (78.5)
Black	20 (19.6)	11 (7.0)	6 (11.5)	37 (11.9)
Asian	3 (2.9)	3 (1.9)	1 (1.9)	7 (2.2)
Hispanic/Latino	9 (8.8)	11 (7.0)	2 (3.8)	22 (7.1)
Other	1 (1.0)	0	0	1 (0.3)
Weight group, n (%)				
<60 kg	13 (12.7)	9 (5.7)	4 (7.7)	26 (8.3)
60-<90 kg	56 (54.9)	86 (54.4)	31 (59.6)	173 (55.4)
≥90 kg	33 (32.4)	63 (39.9)	17 (32.7)	113 (36.2)
ASA status, n (%)				
P1	27 (26.5)	54 (34.2)	17 (32.7)	98 (31.4)
P2	71 (69.6)	99 (62.7)	32 (61.5)	202 (64.7)
P3	4 (3.9)	5 (3.2)	3 (5.8)	12 (3.8)
P4	0	0	0	0
Sedation history, n (%)				
Yes, with adverse reaction	3 (2.9)	3 (1.9)	1 (1.9)	7 (2.2)
Yes, without adverse reaction	94 (92.2)	149 (94.3)	49 (94.2)	292 (93.6)
No sedation history	5 (4.9)	6 (3.8)	2 (3.8)	13 (4.2)
Dose of study drug, n (%)				
Standard dose	89 (87.3)	136 (86.1)	42 (80.8)	267 (85.6)
Dose reduced by 25% ²	13 (12.7)	22 (13.9)	10 (19.2)	45 (14.4)

¹Age ≥75 is also included in ≥65.

²Patients who were ≥65 years of age or had an ASA status of P4 were to receive initial and supplemental doses of study medication that was 75% of the standard dose. Patients who had an ASA status of P3 may also have received initial and supplemental reduced doses, if the Investigator deemed necessary.

Source data: Study Report for 3000-0522, Table 1.5 (Section 14.1)

Table 11 Demographics and Baseline Characteristics(Study 3000-0524, Bronchoscopy [mITT Population])

	Fospropofol 2.0 mg/kg N=102	Fospropofol 6.5 mg/kg N=150	Overall N=252
Age (years)			
Mean	60.1	60.8	60.5
Standard deviation	14.1	12.7	13.3
Range (min, max)	22, 84	25, 83	22, 84
Age group ¹ , n (%)			
18 to 64 years	60 (58.8)	89 (59.3)	149 (59.1)
≥ 65 years	42 (41.2)	61 (40.7)	103 (40.9)
≥ 75 years	18 (17.6)	19 (12.7)	37 (14.7)
Gender, n (%)			
Male	54 (52.9)	86 (57.3)	140 (55.6)
Female	48 (47.1)	64 (42.7)	112 (44.4)
Race, n (%)			
White	84 (82.4)	130 (86.7)	214 (84.9)
Black	14 (13.7)	16 (10.7)	30 (11.9)
Asian	0	1 (0.7)	1 (0.4)
Hispanic/Latino	3 (2.9)	3 (2.0)	6 (2.4)
Other	1 (1.0)	0	1 (0.4)
Weight group, n (%)			
<60 kg	19 (18.6)	27 (18.0)	46 (18.3)
60 to <90 kg	51 (50.0)	81 (54.0)	132 (52.4)
≥ 90 kg	32 (31.4)	42 (28.0)	74 (29.4)
ASA status, n (%)			
P1	6 (5.9)	7 (4.7)	13 (5.2)
P2	58 (56.9)	74 (49.3)	132 (52.4)
P3	31 (30.4)	61 (40.7)	92 (36.5)
P4	7 (6.9)	8 (5.3)	15 (6.0)
Sedation history, n (%)			
Yes, with adverse reaction	2 (2.0)	3 (2.0)	5 (2.0)
Yes, without adverse reaction	96 (94.1)	145 (96.7)	241 (95.6)
No sedation history	4 (3.9)	2 (1.3)	6 (2.4)
Dose of study drug, n (%)			
Standard dose	55 (53.9)	79 (52.7)	134 (53.2)
Dose reduced by 25% ²	47 (46.1)	71 (47.3)	118 (46.8)

¹ Age ≥ 75 was also included in the ≥ 65 group.

² Patients who were ≥ 65 years of age or had an ASA status of P4 were to receive initial and supplemental doses of study medication that was 75% from the randomized dose. Patients who had an ASA status of P3 may also have received initial and supplemental reduced doses, if the Investigator deemed necessary.

Source data: Study Report for 3000-0514, Table 1.5 (Section 14.1)

7.1.2.3 Primary Efficacy Endpoint

The primary efficacy endpoint for studies 3000-0522 and 3000-0524 was Sedation Success. In study 3000-0522, the midazolam arm demonstrated a Sedation Success rate of 69.2% (36/52 patients), indicating the appropriateness of the measure used to determine the level of sedation.

The Sedation Success rate was significantly higher in the fospropofol disodium 6.5 mg/kg group compared with the control 2.0 mg/kg group in both pivotal studies at a significance level of $p < 0.001$ (Table 12).

Table 12 Sedation Success (Studies 3000-0522, Colonoscopy and 3000 -0524, Bronchoscopy [mITT Population])

3000-0522 Colonoscopy	Sedation Success n/N (%)	95% CI¹ of Sedation Success Rate (%)	
Fospropofol 2.0 mg/kg (N=102)	26/102 (25.5)	(17.4, 35.1)	
Fospropofol 6.5 mg/kg (N=158)	137/158 (86.7)	(80.4, 91.6)	
Midazolam 0.02 mg/kg (N=52)	36/52 (69.2)	(54.9, 81.3)	
Comparison Between Groups	Difference %	95% CI of Difference	p-value ²
Fospropofol 6.5 mg/kg vs. 2.0 mg/kg	61.2	(51.2, 71.2)	<0.001
3000-0524 Bronchoscopy	Sedation Success n/N (%)	95% CI¹ of Sedation Success Rate (%)	
Fospropofol 2.0 mg/kg (N=102)	28/102 (27.5)	(19.1, 37.2)	
Fospropofol 6.5 mg/kg (N=150)	133/150 (88.7)	(82.5, 93.3)	
Comparison Between Groups	Difference %	95% CI of Difference	p-value ²
Fospropofol 6.5 mg/kg vs. 2.0 mg/kg	61.2	(51.2, 71.3)	<0.001

¹ The 95% confidence interval (CI) is an exact computation.

² Based on Fisher's exact test.

Source data: Study 3000-0522 Table 2.1.1 (section 14.2) and Study 3000-0524 Table 2.1.1 (Section 14.2)

Sedation success was a composite endpoint that measured the requirement for an alternative sedative agent and the need for advanced airway maneuvers (Table 13). In these studies, 60/102 (58.8%) (bronchoscopy) and 73/102 (71.6%) (colonoscopy) of patients receiving a low dose (2.0 mg/kg) of fospropofol disodium were sedation failures

and received an alternative sedative to reach the desired level of sedation and complete the procedure.

Of the patients receiving alternative sedation in the colonoscopy, sedation with midazolam was administered to 71/73 patients in the 2.0 mg/kg dose group (mean dose, 3.5 mg [SD, 1.6 mg]); 19/19 patients in the 6.5 mg/kg dose group (mean dose, 2.6 mg [SD, 1.5 mg]) and to 10/10 patients in the midazolam dose group (mean dose, 4.0 mg [SD, 2.7 mg]). In addition 2/102 (2.0 %) and 1/102 (1.0 %) patients in the 2.0 mg/kg fospropofol treatment group in the colonoscopy study received diazepam and lorazepam, respectively.

Of the patients receiving alternative sedation in the bronchoscopy study, sedation with midazolam was provided to 60/60 patients in the 2 mg/kg dose group (mean dose, 4.5 mg [SD, 2.3 mg], and to 12/12 patients in the 6.5 mg/kg dose group [mean dose, 3.5 mg [SD, 3.1 mg].

Table 13 Sedation Success and The proportion of Patients for Each Component of Sedation Success for Controlled Phase 3 Studies (3000-0522 and 3000-524 [mITT population])

Efficacy Endpoint	Fospropofol		Fospropofol 6.5 mg/kg vs. 2 mg/kg
	2 mg/kg	6.5 mg/kg	Fisher's Exact p value
Study 3000-0522	(N=102) n (%)	(N=158) n (%)	
Sedation Success	26 (25.5)	137 (86.7)	<0.001
Proportion of patients with MOAA/S ≤4 on 3 consecutive measurements taken every 2 minutes	91 (89.2)	155 (98.1)	0.003
Proportion of patients completing procedure ¹	102 (100.0)	157 (99.4)	1.000
Proportion of patients not requiring an alternative sedative	29 (28.4)	139 (88.0)	<0.001
Proportion of patients who did not require manual or mechanical ventilation	102 (100.0)	158 (100.0)	N/A
Study 3000-0524	(N=102) n (%)	(N=150) n (%)	
Sedation Success	28 (27.5)	133 (88.7)	<0.001
Proportion of patients with MOAA/S ≤4 on 3 consecutive measurements taken every 2 minutes	79 (77.5)	144 (96.0)	<0.001
Proportion of patients completing procedure ¹	101 (99.0)	149 (99.3)	1.000
Proportion of patients not requiring an alternative sedative	42 (41.2)	138 (92.0)	<0.001
Proportion of patients who did not require manual or mechanical ventilation	102 (100.0)	149 (99.3)	1.000

¹ Includes patients who completed the procedure with an alternative sedative medication.
Source: Module 5.3.5.3, Table 66 and 67 of original NDA

7.1.3 Secondary Efficacy Results

The results of the secondary endpoints for patients receiving midazolam in study 3000-0522 were: Treatment success, 78.8%; Need for Supplemental Analgesic, 63.5%; Not Recall Being Awake, 44.2%; and Willingness to Receive Study Sedative Again, 92.3%. These values are consistent with those expected for an effective sedative agent and support the sensitivity of the measures used to determine sedation and clinical benefit.

Analysis of data used to examine secondary endpoints in the 6.5 mg/kg vs. 2.0 mg/kg fospropofol treatment groups also suggested the advantage of the proposed dose titration regimen over the low dose control (2.0 mg/kg) as outlined below ([Table 14](#)).

In both study 3000-0522 (colonoscopy) and study 3000-0524 (bronchoscopy), the proportion of patients with Treatment Success was significantly higher in the 6.5 mg/kg dose group compared with the 2.0 mg/kg group. In both study 3000-0522 (colonoscopy) and study 3000-0524 (bronchoscopy), the proportion of patients requiring Supplemental Analgesics was significantly lower in the 6.5 mg/kg dose group compared with the 2.0 mg/kg dose group. The proportion of patients who did Not Recall Being Awake during the procedure was significantly higher in the 6.5 mg/kg dose group compared to the 2.0 mg/kg dose group in study 3000-0524. While this endpoint did not reach significance in study 3000-0522, the results favored the 6.5 mg/kg dose group. The proportion of patients Willing to Receive Study Sedative Again was significantly higher in the 6.5 mg/kg dose group compared with the 2.0 mg/kg dose group in study 3000-0524 (bronchoscopy). While this endpoint did not reach significance in study 3000-0522, the results favored the 6.5 mg/kg dose group.

Table 14 Summary of Secondary Efficacy Endpoints for Controlled Phase 3 Studies (3000-0522 and 3000-0524 [mITT population])

Secondary Efficacy Endpoint	Fospropofol Dosing Regimen					
	3000-0522 (Colonoscopy)			3000-0524 (Bronchoscopy)		
	2.0 mg/kg (%)	6.5 mg/kg (%)	p-value ¹	2.0 mg/kg (%)	6.5 mg/kg (%)	p-value ¹
Results based on mITT population						
Treatment Success	28.4	88.0	<0.001	41.2	91.3	<0.001
Supplemental Analgesic	76.5	55.1	<0.001	37.3	16.7	<0.001
Not Recall Being Awake	44.1	52.5	0.205	55.4	83.3	<0.001
Willingness to Receive Study Sedative Again	91.2	95.6	0.188	78.2	94.6	<0.001

¹ p-value of 6.5 mg/kg fospropofol disodium group vs 2.0 mg/kg group was based on Fisher's exact test.
mITT = all patients who received fospropofol disodium and had at least 1 post-dose observation recorded
Source: Module 5.3.5.3 Table 12 to Table 15 of the original NDA

7.1.4 Other Efficacy Endpoints

Exploratory tertiary endpoints also supported the benefit of the 6.5 mg/kg over 2.0 mg/kg dose of fospropofol disodium, including measures of recovery.

The use of opioid analgesics was reduced in the 6.5 mg/kg group compared to the low dose control (2.0 mg/kg) (Table 15). The reduction in opioid use may be explained by improved sedation which minimizes the tendency for a patient to report mild or moderate discomfort as pain. As most opioid analgesics have delayed side effects (particularly respiratory depression), the reduced use of these analgesics is desirable in order to reduce the risk to patients who are discharged soon after the procedure and for patients with compromised respiratory or cardiovascular reserve (Harper, 1976).

A tabular summary of the total number of analgesic doses patients received from the first dose of fentanyl pretreatment through the end of procedure in the mITT population in Studies 3000-0522 and 3000-0524 is presented in Table 15. In both studies, patients treated with the fospropofol disodium 6.5 mg/kg dose group experienced effective sedation with less use of supplemental analgesic. Patients in the midazolam arm (3000-0522) received a mean of 1.7 doses of supplemental analgesic.

Table 15 Total Number of Analgesic Doses Patients Received (mITT Population)

Number of Doses	3000-0522 Colonoscopy		3000-0524 Bronchoscopy	
	Fospropofol 2.0 mg/kg N=102	Fospropofol 6.5 mg/kg N=158	Fospropofol 2.0 mg/kg N=102	Fospropofol 6.5 mg/kg N=150
	Number and % of Patients		Number and % of Patients	
0	0	0	0	1 (0.7) ¹
1	24 (23.5)	71 (44.9)	64 (62.7)	124 (82.7)
2	53 (52.0)	79 (50.0)	19 (18.6)	23 (15.3)
3	22 (21.6)	8 (5.1)	10 (9.8)	1 (0.7)
4	1 (1.0)	0	4 (3.9)	0
5	1 (1.0)	0	0	0
>5	1 (1.0)	0	5 (4.9)	1 (0.7)
Mean	2.1	1.6	1.8	1.2
Std deviation	0.9	0.6	1.7	0.7
Median	2.0	2.0	1.0	1.0

All analgesic drugs (including fentanyl doses) administered between the first dose of fentanyl to the end of the procedure were counted as analgesic doses. Per study design, every patient was to receive 1 dose of fentanyl as a pretreatment.

¹One patient in study 3000-0524 did not receive fentanyl pretreatment as specified in the protocol.

Source data: Study 3000-0522 Table 2.6.1 (Section 14.2) and 3000-0524 Tables 2.6.1 (Section 14.2)

Patients in the 6.5 mg/kg fospropofol disodium group experienced effective sedation with fewer doses of study sedative medication as compared to the low-dose control group in both the colonoscopy (3000-0522) and bronchoscopy (3000-0524) studies (Table 16). Patients in the midazolam arm (3000-0522) received a mean of 2.8 doses of supplemental study medication.

Table 16 Number of Supplemental Doses of Study Medication¹ Administered by Study Period (mITT Population)

Sedation Period	3000-0522 Colonoscopy		3000-0524 Bronchoscopy	
	Fospropofol 2.0 mg/kg (N=102)	Fospropofol 6.5 mg/kg (N=158)	Fospropofol 2.0 mg/kg (N=102)	Fospropofol 6.5 mg/kg (N=150)
Total				
Mean	3.2	2.3	2.9	1.7
Standard Deviation	1.0	1.4	0.9	1.6
Initiation				
Mean	2.8	1.6	2.4	0.9
Standard Deviation	0.7	1.1	0.9	1.0
Maintenance				
N ²	32	143	48	141
Mean	1.3	0.8	1.0	0.9
Standard Deviation	1.3	0.9	1.3	1.3

¹ The initial bolus dose is not included in this table.

² The number of patients who did not receive alternative sedative medications during the Initiation Period. Source data: Study 3000-0522 Table 2.9 (Section 14.2) and Study 3000-0524 Table 2.9 (Section 14.2)

Patients in study 3000-0522 (colonoscopy), randomized to receive the proposed dose titration regimen had a mean time to Fully Alert (defined as the time to the first of 3 MOAA/S scores of 5 beginning on or after the end of the procedure) of 6.7 (SD 7.5) minutes (median = 5.0 minutes, range 0-47 minutes), and a mean time to Ready for Discharge (defined as an Aldrete score \geq 9) of 8.7 (SD 7.6) minutes (median = 7.0 minutes, range 0 - 47 minutes). In the 2.0 mg/kg dose group, results were a mean time to Fully Alert of 6.9 (SD 8.4) minutes (median = 3.0 minutes, range 0-54 minutes) and a mean time to Ready for Discharge of 8.9 (SD 8.9) minutes (median = 7.0 minutes, range 0-54 minutes). In the midazolam group, results were a mean time to Fully Alert of 6.6 (SD 9.8) minutes (median = 3.0 minutes, range 0-47 minutes) and a mean time to Ready for Discharge of 8.2 (SD 10.5) minutes (median = 5.0 minutes, range 0-47 minutes).

Results from study 3000-0524 (bronchoscopy) were similar for the group randomized to the 6.5 mg/kg arm, with a mean time to Fully Alert of 8.3 (SD 10.1) minutes (median = 5.5 minutes, range 0-61 minutes) and mean time to Ready for Discharge of 12.1 (SD 12.3) minutes (median = 8.5 minutes, range 0-66 minutes). In the 2.0 mg/kg dose group, results were a mean time to Fully Alert of 9.1 (SD 15.3) minutes (median = 3.0 minutes, range 0-114 minutes) and a mean time to Ready for Discharge of 14.1 (SD 19.7) minutes (median = 8.0 minutes, range 0-124 minutes).

Results of the Hopkins Visual Learning Test-Revised (HVLT-R) also revealed similar findings between studies 3000-0522 and 3000-0524 in patients randomized to receive the proposed dose titration regimen, with mean (SD) retention scores at recovery of 67.0% (33.2) and 64.2% (51.7), respectively. In patients randomized to the 2.0 mg/kg dose group, mean (SD) retention scores for studies 3000-0522 and 3000-0524 were 59.2% (36.3) and 63.6% (42.3), respectively. In patients randomized to midazolam, mean retention scores were 41.0% (32.0).

7.1.5 MOAA/S Levels

In study 3000-0522 (colonoscopy), 3 (1.9 %) and 5 (3.2%) of patients in the fospropofol 6.5 mg/kg treatment group reached MOAA/S scores of 1 or 0, respectively (Table 17 and Table 40). Of the 5 patients who reached a MOAA/S score of 0, 4 were sedation failures and received midazolam as an alternative sedative agent prior to reaching a MOAA/S score of 0. Of the patients who reached a MOAA/S score of 0 in this treatment group, 3 of 5 were ASA P1, 2 of 5 were ASA P2, 5 of 5 were < 65 years, 4 of 5 weighed between 60 and 90 kg, and 1 of 5 weighed > 90 kg (107 kg). No patient in the fospropofol 2.0 mg/kg group reached a MOAA/S score of 0. No patient in the midazolam group reached a MOAA/S score of 0 or 1. The relationship of MOAA/S 0 or 1 and the occurrence of SRAE in study 3000-0522 is shown in Table 40.

In study 3000-0524 (bronchoscopy), 22 (14.7 %) and 3 (2.0 %) of patients in the fospropofol 6.5 mg/kg treatment group reached MOAA/S scores of 1 or 0, respectively (Table 17 and Table 41). Of the 3 patients who reached a MOAA/S score of 0, none received alternative sedative agents. Of the patients who reached a MOAA/S score of 0 in this treatment group, 1 of 3 were ASA P2, 1 was P3, and 1 was P4, 2 of 3 were ≥65 years, 2 of 3 weighed between 60 and 90 kg, and 1 of 3 weighed > 90 kg (92 kg). No patient in the fospropofol 2.0 mg/kg group reached a MOAA/S score of 0. The relationship of MOAA/S 0 or 1 and the occurrence of SRAE in study 3000-0524 is shown in Table 41.

Table 17 Number and Percent of patients at MOAA/S Scale Scores of 0 or 1 Between First Dose of Study Sedative Medication and Fully Alert (mITT population)

	3000-0522 (Colonoscopy)		3000-0524 (Bronchoscopy)	
	Fospropofol 2 mg/kg N=102	Fospropofol 6.5 mg/kg N=158	Fospropofol 2 mg/kg N=102	Fospropofol 6.5 mg/kg N=150
MOAA/S score of 1 at any time n (%)	1 (1.0)	3 (1.9)	8 (7.8)	22 (14.7)
MOAA/S score of 0 at any time n (%)	0	5 (3.2)	0	3 (2.0)
MOAA/S score of 0 or 1 at any time n (%)	1 (1.0)	6 (3.8)	8 (7.8)	24 (16.0)

Source data: Study 3000-0522 Table 4.4.1 (Section 14.2) and Study 3000-0524 Table 4.4.1 (Section 14.2)

7.1.6 Efficacy in Subpopulations

Analysis also demonstrated that Sedation Success in several subpopulations (race, gender, age, weight, ASA P3/P4, renal impairment) was significantly greater in the fospropofol disodium 6.5 mg/kg group than in the 2.0 mg/kg group in both the phase 3 colonoscopy and bronchoscopy studies (Table 18).

A meta-analysis by subpopulations for Sedation Success was conducted for the phase 3 pivotal studies (3000-0522 and 3000-0524) (Figure 9). The findings demonstrate that Sedation Success rate in each of the age (18 to <65 years, >65 years and >75 years), sex (male, female), race (white, black, other), weight (≤ 60 kg, 60 to <90kg, ≥ 90 kg), and special (ASA P3 and P4, renal impairment [creatinine clearance ≤ 50 mL/min]) subpopulations was higher for patients in the fospropofol 6.5 mg/kg group than in the 2.0mg/kg group in both the colonoscopy and bronchoscopy studies.

Analysis of secondary endpoints (Treatment Success, use of Supplemental Analgesic medication, Recall Being Awake during the procedure, and Willingness to be Treated with the same study medication Again) were also summarized by the same subpopulations. The results of these analyses were consistent with those of Sedation Success for the subpopulations.

Table 18 Sedation Success: Comparison Across Subgroups

Study	Parameter	Treatment Group		Fospropofol 6.5 mg/kg vs. 2.0 mg/kg comparison	
		Fospropofol 2.0 mg/kg	Fospropofol 6.5 mg/kg	Difference in % and 95 % CI ¹	p-value ²
Age (yrs)					
3000-0522	18 < 65	24/88 (27.3)	119/137 (86.9)	59.6 (48.7, 70.5)	<0.001
	≥65	2/14 (14.3)	18/21 (85.7)	71.4 (47.8, 95.1)	<0.001
	≥75	0/1	4/4 (100.0)	100.0 (100.0, 100.0)	0.200
3000-0524	18 < 65	17/60 (28.3)	77/89 (86.5)	58.2 (44.8, 71.6)	<0.001
	≥65	11/42 (26.2)	56/61 (91.8)	65.6 (50.6, 80.6)	<0.001
	≥75	5/18 (27.8)	18/19 (94.7)	67.0 (44.0, 90.0)	<0.001
Sex					
3000-0522	Male	12/46 (26.1)	64/76 (84.2)	58.1 (43.0, 73.2)	<0.001
	Female	14/56 (25.0)	73/82 (89.0)	64.0 (50.8, 77.2)	<0.001
3000-0524	Male	12/54 (22.2)	74/86 (86.0)	63.8 (50.5, 77.1)	<0.001
	Female	16/48 (33.3)	59/64 (92.2)	58.9 (44.0, 73.7)	<0.001
Race					
3000-0522	White	13/69 (18.8)	114/133 (85.7)	66.9 (55.9, 77.9)	<0.001
	Black	10/20 (50.0)	11/11 (100.0)	50.0 (28.1, 71.9)	0.005
	Other	3/13 (23.1)	12/14 (85.7)	62.6 (33.3, 92.0)	0.002
3000-0524	White	24/84 (28.6)	114/130 (87.7)	59.1 (47.9, 70.3)	<0.001
	Black	4/14 (28.6)	15/16 (93.8)	65.2 (38.7, 91.6)	<0.001
	Other	0/4	4/4 (100.0)	100.0 (100.0, 100.0)	0.029
Weight (kg)					
3000-0522	<60	2/13 (15.4)	9/9 (100.0)	84.6 (65.0, 100.0)	<0.001
	60 - <90	13/56 (23.2)	72/86 (83.7)	60.5 (47.0, 74.0)	<0.001
	≥90	11/33 (33.3)	56/63 (88.9)	55.6 (37.7, 73.4)	<0.001
3000-0524	<60	7/19 (36.8)	25/27 (92.6)	55.8 (31.9, 79.6)	<0.001
	60 - <90	14/51 (27.5)	75/81 (92.6)	65.1 (51.6, 78.7)	<0.001
	≥90	7/32 (21.9)	33/42 (78.6)	56.7 (37.7, 75.6)	<0.001
Subpopulation³					
3000-0522	ASA P3/P4	0/4	4/5 (80.0)	80.0 (44.9, 100.0)	0.048
	Renal ⁴ Impairment	0	2/2 (100.0)		
3000-0524	ASA P3/P4	10/38 (26.3)	62/69 (89.9)	63.5 (47.8, 79.2)	<0.001
	Renal ⁴ Impairment	4/10 (40.0)	17/17 (100.0)	60.0 (29.6, 90.4)	<0.001

¹ Confidence Interval

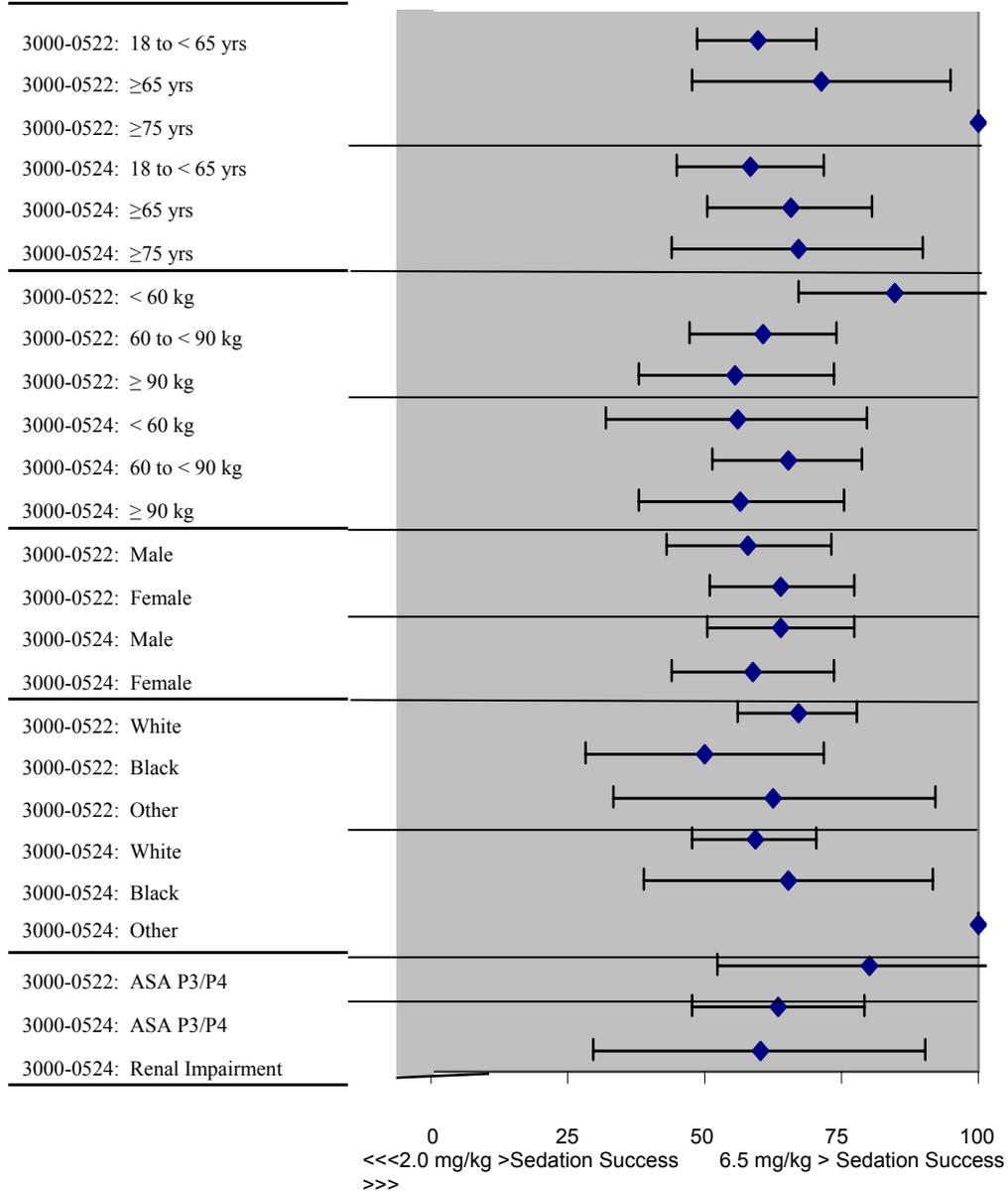
² Fisher's exact test.

³ There were no patients with Hepatic Impairment (defined after review of Child-Pugh score and medical history) in the 3000-0522 or 3000-0524 studies..

⁴ Renal Impairment defined as patient's creatinine clearance ≤50 mL/min at baseline.

Source: Module 5.3.5.3 Tables 40 to 44 of the NDA

Figure 9 95% CI for the Difference (fospropofol disodium 6.5 mg/kg -2.0 mg/kg) in Percent Patients with Sedation Success



Source: Module 2.5, Figure 3, NDA

7.1.7 Other Studies

7.1.7.1 Minor Surgical Procedures

Study 3000-0523 was an open-label, single arm, safety study in patients undergoing minor surgical procedures in which patients were treated with the proposed fospropofol dose titration regimen. Patients enrolled in the study underwent the following types of procedures: arthroscopy (n=22); arteriovenous shunt placement (n=1); bunionectomy (n=18); dilation and curettage (n=3); esophagogastroduodenoscopy (n=27); hysteroscopy (n=21); lithotripsy (n=8); transesophageal echocardiogram (n=13); and ureteroscopy (n=10). Of the 123 patients enrolled in the study, 117 (95.1 %) completed the procedure without the use of an alternative sedative medication. No patient in the study required manual or mechanical ventilation. In this study, 6 of 123 (4.9%) and 2 of 123 (1.6%) patients reached MOAA/S scores of 1 or 0, respectively. Of the 2 patients who reached a MOAA/S score of 0, both were ASA P2 and were < 65 years. One of the patients weighed 99 kg and the other weighed 75 kg. Neither of these two patients experienced a SRAE. The relationship of MOAA/S 0 or 1 and the occurrence of SRAE in study 3000-0523 is shown in [Table 42](#).

7.1.7.2 Fixed Dose Regimen Studies

The original goal in the early development stages of fospropofol disodium (studies 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415) was to identify a dose at which a single bolus administration could achieve and maintain the desired level of sedation for the majority of patients. Thus, studies conducted in initial clinical development used a relatively high, fixed dose regimen in which the same dose, in milligrams (mg) was administered to all patients who fell within broad weight ranges and the data showed that a single dose of between 10 and 12.5 mg/kg sedated the majority of patients (study 3000-0207). Results of subsequent studies showed high rates of Sedation Success: (study 3000-0409, 38/40 (95%); study 3000-0410, 183/189 (96.8%); study 3000-0411, 5/6 (83.3%); study 3000-0412, 114/121 (94.2%) and study 3000-0415 15/15 (100%)). However, several patients receiving fospropofol disodium by this regimen reached a MOAA/S score of 1 (148/392) (37.8%) or 0 (155/392 (39.5%) ([Appendix A, Table 11-A](#)).

8. CLINICAL SAFETY

General conclusions drawn from safety analyses of the pivotal phase 3 studies suggest that when administered according to the proposed dose titration regimen, fospropofol

disodium injection is well tolerated and adverse events are generally transient, rarely treatment limiting, and manageable in the clinical setting for which the drug is intended.

The majority of patients who received the proposed dose titration regimen of fospropofol disodium in the pivotal studies, reached moderate levels of sedation, and experienced a low incidence of SRAEs requiring intervention. The most common airway assistance provided was increased oxygen flow through the existing nasal cannula, chin lift and verbal stimulation.

8.1 Safety Analysis Plan

This safety summary includes individuals treated in the fospropofol disodium clinical development program (Table 3). All analyses were based on the Safety Population, which is defined as all patients who received at least one dose of the study drug. Patient data were analyzed by several different categories, for example total study drug received and the initial study drug regimen randomization. When not categorized, patient data were analyzed by the assigned treatment group.

Safety endpoints for the clinical studies included: nature, frequency, severity, relationship to treatment, and outcome of all TEAEs, SAEs, and deaths, frequency of SRAEs (apnea, hypoxemia bradycardia, and hypotension), nature, frequency, and indication of airway assistance, laboratory assessments and vital signs.

8.2 Summary of Exposure to Study Drug

A total of 1611 patients and healthy subjects received fospropofol disodium, including 1338 patients undergoing procedures or prolonged exposure and 273 healthy subjects. An additional 209 patients received midazolam and 30 received propofol lipid emulsion.

Early in the development program, patients were treated with a fixed-dose of fospropofol disodium based on broad weight ranges. Evolution to the proposed dose titration regimen led to an overall reduction in patient exposure to study drug. In order to display exposure data, categories (e.g. ≤ 5 mg/kg, $>5-8$ mg/kg, $>8-11$ mg/kg, $>11-14$, >14 mg/kg) were selected for grouping patients. The primary category ($>5-8$ mg/kg), was chosen with an intent to keep the majority of patients randomized to the 6.5 mg/kg fospropofol study arm grouped together. Thus, boundaries were established in consideration of the proposed modified dosing regimen (75% of standard dose) and weight boundaries <60 kg or >90 kg utilized in the modified dose titration regimen.

A greater percentage of patients in the fixed dose studies received initial doses of fospropofol >8mg/kg compared to those in the dose titration studies. For example, 27.5% of patients in the fixed dose bronchoscopy study (3000-0409) received an initial dose of <8 mg/kg fospropofol; compared with 97.2% of patients in study 3000-0524 who received this initial dose (Table 19). This was also evident in the colonoscopy studies when comparing initial dose received in fixed dose studies 3000 -207, 3000-0410, 3000-0415 with the dose titration regimen studies 3000-0520, 3000-0522 (Table 19).

Patients in the fixed dose studies also received a larger total dose of fospropofol disodium (mg/kg) in comparison to those treated with the proposed dose titration regimen for both the bronchoscopy and colonoscopy studies (Table 20).

On average, patients in the colonoscopy study (3000-0522) received a greater total amount of fospropofol compared to those in the bronchoscopy study (3000-0524), 789.1 mg versus 623.8 mg (Table 21).

Table 19 Number (%) of Patients by Initial Fospropofol Dose (mg/kg) Received by Study and Procedure Type for Fospropofol-Treated Patients in Colonoscopy and Bronchoscopy Studies

Protocol	Procedure	Initial Fospropofol Dose (mg/kg) Received				
		≤5 n (%)	>5-8 n (%)	>8-11 n (%)	>11-14 n (%)	>14 n (%)
Overall (N=749)		187 (25.0)	211 (28.2)	178 (23.8)	157 (21.0)	16 (2.1)
3000-0522 (N=260)		135 (51.9)	124 (47.7)	1 (0.4)	0	0
3000-0520 (N=101)	Colonoscopy	51 (50.5)	45 (44.6)	5 (5.0)	0	0
3000-0410 (N=209)		0	8 (3.8)	88 (42.1)	102 (48.8)	11 (5.3)
3000-0415 (N=15)		0	4 (26.7)	11 (73.3)	0	0
3000-0207 (N=164)		1 (0.6)	30 (18.3)	73 (44.5)	55 (33.5)	5 (3.0)
Overall (N=292)		Bronchoscopy	170 (58.2)	86 (29.5)	26 (8.9)	8 (2.7)
3000-0524 (N=252)	170 (67.5)		75 (29.8)	7 (2.8)	0	0
3000-0409 (N=40)	0		11 (27.5)	19 (47.5)	8 (20.0)	2 (5.0)
Grand Total (N=1041)		357 (34.3)	297 (28.5)	204 (19.6)	165 (15.9)	18 (1.7)

Source data: Module 5.3.5.3, Table 38 of the NDA

Table 20 Total Fospropofol Doses (mg/kg) Received by Fospropofol-Treated Patients/Subjects in the Clinical Development Program

Population/ procedure	Study	Median duration (Min) of procedure (min, max)	Total fospropofol dose (mg/kg) received				
			≤5 n (%)	>5-8 n (%)	>8-11 n (%)	>11-14 n (%)	>14 n (%)
Pivotal, Adequate, Well-controlled, Double-Blind, studies							
Colonoscopy	3000-0520 (N=101)	12 (3, 32)	28 (27.7)	30 (29.7)	34 (33.7)	6 (5.9)	3 (3.0)
Colonoscopy	3000-0522 (N=260)	11 (4, 60)	102 (39.2)	46 (17.7)	66 (25.4)	41 (15.8)	5 (1.9)
Bronchoscopy	3000-0524 (N=252)	10 (1, 62)	114 (45.2)	66 (26.2)	54 (21.4)	11 (4.4)	7 (2.8)
	Total N = 613	NA	244 (39.8)	142 (23.2)	154 (25.1)	58 (9.5)	15 (2.4)
Open-label Supportive Studies							
Minor Procedures	3000-0523 (N=123)	17 (2, 110)	6 (4.9)	40 (32.5)	43 (35.0)	22 (17.9)	12 (9.8)
Colonoscopy	3000-0207 (N=164)	10 (2, 50)	0 (0.0)	11 (6.7)	56 (34.1)	63 (38.4)	34 (20.7)
	Total N = 287	NA	6 (2.1)	51 (17.8)	99 (34.5)	85 (29.6)	46 (16.0)
Open-label Fixed –dose Supportive Studies							
Bronchoscopy	3000-0409 (N=40)	10 (3, 34)	0 (0.0)	8 (20.0)	20 (50.0)	8 (20.0)	4 (10.0)
Colonoscopy	3000-0410 (N=210)	11 (2, 54)	0 (0.0)	4 (1.9)	67 (31.9)	100 (47.6)	39 (18.6)
Colonoscopy	3000-0415 (N=15)	14 (5, 28)	0 (0.0)	4 (26.7)	9 (60.0)	2 (13.3)	0 (0.0)
Minor procedures	3000-0411 (N=6)	26 (13, 41)	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)
Minor procedures	3000-0412 (N=121)	18 (2, 102)	0 (0.0)	5 (4.1)	38 (31.4)	58 (47.9)	20 (16.5)
	Total N = 392	NA	0 (0.0)	24 (6.1)	137 (34.9)	168 (42.9)	63 (16.1)
Prolonged Exposure (ICU/CABG)							
Prolonged exposure	3000-0104 (N=8)	405 (369, 540)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100.0)
Prolonged Exposure	3000-0413 (N=38)	223 (90, 733)	10 (26.3)	4 (10.5)	6 (15.8)	0 (0.0)	18 (47.4)
	Total N = 46	NA	10 (21.7)	4 (9.2)	6 (13.0)	0 (0.0)	26 (56.5)
Healthy Subjects¹							
Healthy Subjects	3000-0001 (N=12)	N/A	1 (8.3)	0 (0.0)	1 (8.3)	1 (8.3)	9 (75.0)
Healthy Subjects	3000-0102 (N=12)	N/A	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)
Healthy Subjects	3000-0103 (N=36)	N/A	6 (16.7)	0 (0.0)	6 (16.7)	0 (0.0)	24 (66.7)
Healthy Subjects	3000-0205 (N=8)	N/A	2 (25.0)	6 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)
Healthy Subjects	3000-0206 (N=54)	N/A	21 (38.9)	33 (61.1)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 20 Total Fospropofol Doses (mg/kg) Received by Fospropofol-Treated Patients/Subjects in the Clinical Development Program

Population/ procedure	Study	Median duration (Min) of procedure (min, max)	Total fospropofol dose (mg/kg) received				
			≤5 n (%)	>5-8 n (%)	>8-11 n (%)	>11-14 n (%)	>14 n (%)
Healthy Subjects	3000-0308 (N=10)	N/A	0 (0.0)	0 (0.0)	0 (0.0)	10 (100.0)	0 (0.0)
Healthy Subjects	3000-0414 (N=60)	N/A	0 (0.0)	13 (21.7)	34 (56.7)	9 (15.0)	4 (6.7)
Healthy Subjects	3000-0521 (N=69)	N/A	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	68 (98.6)
Healthy Subjects	3000-0625 (N=12)	N/A	0 (0.0)	0 (0.0)	12 (100.0)	0 (0.0)	0 (0.0)
	Total N=273	N/A	30 (11.0)	53 (19.4)	53 (19.4)	20 (7.3)	117 (42.9)
Grand Total	Overall N=1611	12 (1,733)	290 (18.0)	274 (17.0)	449 (27.9)	331 (20.5)	267 (16.6)

NA = Not Applicable

Source data: Module 5.3.5.3, Table 70 of the NDA

¹ Patients in the crossover design are counted in the dose group for which they received the highest dose.

Midazolam dosing (0.02 mg/kg) in the phase 3 colonoscopy study (3000-0522) was based on the prescribing information in the package insert and patients received an average of 4.3 mg (SD, 1.54 mg) midazolam to initiate the procedure ([Table 21](#)).

During the study, if patients were not successfully sedated, the Investigator could administer an alternative sedative agent per the study site standard of care. To avoid confounding the PK analysis, the protocols prohibited the use of propofol lipid emulsion and nearly all patients who received alternative sedative were treated with midazolam. In study 3000-0522, 71 of 76 (93.4%) patients in the 2.0 mg/kg treatment group who received alternative sedative and 19 of 21 (90.5%) patients in the 6.5 mg/kg treatment group who received alternative sedative were administered midazolam as an alternative sedative. The average dose of midazolam patients in the 2.0 mg/kg and 6.5 mg/kg treatment arms received was 3.5 mg (SD, 1.6mg) and 2.6 (SD, 1.5 mg), respectively. In study 3000-0524, 60 of 74 (81.1%) patients who received alternative sedative in the 2.0 mg/kg treatment group and 12 of 17 (70.6%) of patients who received alternative sedative in the 6.5 mg/kg treatment group were administered midazolam as an alternative sedative. The average dose of midazolam patients in the 2.0 mg/kg and 6.5 mg/kg treatment arms received was 4.5 mg (SD, 2.3 mg) and 3.5 mg (SD, 3.1 mg), respectively.

A greater percentage of patients in the fospropofol disodium 2.0 mg/kg arm received midazolam in colonoscopy study 3000-0522 (69.6%) and bronchoscopy study 3000-0524 (58.8%) than did patients treated with the proposed dose titration regimen, 12.0% and 8.0%, respectively; ([Table 21](#)).

Many patients undergoing diagnostic and therapeutic procedures such as colonoscopy and bronchoscopy are administered an opioid prior to dosing with an anesthetic agent ([Cohen, 2006](#)). Consistent with clinical practice, fentanyl was administered prior to fospropofol dosing for nearly all of the clinical studies in the fospropofol disodium clinical development program. A tabular summary of the extent of fentanyl exposure by population/procedure and by study is provided in [Appendix A, Table 2-A](#). The phase 2 dose ranging (3000-0520) and phase 3 pivotal study (3000-0522, 3000-0523, 3000-0524) protocols called for fentanyl pre-treatment (50 µg dose) 5 min prior to administration of fospropofol dosing. Investigators were permitted (per protocol) to administer 1 additional dose of 25 µg dose of fentanyl for procedural pain. The average total fentanyl dose received by patients in the pivotal studies ranged from 57.0 to 89.7 mcg ([Table 21](#)). In comparison to patients receiving the proposed dose titration regimen, higher doses were received by patients in the low dose fospropofol disodium control arms ([Table 21](#)) in both the bronchoscopy and colonoscopy studies.

Table 21 Total Study Drug Exposure by Study and Dose Group (Studies 3000-0522, 3000-0523, 3000-0524)

	Study 3000-0522 (Colonoscopy)			Study 3000-0523 ¹ (Minor Surgical Procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102	Fospropofol 6.5 mg/kg N = 158	Midazolam 0.02 mg/kg N = 52	Fospropofol 6.5 mg/kg N = 123	Fospropofol 2.0 mg/kg N = 103	Fospropofol 6.5 mg/kg N = 149
Initiation Phase	N = 102	N = 158	N = 52	NA	N = 103	N = 149
Mean (mg)	249.3	704.3	3.20	NA	209.0	532.6
SD (mg)	36.9	178.1	1.20	NA	54.7	167.3
Median (mg)	245.0	717.5	3.13	NA	227.5	507.5
Min, Max (mg)	140.0, 350.0	297.5, 1277.5	1.0, 5.5	NA	87.5, 280.0	280.0, 997.5
				NA		
Maintenance Phase	N = 21	N = 75	N = 31	NA	N = 24	N = 64
Mean (mg)	71.7	178.5	1.92	NA	64.9	212.2
SD (mg)	39.1	89.2	1.02	NA	44.2	161.1
Median (mg)	70.0	140.0	2.00	NA	43.8	140.0
Min, Max (mg)	35.0, 175.0	70.0, 490.0	0.7, 5.0	NA	17.5, 175.0	70.0, 700.0
Total	N = 102	N = 158	N = 52	N = 123	N = 103	N = 149
Mean (mg)	264.0	789.1	4.34	742.0	224.1	623.8
SD (mg)	46.1	206.7	1.54	240.9	56.0	241.0
Median (mg)	262.5	778.8	4.30	717.5	227.5	577.5
Min, Max (mg)	140.0, 420.0	297.5, 1277.5	1.6, 9.6	280.0, 1592.5	122.5, 385.0	280.0, 1557.5
Fentanyl						
Mean (mcg)	89.7	66.6	72.6	58.5	80.6	57.0
SD (mcg)	36.6	17.8	23.4	14.6	63.9	34.8
Median (mcg)	75.0	75.0	75.0	50.0	50.0	50.0
Min, Max (mcg)	50.0, 250.0	50.0, 150.0	50.0, 150.0	25.0, 100.0	50.0, 400.0	0, 450.0

Table 21 Total Study Drug Exposure by Study and Dose Group (Studies 3000-0522, 3000-0523, 3000-0524)

	Study 3000-0522 (Colonoscopy)			Study 3000-0523 ¹ (Minor Surgical Procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102	Fospropofol 6.5 mg/kg N = 158	Midazolam 0.02 mg/kg N = 52	Fospropofol 6.5 mg/kg N = 123	Fospropofol 2.0 mg/kg N = 103	Fospropofol 6.5 mg/kg N = 149
Number of patients receiving midazolam rescue	71 (69.6)	19 (12.0)	10 (19.2)	3 (2.4)	60 (58.8)	12 (8.0)

¹ The study was not designed by study phase.

Source: Study Report for 3000-0522, Table 29, Table 30, Table 38; Study Report for 3000-0523, Table 16, Table 17, Table 4.1; Study Report for 3000-0524, Table 27, Table 28, Table 36

8.3 Demographics

The distribution of patients across the subgroups of age, sex, race, weight and special populations for the dose-titration studies 3000-0522, and 3000-0524 are provided ([Table 10](#) and [Table 11](#)). The subpopulation distribution for most demographic variables was similar across studies, however patients in the bronchoscopy study were older and a greater percentage were classified as ASA P3 or P4 than those in the colonoscopy study ([Table 10](#) and [Table 11](#)). ([Appendix A; Table 3-A, Table 4-A, Table 5-A, Table 6-A, Table 7-A](#)).

8.4 Medical History

Certain pre-existing medical conditions were noted at a higher frequency in the bronchoscopy compared to colonoscopy phase 3 studies and these included: hypertension, gastroesophageal reflux disease, chronic obstructive pulmonary disease, anxiety, hyperlipidemia, coronary artery disease, cough, pulmonary mass, and haemoptysis. Seasonal allergy was the only medical condition reported more frequently in the colonoscopy study ([Table 22](#)). In general, patients undergoing bronchoscopy had a greater degree of underlying illness, including airway associated conditions such as chronic obstructive pulmonary disease ([Table 22](#)).

Table 22 Medical Conditions Reported in $\geq 15\%$ of Patients in the Phase 3 Controlled Studies (3000-0522, 3000-0524)

Preferred Term	Colonoscopy 3000-0522 (N=260) n (%)	Bronchoscopy 3000-0524 (N=252) n (%)
Hypertension	83 (31.9)	125 (49.6)
Gastroesophageal reflux disease	63 (24.2)	98 (38.9)
Drug hypersensitivity	48 (18.5)	70 (27.8)
Depression	47 (18.1)	57 (22.6)
Hysterectomy	57 (21.9)	58 (23.0)
Chronic obstructive pulmonary disease	4 (1.5)	115 (45.6)
Hypercholesterolemia	48 (18.5)	32 (12.7)
Anxiety	27 (10.4)	58 (23.0)
Hyperlipidaemia	15 (5.8)	53 (21.0)
Seasonal allergy	38 (14.6)	16 (6.3)
Coronary artery disease	9 (3.5)	40 (15.9)
Cough	1 (0.4)	41 (16.3)
Pulmonary mass	0	41 (16.3)
Haemoptysis	0	38 (15.1)

Source: Module 5.3.5.3, Table 209 of the NDA

8.5 Concomitant Medications

The concomitant medications reflected the comorbidities present in the 2 populations. Patients with a history of allergic reactions or hypersensitivity to any anesthetic agent or opioid were excluded as well as those for whom the use of fentanyl citrate was contraindicated.

8.6 Adverse Events

8.6.1 Adverse Events Characteristic of the Pharmacological Class

Patients who received fospropofol disodium demonstrated adverse events that are commonly associated with phosphate prodrugs such as fosphenytoin (e.g. paresthesia and pruritus); or sedation (e.g., hypoxemia) and/or the procedure being performed (e.g., procedural pain). Studies of propofol and midazolam, with or without fentanyl, have reported hypoxemia, bradycardia, and hypotension ([Campbell, 2006](#)). Addition of fentanyl further increases the frequency of respiratory events ([Bailey, 1990b](#); [Vicari, 2002](#)).

Recent trials reported in the published literature have evaluated the safety of procedural sedation for endoscopy and bronchoscopy. The safety of propofol sedation, in the ambulatory outpatient setting, was examined in 3,610 patients undergoing colonoscopy ([Sieg, 2007](#)). Hypoxemia was observed in 1.4 % of patients and respiratory events requiring mask ventilation occurred in 0.14 %. Bradycardia (heart rate < 60/min) occurred in 0.5% of patients and arterial hypotension (systolic < 90 mm Hg) in 0.3 %.

In an outpatient setting, 100 patients undergoing colonoscopy were randomized (1:1) to receive propofol or midazolam plus fentanyl ([Ulmer, 2003](#)). In the propofol group, 4 episodes of hypotension, and 1 episode of bradycardia was observed; in the midazolam group, 1 episode of oxygen desaturation requiring mask ventilation and 4 episodes of hypotension were observed.

Safety experience with registered nurse (RN) administered propofol was reported for 27,500 consecutive Japanese endoscopy patients ([Tohda, 2006](#)). Hypoxemia (oxygen saturation <90%) developed in 6.7% of endoscopy patients; 0.25% had an oxygen saturation < 85% during colonoscopy. A decline in blood pressure (systolic blood pressure < 90 mm Hg) was seen in 3.5% of the colonoscopy patients. As stated in Ozturk, et al, 100 patients undergoing fiberoptic bronchoscopy were randomized to receive either propofol or midazolam ([Ozturk, 1999](#)). In this study population, the incidence of hypoxemia (oxygen saturation <90%) was 16% in the midazolam arm and 5% in the propofol arm. In a small study of 41 patients undergoing fiberoptic bronchoscopy and randomized to receive propofol or midazolam; Clarkson, et al, found hypoxemia (oxygen saturation <90%) in 10 of 21 (48%) and 7 of 20 (35%) patients treated with propofol or midazolam, respectively ([Clarkson 1993](#)). Approximately 10% of patients in both treatment groups experienced an oxygen saturation of < 85%.

8.6.2 Brief Summary of Adverse Events in the Phase 3 Studies (3000-0522, 3000-0524, 3000-0523)

A brief summary of adverse events for studies 3000-0522, 3000-0523, and 3000-0524 is presented in [Table 23](#). Safety data were tabulated by randomized treatment group. An overview of the AE profile generated during the conduct of the phase 3 clinical studies demonstrates that the observed safety profile was consistent with that observed with other phosphate prodrugs and sedative-hypnotics ([Table 23](#)). Most TEAEs were mild to moderate in severity.

Serious adverse events occurred in a greater percentage of patients in the bronchoscopy study (3000-0524) than in colonoscopy study (3000-0522) and the minor surgical

procedures study (3000-0523). The incidence of SAEs in study 3000-0524 was similar between treatment arms, 13/103 (12.6 %) and 15/149 (10.1 %) in the 2.0 mg/kg and the 6.5 mg/kg groups, respectively. Of the patients randomized to the 6.5 mg/kg fospropofol group in studies 3000-0522, 3000-0523, and 3000-0524, one experienced an SAE that was considered to be treatment related. This patient (0524-430-0006) experienced severe hypoxemia that required mask ventilation. A brief narrative for this patient is included in [section 8.7.2](#).

Few patients were discontinued from the procedure or the study drug and no patient was discontinued from the study. No deaths were considered related to study drug. Patient narratives for SAEs that were considered at least possibly related to study drug are included in [Appendix C](#).

Table 23 Brief Summary of Adverse Events Reported During the Phase 3 Studies (3000-0522, 3000-0523, 3000-0524)

	Study 3000-0522 (Colonoscopy)			Study 3000-0523 (Minor Surgical Procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)	Fospropofol 6.5 mg/kg N = 123 n (%)	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Treatment-emergent AEs (TEAEs)	89 (87.3)	145 (91.8)	31 (59.6)	111 (90.2)	79 (76.7)	124 (83.2)
Severe TEAEs	1 (1.0)	4 (2.5)	0	11 (8.9)	13 (12.6)	22 (14.8)
Serious AEs	1 (1.0)	0	1 (1.9)	4 (3.3)	13 (12.6)	15 (10.1)
Related Serious AEs	0	0	0	0	0	1 (0.7)
Deaths	0	0	0	0	2 (1.9)	3 (2.0)
Related Deaths	0	0	0	0	0	0
AEs leading to study drug discontinued	0	0	0	1 (0.8)	0	2 (1.3)
AEs leading to procedure discontinued	0	1 (0.6)	1 (1.9)	0	1 (1.0)	1 (0.7)
AE leading to discontinuation from study	0	0	0	0	0	0
Sedation-related AEs	2 (2.0)	3 (1.9)	1 (1.9)	5 (4.1)	13 (12.6)	30 (20.1)
Sedation-related AEs requiring airway assistance	0	1 (0.6)	0	1 (0.8)	11 (10.7)	25 (16.8)

Source: Study Report for 3000-0522, Table 31, Table 3.4.5, Table 3.3.1, Table 3.2.4, Listing 3.2.3; Study Report for 3000-0513, Table 18, Table 2.5.5, Table 2.3.1, Table 2.2.6, Listing 2.2.3; Study Report for 3000 0524, Table 29, Table 3.4.5, Table 3.3.1, Table 3.2.5, Listing 3.2.3

8.6.3 Common Adverse Events in the Phase 3 Studies (3000-0522, 3000-0523, 3000-0524)

The most commonly reported TEAEs in all studies of fospropofol disodium in diagnostic and therapeutic procedures were paresthesia (burning, tingling, stinging, prickling) and pruritus (itching) (Table 24, Table 25, Table 26). These events were independent of

initial dose, typically occurred in the perineal area, were generally mild to moderate in intensity, self limited, lasted a few minutes and resolved without sequelae. In one patient (study 3000-0524), treatment with fospropofol disodium was discontinued due to severe paresthesia (Table 35).

Other notable TEAEs were procedural pain, hypotension and hypoxemia. AEs with the verbatim term of hypoxemia map to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of “hypoxia.” Hypoxia is a shortage of oxygen in the body; whereas, hypoxemia is the reduction of oxygen specifically in the blood and was the parameter monitored in the clinical studies. Accordingly, the text and tables of this briefing document uses the term hypoxemia rather than hypoxia even though the MedDRA term, hypoxia, remains in tabular presentations in the NDA.

Hypotension and hypoxemia occurred more frequently in the bronchoscopy (Table 25) than colonoscopy study (Table 24). The most common form of intervention for hypoxemia was increased oxygen flow through the existing nasal cannula, tactile and verbal stimulation, hypotension was managed by administration of IV fluids, repositioning, or administration of concomitant medication.

Of the reported TEAEs, only procedural pain occurred at a higher frequency in the colonoscopy data set compared to bronchoscopy; (Table 24, Table 25). Much of the pain from colonoscopy comes from distension of the bowel in order to improve visibility. In bronchoscopies, adequate local anesthesia and avoidance of trauma to the upper airway has been shown to relieve discomfort that occurs during the procedure (Lechtzin, 2000).

Patients in the midazolam arm of study 3000-0522 also reported procedural pain (59.6%) (Table 24). For this study, hypotension was reported by 1/52 (1.9%) patients and other TEAEs included: abdominal pain, abdominal tenderness, diarrhea, catheter site pain, fatigue, hypokalemia, headache, depression, and flushing each reported by 1/52 (1.9%) patients.

The most frequently experienced TEAEs in the open-label study 3000-0523 (minor surgical procedures) were paresthesia 66/123 (53.7%), procedural pain 62/123 (50.4%), pruritus 32/123 (26.0%), nausea 10/123 (8.1%), vomiting 7/123 (5.7%) (Table 26). Hypotension was experienced by 5/123 (4.1%)

Table 24 Patient Incidence of Treatment-Emergent Adverse Events in ≥5% of Patients (Study 3000-0522, Colonoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)
<i>Injury, poisoning and procedural complications</i>			
Procedural pain	57 (55.9)	83 (52.5)	31 (59.6)
<i>Nervous system disorders</i>			
Paresthesia	61 (59.8)	108 (68.4)	0
<i>Skin and subcutaneous tissue disorders</i>			
Pruritus	26 (25.5)	25 (15.8)	0

Source: Study Report for 3000-0522, Table 3.4.4

Table 25 Patient Incidence of Treatment-Emergent Adverse Events in ≥5% of Patients (Study 3000-0524, Bronchoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
<i>Injury, poisoning & procedural complications</i>		
Procedural pain	12 (11.7)	18 (12.1)
<i>Nervous system disorders</i>		
Paresthesia	46 (44.7)	74 (49.7)
<i>Respiratory, thoracic and mediastinal disorders</i>		
Cough	4 (3.9)	13 (8.7)
Hypoxia	14 (13.6)	26 (17.4)
<i>Skin and subcutaneous tissue disorders</i>		
Pruritus	15 (14.6)	22 (14.8)
<i>Vascular disorders</i>		
Hypotension	2 (1.9)	12 (8.1)

Source: Study Report for 3000-0524, Table 3.4.4, modified for ≥5%

Table 26 Patient Incidence of Treatment-Emergent Adverse Events in ≥5% of Patients (Study 3000-0523, Minor Surgical Procedures)

<i>System Organ Class</i> Preferred Term	Fospropofol 6.5 mg/kg N = 123 n (%)
<i>Gastrointestinal disorders</i>	
Nausea	10 (8.1)
Vomiting	7 (5.7)
<i>Injury, poisoning and procedural complications</i>	
Procedural pain	62 (50.4)
<i>Nervous system disorders</i>	
Paresthesia	66 (53.7)
<i>Skin and subcutaneous tissue disorders</i>	
Pruritus	32 (26.0)

Source: Study Report for 3000-0523, Table 2.5.3

8.6.4 Severe Treatment Emergent Adverse Events in the Phase 3 Studies

The majority of TEAEs experienced by patients in the phase 3 studies of the proposed fospropofol dose titration regimen (3000-0522, 3000-0523, 3000-0524) were considered mild or moderate in severity. Severe TEAEs for these studies by System Organ Class (SOC) and Preferred Term (PT) are summarized in [Table 27](#), [Table 28](#) and [Table 29](#).

Five patients, 4 in the fospropofol 6.5 mg/kg group and 1 in the fospropofol 2.0 mg/kg group of colonoscopy study 3000-0522, experienced severe TEAEs. No patients in the midazolam group experienced a severe TEAE. Two patients in the 6.5 mg/kg group experienced AEs that were considered related to study drug: paresthesia in one patient and pruritus and paresthesia in a second patient. Two patients in this group experienced severe procedural pain that was considered not related to study medication. One patient in the 2.0 mg/kg group experienced severe urinary retention that was not related to study medication. This patient had a low creatinine clearance at screening (65 mL/min), but it was not considered clinically significant.

Table 27 Patient Incidence of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Study 3000-0522, Colonoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)
<i>Any Severe Treatment-Emergent AE</i>	1 (1.0)	4 (2.5)	0
<i>Injury, poisoning and procedural complications</i>	0	2 (1.3)	0
Procedural pain	0	2 (1.3)	0
<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i>	1 (1.0)	0	0
Colon cancer	1 (1.0)	0	0
<i>Nervous system disorders</i>	0	2 (1.3)	0
Paresthesia	0	2 (1.3)	0
<i>Renal and urinary disorders</i>	1 (1.0)	0	0
Urinary retention	1 (1.0)	0	0
<i>Skin and subcutaneous tissue Disorders</i>	0	1 (0.6)	0
Pruritus	0	1 (0.6)	0

Source: Study Report for 3000-0522, Table 3.4.5

Twenty-two patients (14.8%) in the fospropofol 6.5 mg/kg group and 13 patients (12.6%) in the 2.0 mg/kg group experienced severe TEAEs during study 3000-0524 (Table 28). These included paresthesia (6 patients); chronic obstructive pulmonary disease (COPD), malignant lung neoplasm, and respiratory failure (5 patients each); pneumonia (4 patients); hypoxemia, pruritus, hypotension, and bacterial bronchitis (2 patients each); and cough and laryngospasm (1 patient each). In the 2.0 mg/kg group severe paresthesia (1 patient) and pruritus (1 patient) were reported. In the 6.5 mg/kg group severe paresthesia (5 patients) one of which led to discontinuation of study drug), pruritus (1 patient) and hypoxemia (2 patients) was reported.

Table 28 Patient Incidence of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Study 3000-0524, Bronchoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
<i>Any Severe Treatment-Emergent AE</i>	13 (12.6)	22 (14.8)
<i>Blood and lymphatic system disorders</i>	1 (1.0)	0
Neutropenia	1 (1.0)	0
<i>Cardiac disorders</i>	1 (1.0)	3 (2.0)
Cardiac arrest	0	1 (0.7)
Cardiac failure congestive	1 (1.0)	0
Cardiomyopathy	1 (1.0)	0
Coronary artery disease	0	1 (0.7)
Ventricular tachycardia	0	1 (0.7)
<i>Gastrointestinal disorders</i>	0	1 (0.7)
Intestinal perforation	0	1 (0.7)
Large intestine perforation	0	1 (0.7)
<i>Infections and infestations</i>	3 (2.9)	7 (4.7)
Abdominal abscess	0	1 (0.7)
Abdominal sepsis	0	1 (0.7)
Bronchitis acute	0	1 (0.7)
Bronchitis bacterial	1 (1.0)	1 (0.7)
Lung infection pseudomonal	0	1 (0.7)
Pneumonia	1 (1.0)	3 (2.0)
Pneumonia pneumococcal	0	1 (0.7)
Sepsis	0	1 (0.7)
Septic shock	1 (1.0)	0
<i>Injury, poisoning & procedural complications</i>	0	1 (0.7)
Brain herniation	0	1 (0.7)
<i>Metabolism and nutrition disorders</i>	1 (1.0)	0
Hypovolemia	1 (1.0)	0
<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i>	0	6 (4.0)
Lung neoplasm malignant	0	5 (3.4)
Lung squamous cell carcinoma stage unspecified	0	1 (0.7)
<i>Nervous system disorders</i>	2 (1.9)	6 (4.0)
Anoxic encephalopathy	0	1 (0.7)
Brain edema	0	1 (0.7)
Cerebrovascular accident	1 (1.0)	0
Paresthesia	1 (1.0)	5 (3.4)
<i>Respiratory, thoracic and mediastinal disorders</i>	7 (6.8)	7 (4.7)
Acute respiratory failure	0	1 (0.7)
Chronic obstructive pulmonary disease	3 (2.9)	2 (1.3)
Cough	0	1 (0.7)

Table 28 Patient Incidence of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Study 3000-0524, Bronchoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Hypoxemia	0	2 (1.3)
Laryngospasm	1 (1.0)	0
Pneumothorax	1 (1.0)	0
Respiratory arrest	1 (1.0)	0
Respiratory failure	2 (1.9)	3 (2.0)
<i>Skin and subcutaneous tissue disorders</i>	1 (1.0)	1 (0.7)
Pruritus	1 (1.0)	1 (0.7)
<i>Vascular disorders</i>	1 (1.0)	1 (0.7)
Hypotension	1 (1.0)	1 (0.7)

Source: Study Report for 3000-0524, Table 3.4.5

A total of 11 of 123 patients (8.9%) experienced severe TEAEs during minor surgical procedures in study 3000-0523, the majority of which were procedural pain (5 of 123 patients [4.1%]) and nervous system disorders (3 of 123 patients [2.4%]) (Table 29). With the exception of 2 events, the severe TEAEs were considered by the Investigator to be unrelated to the study drug. One patient experienced severe paresthesia and an episode of severe crying, both of which were considered to be probably related to study drug.

Table 29 Patient Incidence of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Study 3000-0523, Minor Surgical Procedures)

<i>System Organ Class Preferred Term</i>	Fospropofol 6.5 mg/kg N = 123 n (%)
<i>Any Severe Treatment-Emergent AE</i>	11 (8.9)
<i>Cardiac disorders</i>	1 (0.8)
Cardiac arrest	1 (0.8)
<i>General disorders and admin site conditions</i>	1 (0.8)
Pain	1 (0.8)
<i>Infections and infestations</i>	1 (0.8)
Mycotic aneurysm	1 (0.8)
<i>Injury, poisoning & procedural complications</i>	5 (4.1)
Procedural pain	5 (4.1)
<i>Investigations</i>	1 (0.8)
Ammonia increased	1 (0.8)
<i>Musculoskeletal and connective tissue disorders</i>	1 (0.8)
Pain in extremity	1 (0.8)
<i>Nervous system disorders</i>	3 (2.4)
Burning sensation	1 (0.8)
Hepatic encephalopathy	1 (0.8)
Paresthesia	1 (0.8)
<i>Psychiatric disorders</i>	1 (0.8)
Crying	1 (0.8)
<i>Respiratory, thoracic and mediastinal disorders</i>	1 (0.8)
Apnea	1 (0.8)
<i>Vascular disorders</i>	1 (0.8)
Hypertension	1 (0.8)

Source: Study Report for 3000-0524, Table 2.5.5

8.7 Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation of Study Medication

8.7.1 Deaths

There were no deaths in the fospropofol disodium clinical program that were considered by the Investigator to be related to fospropofol dosing. There were a total of 10 patient deaths; all were considered to be related to the underlying disease state of patients and unrelated to the study drug. Five deaths each occurred in the prolonged exposure (ICU) study (3000-0413) and the phase 3 bronchoscopy study (3000-0524). One of the 5 patients who died in study 3000-0413 was randomized to propofol lipid emulsion and

did not receive fospropofol. Detailed patient narratives for these 10 patients are found in [Appendix C](#).

Table 30 Deaths (Study 3000-0524, Bronchoscopy) by Patient

Patient ID Demographics (age, sex, Wt, ASA)	Medical history	Randomized dose Total dose	Primary cause of death System Organ Class Preferred Term	Interval from dose to onset of fatal event
0524-544-0009 46, Male, 45 kg, ASA P2	HIV, TB, meningitis	Fospropofol 6.5 mg/kg (385 mg total) Fentanyl 50 mcg	<i>Nervous system disorders</i> Anoxic encephalopathy	3 days
0524-544-0003 61, Male, 74 kg, ASA P4	Lung cancer, liver metastases COPD, diabetes	Fospropofol 2.0 mg/kg (280 mg total) Fentanyl 50 mcg	<i>Respiratory, thoracic and mediastinal disorders</i> Respiratory arrest	11 days
0524-533-0008 67, Male, 61 kg, ASA P2	Prostate cancer, hypertension, malignant lung mass, renal lesions	Fospropofol 2.0 mg/kg (140 mg total) Fentanyl 150 mcg Midazolam 2 mg	<i>Infections and infestations</i> Septic shock	17 days
0524-312-0003 77, Male, 67 kg, ASA P3	Lung mass, COPD, hypertension, hyperlipidemia	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 50 mcg	<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i> Malignant lung neoplasm	Lung cancer diagnosed during bronchoscopy (Died 19 days later)
0524-309-0006 70, Female, 47 kg, ASA P2	COPD, smoker, lung mass, pulmonary embolism	Fospropofol 6.5 mg/kg (350 mg total) Fentanyl 50 mcg	<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i> Malignant lung neoplasm	Lung cancer diagnosed during bronchoscopy (Died 23 days later)

Source: Study Report for 3000-0524, Listing 3.2.3, Listing 1.2, Listing 2.2, Listing 1.5.1

8.7.2 Serious Adverse Adverts

A total of 58 of 1611 (3.6%) subjects experienced 100 SAEs in the fospropofol disodium development program. In addition, 4 of 30 (13.3%) subjects who received propofol lipid emulsion experienced 7 SAEs and 2 of 209 (1.0%) subjects who received midazolam experienced 3 SAEs. Summaries of SAEs (patient incidence) by SOC and preferred term for studies 3000-0522, 3000-0524, and 3000-0523 are presented in [Table 31](#), [Table 32](#), and [Table 33](#), respectively. A tabular summary of SAEs considered unrelated to study drug is provided in [Appendix A, Table 10-A](#).

A total of 6 patients experienced SAEs that were considered at least possibly related to study drug. Four of these 6 patients experienced SAEs that were considered to be sedation-related and which required airway assistance. Narratives for these patients are provided in [Appendix C](#).

Three patients treated with fospropofol in the fixed-dose studies had treatment-related SAEs: apnea in 2 patients who received initial doses ≥ 8 mg/kg; (patients 0207-265-0004 and 0411-412-0001) and apnea and hypotension in 1 patient who received an initial dose of >11 mg/kg (patient 0409-316-0001). One healthy subject (0414-493-1050) experienced a severe, treatment-related SAE of paralysis and muscular weakness of psychogenic origin (verbatim term: psychogenic paralysis; preferred term: mental disorder) approximately 1 hour after the administration of fospropofol. One patient who received fospropofol by prolonged infusion (0413-497-0020) experienced a treatment-related SAE of non-sustained ventricular tachycardia of 5 to 10 seconds duration.

One patient, 0524-430-0006, who received fospropofol by the proposed dose titration regimen experienced a severe SAE. The patient was a 78-yr-old male with an ASA status of P3. His medical history included chronic obstructive pulmonary disease, chronic lymphocytic leukemia, hypoxemia on ambulatory oxygen, renal impairment, congestive heart failure, coronary artery disease, hypertension, hyperlipidemia, and diabetes. He was randomized to the 6.5 mg/kg dosing regimen, and received a 25% dose reduction based on his age. He received 50 mcg of fentanyl followed by 4.8 mg/kg (437.5 mg) of fospropofol disodium. The bronchoscope was inserted 2 minutes following administration of fospropofol. The patient then experienced severe hypoxemia 3 min later, which required manual ventilation with bag valve mask on 3 separate occasions. This event was not considered serious by the Investigator; however, the Sponsor upgraded the event to serious. The event was considered to be probably related to study drug. The event resolved and the patient was discharged home with increased O₂ flow (5 L/min from 4 L/min).

All unrelated SAEs were considered to be related to underlying disease, the majority of which occurred in the prolonged exposure (CABG and ICU studies, 3000-0104 and 3000-0413) and the bronchoscopy studies (3000-0409, 3000-0524).

Thirty-seven of the 58 (63.1%) patients who experienced unrelated SAEs (including patients who died) were in the bronchoscopy studies (3000-0409, 3000-0524) and experienced 65 of the 100 (65%) SAEs. Of these 36 patients, 7 had SAEs that occurred as a result of diagnostic findings (lung cancer) and 12 patients had SAEs that represented exacerbation of their underlying disease (e.g. COPD, cystic fibrosis, congestive heart failure, coronary artery disease, bronchitis) ([Appendix A, Table 10-A](#)).

Table 31 Patient Incidence of Serious Adverse Events by System Organ Class and Preferred Term (Study 3000-0522, Colonoscopy)

<i>System Organ Class Preferred Term</i>	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)
<i>Any SAE</i>	1 (1.0)	0	1 (1.9)
<i>Gastrointestinal disorders</i>	0	0	1 (1.9)
Peritoneal hemorrhage	0	0	1 (1.9)
<i>Injury, poisoning and procedural complications</i>	0	0	1 (1.9)
Splenic hematoma	0	0	1 (1.9)
<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i>	1 (1.0)	0	0
Colon cancer	1 (1.0)	0	0

Source: Study Report for 3000-0522, Table 3.4.9

Table 32 Patient Incidence of Serious Adverse Events by System Organ Class and Preferred Term (Study 3000-0524, Bronchoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
<i>Any SAE</i>	13 (12.6)	15 (10.1)
<i>Cardiac disorders</i>	1 (1.0)	3 (2.0)
Cardiac arrest	0	1 (0.7)
Cardiac failure congestive	1 (1.0)	0
Cardiomyopathy	1 (1.0)	0
Coronary artery disease	0	1 (0.7)
Ventricular tachycardia	0	1 (0.7)
<i>Congenital, familial and genetic disorders</i>	1 (1.0)	0
Cystic fibrosis	1 (1.0)	0
<i>Gastrointestinal disorders</i>	0	1 (0.7)
Intestinal perforation	0	1 (0.7)
Large intestine perforation	0	1 (0.7)
<i>Infections and infestations</i>	4 (3.9)	7 (4.7)
Abdominal abscess	0	1 (0.7)
Abdominal sepsis	0	1 (0.7)
Bronchitis acute	0	1 (0.7)
Bronchitis bacterial	1 (1.0)	1 (0.7)
Enterococcal bacteremia	1 (1.0)	0
Lung infection pseudomonal	0	1 (0.7)
Pneumonia	1 (1.0)	3 (2.0)
Pneumonia pneumococcal	0	1 (0.7)
Sepsis	0	1 (0.7)
Septic shock	1 (1.0)	0
<i>Injury, poisoning and procedural complications</i>	0	1 (0.7)
Brain herniation	0	1 (0.7)
<i>Investigations</i>	1 (1.0)	0
HIV test positive	1 (1.0)	0
<i>Metabolism and nutrition disorders</i>	1 (1.0)	0
Hypovolemia	1 (1.0)	0
<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i>	0	7 (4.7)
Lung neoplasm malignant	0	5 (3.4)
Lung squamous cell carcinoma stage unspecified	0	1 (0.7)
Non-small cell lung cancer	0	1 (0.7)
<i>Nervous system disorders</i>	1 (1.0)	1 (0.7)
Anoxic encephalopathy	0	1 (0.7)
Brain edema	0	1 (0.7)
Cerebrovascular accident	1 (1.0)	0
<i>Respiratory, thoracic and mediastinal disorders</i>	7 (6.8)	5 (3.4)
Acute respiratory failure	0	1 (0.7)
Chronic obstructive pulmonary disease	3 (2.9)	3 (2.0)

Table 32 Patient Incidence of Serious Adverse Events by System Organ Class and Preferred Term (Study 3000-0524, Bronchoscopy)

<i>System Organ Class</i> Preferred Term	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Laryngospasm	1 (1.0)	0
Pneumothorax	1 (1.0)	0
Respiratory arrest	1 (1.0)	0
Respiratory failure	2 (1.9)	3 (2.0)
<i>Vascular disorders</i>	1 (1.0)	0
Hypotension	1 (1.0)	0

Source: Study Report for 3000-0524, Table 3.4.9

Table 33 Patient Incidence of Serious Adverse Events by System Organ Class and Preferred Term (Study 3000-0523, Minor Surgical Procedures)

<i>System Organ Class</i> Preferred Term	Fospropofol 6.5 mg/kg N = 123 n (%)
<i>Any SAE</i>	4 (3.3)
<i>Cardiac disorders</i>	1 (0.8)
Cardiac arrest	1 (0.8)
<i>Congenital, familial, and genetic disorders</i>	2 (1.6)
Atrial septal defect	2 (1.6)
<i>Investigations</i>	1 (0.8)
Ammonia increased	1 (0.8)
<i>Nervous system disorders</i>	1 (0.8)
Hepatic encephalopathy	1 (0.8)
<i>Respiratory, thoracic and mediastinal disorders</i>	1 (0.8)
Apnea	1 (0.8)

Source: Study Report for 3000-0523, Table 2.5.8

8.7.3 Other Significant Adverse Events

8.7.3.1 Events Leading to Discontinuation of Study Drug or Study Procedure

In the phase 3 studies, 6 patients experienced an AE that led to discontinuation of study drug and/or procedure. No patient experienced an AE that led to discontinuation from the study. One patient discontinued the procedure due to hypotension that was considered related to study drug (3000-0522) and 2 patients discontinued study drug, 1 due to

hypotension considered related to study drug (3000-0523) and 1 who experienced severe paresthesia that was considered related to study drug (3000-0524). One patient who discontinued study procedure was in the midazolam dosing group (study 3000-0522) (Table 34 and Table 35).

Table 34 Adverse Events Leading to Discontinuation of Study Drug and/or Procedure (Studies 3000-0522, 3000-0523, and 3000-0524)

Reason for discontinuation	Study 3000-0522 (Colonoscopy)			3000-0523 (Minor surgical procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)	Fospropofol 6.5 mg/kg N = 123 n (%)	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Discontinued Procedure	0	1 (0.6)	1 (1.9)	0	1 (1.0)	0
Hypotension	0	1 (0.6)	0	0	0	0
Abdominal tenderness	0	0	1 (1.9)	0	0	0
Pneumothorax	0	0	0	0	1 (1.0)	0
Discontinued Study Drug	0	0	0	1 (0.8)	0	1 (0.7)
Hypotension	0	0	0	1 (0.8)	0	0
Paresthesia	0	0	0	0	0	1 (0.7)
Discontinued Study Drug and Procedure	0	0	0	0	0	1 (0.7)
Cough	0	0	0	0	0	1 (0.7)

Source: Study Report for 3000-0522, page 84; Study Report for 3000-0523, page 58; Study Report for 3000-0524, page 91

**Table 35 Patients who Discontinued Study Drug and/or Procedure due to an Adverse Event
(Studies 3000-0522, 3000-0523, and 3000-0524)**

Study / Demographics (age, sex, ASA) Procedure	Randomized dose Total dose	Reason for discontinuation of procedure and/or study drug	Relationship to study drug
3000-0522 / 43 yrs, female, ASA P3; Colonoscopy	Fospropofol 6.5 mg/kg (998 mg total) Fentanyl 100 mcg	Discontinued Procedure due to Hypotension	Related
3000-0522 / 54 yrs, female, ASA P1; Colonoscopy	Midazolam 0.02 mg/kg (5.2 mg total) Fentanyl 75 mcg	Discontinued Procedure due to Lower Left Quadrant Abdominal Tenderness	Unrelated
3000-0523 / 39 yrs, female, ASA P2; Lithotripsy	Fospropofol 6.5 mg/kg (805 mg total) Fentanyl 100 mcg Propofol lipid emulsion 6 mL	Discontinued study drug due to Hypotension	Related
3000-0524 / 55 yrs female, ASA P2; Bronchoscopy	Fospropofol 2.0 mg/kg (280 mg total) Fentanyl 50 mcg	Discontinued Procedure due to Pneumothorax	Unrelated
3000-0524 / 47 yrs, male, ASA P2; Bronchoscopy	Fospropofol 6.5 mg/kg (613 mg total) Fentanyl 100 mcg	Discontinued Procedure and study drug due to Severe Coughing	Unrelated
3000-0524 / 52 yrs, female, ASA P3; Bronchoscopy	Fospropofol 6.5 mg/kg (438 mg total) Fentanyl 0 mcg	Discontinued study drug to Severe Paresthesia	Related

Source: Study Report for 3000-0522, Listing 1.2, Listing 2.2, Listing 3.2.1; Study Report for 3000-0523, Listing 1.1, Listing 1.5, Listing 2.2.1; Study Report for 3000-0524, Listing 1.2, Listing 2.2, Listing 3.2.1

8.7.4 Adverse Events of Special Interest

8.7.4.1 Sedation-related Adverse Events

Sedation-related AEs (apnea, hypoxemia, hypotension, and bradycardia) were expected in these clinical studies of a sedative-hypnotic agent and were pre-defined in the protocols. Specific definitions of SRAEs for the phase 3 studies are presented in Table 36.

Table 36 Definition of Sedation-Related Adverse Events (Studies 3000-0522, 3000-0523, 3000-0524)

Event	Definition
Apnea	Lack of spontaneous breathing >30 seconds
Hypoxemia	O ₂ saturation <90% for >30 seconds
Hypotension	Systolic blood pressure <90 mm Hg and required medical intervention
Bradycardia	Heart rate <50 beats per minute (bpm) and required medical intervention

Source: Study Report for 3000-0522, Table 8; Study 3000-0523, Table 5; Study Report for 3000-0524, Table 8

The frequency of SRAEs was higher in bronchoscopy study 3000-0524 compared colonoscopy study 3000-0522 or minor surgical procedures study 3000-0523, which is likely a reflection of the demographics of this patient population (Table 37). When they occurred, SRAEs were generally transient, rarely treatment limiting, and manageable in the clinical setting for which the drug is intended.

In colonoscopy study 3000-0522, 5 patients administered fospropofol experienced SRAEs (hypotension or hypoxemia). One patient randomized to the midazolam group had an SRAE of hypotension. Hypoxemia experienced by 1 patient in the fospropofol 6.5 mg/kg group was considered mild in severity, and was managed with verbal stimulation. Hypotension was experienced by 2 patients in the 2.0 mg/kg group, 2 patients in the 6.5 mg/kg group, and 1 patient in the midazolam group. In the Investigator's opinion, the hypotension was classified as mild in 3 patients and moderate in 2 patients, and considered treatment-related in all 5 patients. There were no episodes of apnea or bradycardia reported in this study.

Of the 6 patients who experienced SRAEs in study 3000-0522, 1 patient received midazolam only, 1 patient received fospropofol only, and 3 patients were administered fospropofol but required administration of an alternative sedative (midazolam) prior to occurrence of the SRAE. One patient received only fospropofol prior to becoming hypotensive, but was subsequently administered midazolam before discontinuation of the colonoscopy.

In bronchoscopy study 3000-0524, 43 patients (17.1%) administered fospropofol experienced SRAEs of apnea, hypotension, or hypoxemia; there were no episodes of bradycardia. The most frequently occurring SRAE was hypoxemia: 15.4% of patients in the fospropofol 6.5 mg/kg group and 12.6% of patients in the 2.0 mg/kg group.

There was a single occurrence of apnea during the study and it was experienced by a patient in the fospropofol 6.5 mg/kg group. The event was moderate, lasted 188 seconds, resolved following chin lift and tactile stimulation.

In study 3000-0524, all 8 of the patients who experienced hypotension were in the fospropofol 6.5 mg/kg group and none of the patients received alternative sedative medication prior to onset of the event. The incidences of hypotension ranged from 66 to 1440 seconds in duration. The hypotension resolved without treatment in 2 patients, following increased oxygen flow in 1 patient, following administration of IV fluids in 4 patients, and following verbal stimulation in addition to IV fluids in 1 patient. Treatment with inotropes was not required. One of the events was assessed by the Investigator to be of mild severity and the other 7 events were assessed by the Investigator to be of moderate severity.

Of the 23 patients in the fospropofol 6.5 mg/kg group who experienced hypoxemia in study 3000-0524, 3 patients received midazolam as an alternative sedative medication prior to onset of the event. The incidences of hypoxemia in the 6.5 mg/kg group ranged from 20 to 7260 seconds. Two patients experienced severe hypoxemia, and the remainder of the events were mild or moderate in severity. Of the 13 patients in the 2.0 mg/kg group who experienced hypoxemia, 10 patients received midazolam as an alternative sedative medication prior to onset of the event (including 1 patient who received both midazolam and propofol). The incidences of hypoxemia in the 2.0 mg/kg group ranged from 40 to 5,177 seconds.

In study 3000-0523, 5/123 patients experienced an SRAE (bradycardia, hypotension, or hypoxemia) during the study. There were no episodes of apnea experienced on the day of the procedure. One patient experienced mild hypoxemia that resolved with chin lift and verbal stimulation. Three patients experienced mild or moderate hypotension that resolved with administration of fluids and/or concomitant medications. One patient experienced both moderate bradycardia and moderate hypotension that resolved with administration of concomitant medications ([Table 37](#), [Table 38](#)).

Table 37 Patient Incidence of Sedation-Related Adverse Events (Studies 3000-0522, 3000-0523, and 3000-0524)

Sedation-Related AE	Study 3000-0522 (Colonoscopy)			Study 3000-0523 (minor surgical procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)	Fospropofol 6.5 mg/kg N = 123 n (%)	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Patients with any SRAE	2 (2.0)	3 (1.9)	1 (1.9)	5 (4.1)	13 (12.6)	30 (20.1)
Apnea	0	0	0	0	0	1 (0.7)
Hypoxemia	0	1 (0.6)	0	1 (0.8)	13 (12.6)	23 (15.4)
Hypotension	2 (2.0)	2 (1.3)	1 (1.9)	4 (3.3)	0	8 (5.4)
Bradycardia	0	0	0	1 (0.8)	0	0

Source: Study Report for 3000-0522, Table 3.3.1; Study Report for 3000-0523, Table 2.3.1; Study Report for 3000-0524, Table 3.3.1

The most common SRAE requiring airway assistance during the conduct of the phase 3 program was hypoxemia (Table 38) and the most frequent intervention for hypoxemia consisted of increased oxygen flow through the existing nasal cannula (Table 39). The study sites were asked to capture the need for airway assistance and the following specific types of airway assistance were tabulated: repositioning, verbal or tactile stimulation, increased oxygen flow, face mask (100% O₂), chin lift, jaw thrust, nasal trumpet, oral airway, manual ventilation [bag-valve-mask] and mechanical ventilation. The SRAEs requiring intervention are summarized in Table 39.

Table 38 Patient Incidence of Sedation-Related Adverse Events Requiring Intervention (Studies 3000-0522, 3000-0523, and 3000-0524)

Sedation-Related AE Requiring Airway Assistance	Study 3000-0522 (Colonoscopy)			Study 3000-0523 (minor surgical procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)	Fospropofol 6.5 mg/kg N = 123 n (%)	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Patients with any SRAE	0	1 (0.6)	0	1 (0.8)	11 (10.7)	25 (16.8)
Apnea	0	0	0	0	0	1 (0.7)
Hypoxemia	0	1 (0.6)	0	1 (0.8)	11 (10.7)	23 (15.4)
Hypotension	0	0	0	0	0	2 (1.3)
Bradycardia	0	0	0	0	0	0

Source: Study Report for 3000-0522, Table 3.2.5; Study Report for 3000-0523, Table 2.2.6; Study Report for 3000-0524, Table 3.2.5

The need for airway assistance was uncommon in colonoscopy study 3000-0522. A single patient experienced hypoxemia that was managed by verbal stimulation. One additional patient in this study experienced snoring that required a chin lift, but it was not considered a SRAE (Table 39 and Table 38).

The need for airway assistance to treat hypoxemia was higher in bronchoscopy study 3000-0524; the majority of these events were treated with increased oxygen flow through the existing nasal cannula (Table 39). One patient (0524-430-0006) in this study required manual ventilation (see Section 8.7.2 Serious Adverse Events).

In the minor surgical procedures study 3000-0523, 1 patient had an SRAE of hypoxemia that required airway assistance (verbal stimulation and chin lift). In this study, airway assistance was administered to 6 additional patients for reasons other than an SRAE. One patient was administered increased O₂ flow and then switched to face mask (100% O₂) due to AEs of crying, dystonia, and urticaria. One patient received increased O₂ flow for SpO₂ 90% (from 92%) that returned to 94% with the increased O₂. One additional patient received a chin lift and an oral airway due to inadequate sedation resulting in administration of sevoflurane. (Table 42) The remaining 3 patients received suctioning 1 to 2 minutes prior to the end of their esophagogastroduodenoscopy.

Table 39 Patient Incidence of Airway Assistance (Studies 3000-0522, 3000-0523, and 3000-0524)

Airway Assistance	Study 3000-0522 (Colonoscopy)			Study 3000-0523 (minor surgical procedures)	Study 3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg N = 102 n (%)	Fospropofol 6.5 mg/kg N = 158 n (%)	Midazolam 0.02 mg/kg N = 52 n (%)	Fospropofol 6.5 mg/kg N = 123 n (%)	Fospropofol 2.0 mg/kg N = 103 n (%)	Fospropofol 6.5 mg/kg N = 149 n (%)
Increased O ₂ flow	0	0	0	2 (1.6)	12 (11.7)	28 (18.8)
Patient repositioning	0	0	0	0	0	3 (2.0)
Verbal stimulation	0	1 (0.6)	0	1 (0.8)	2 (1.9)	6 (4.0)
Tactile stimulation	0	0	0	0	1 (1.0)	4 (2.7)
Face mask (100% O ₂)	0	0	0	1 (0.8)	1 (1.0)	1 (0.7)
Jaw thrust	0	0	0	0	3 (2.9)	2 (1.3)
Chin lift	0	1 (0.6)	0	2 (1.6)	1 (1.0)	5 (3.4)
Nasal trumpet	0	0	0	0	0	0
Oral airway	0	0	0	1 (0.8)	0	0
Suction	0	0	0	3 (2.4)	0	3 (2.0)
Manual ventilation (bag-valve-mask)	0	0	0	0	0	1 (0.7)
Mechanical ventilation (intubation)	0	0	0	0	0	0

Note: Some patients may have more than one type of airway assistance
Study Report for 30000-0522, Table 3.2.1; Study Report for 3000-0523, Table 2.2.1; Study Report for 3000-0524, Table 3.2.1

8.7.4.2 Depth of Sedation and Sedation Related Adverse Events

Patients in studies 3000-0522, 3000-0524, and 3000-0523 who reached MOAA/S scores of 0 or 1 are described in [Table 40](#), [Table 41](#), and [Table 42](#), respectively. These tables also provide information as to whether or not the patient received alternative sedative medication, SRAEs that occurred in these patients, and any airway assistance administered.

In study 3000-0522, 6 (3.8 %) and 1 (1.0 %) of patients in the fospropofol 6.5 mg/kg and 2.0 mg/kg treatment groups, respectively reached MOAA/S scores of 1 or 0 ([Table 17](#) and [Table 40](#)). No patient in the midazolam group reached a MOAA/S score of 1 or 0.

One of 6 patients who reached a MOAA/S score of 1 or 0 experienced a SRAE. This patient was randomized to the 6.5 mg/kg treatment group and reached a MOAA/S score of 0 after receiving a total dose of 770 mg of fospropofol and 2.0 mg midazolam as an

alternative sedative agent. The patient experienced mild hypoxemia that resolved with verbal stimulation.

Table 40 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0522, Colonoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
40, female, 105 kg, ASA P1	Fospropofol 2.0 mg/kg (280 mg total) Fentanyl 50 mcg	Midazolam 2 mg	2	0	None
46, male, 84 kg, ASA P1	Fospropofol 6.5 mg/kg (962.5 mg total) Fentanyl 50 mcg	Midazolam 2 mg	6	10	None
51, female, 69 kg, ASA P1	Fospropofol 6.5 mg/kg (770 mg total) Fentanyl 50 mcg	Midazolam 1.5 mg	2	0	None
52, male, 86 kg, ASA P1	Fospropofol 6.5 mg/kg (980 mg total) Fentanyl 50 mcg	Midazolam 2 mg	8	8	None
55, female, 66 kg, ASA P2	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 125 mcg	Midazolam 3 mg	0	8	None
55, male, 70 kg, ASA P1	Fospropofol 6.5 mg/kg (770 mg total) Fentanyl 75 mcg	Midazolam 2 mg	0	2	Hypoxemia - mild (Verbal stimulation)

Source: Study Report for 3000-0522, Listing 1.2, Listing 2.2, Listing 3.1, Listing 3.2.4, Listing 101

In bronchoscopy study 3000-0524, 24 (16.0 %) and 8 (7.8 %) of patients in the fospropofol 6.5 mg/kg and 2.0 mg/kg treatment groups, respectively reached MOAA/S scores of 1 or 0, (Table 17 and Table 41). Three of the 8 patients in the 2.0 mg/kg group experienced mild or moderate hypoxemia; no episodes of apnea, hypotension, or bradycardia were experienced in this group. All 3 of these patients received midazolam as an alternative sedative. The hypoxemia resolved with increased O₂ only in 2 patients and increased O₂, face mask O₂, and jaw thrust in the third patient.

In the 6.5 mg/kg group, 10 of the 24 patients experienced a SRAE. None of these patients received an alternative sedative. Seven patients in this group experienced hypoxemia, 2 of which were considered severe. One patient experienced apnea,

hypoxemia, and hypotension, all of which were considered moderate. Two patients experienced hypotension, which was considered moderate. No patient in this group experienced bradycardia. The single case of apnea was managed with chin lift; increased O₂; and tactile stimulation. In most cases, hypoxemia was managed with increase O₂ flow. Other tactics to manage this event included verbal or tactile stimulation, patient repositioning, suction, chin lift, or jaw thrust. One patient required increased O₂ flow and mask ventilation for treatment of severe hypoxemia. Hypotension was managed with verbal and tactile stimulation, chin lift, increased O₂ flow.

Table 41 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0524, Bronchoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
65, male, 79 kg, ASA P1	Fospropofol 2.0 mg/kg (262.5 mg total) Fentanyl 50 mcg	Midazolam 5 mg	4	0	None
56, female, 52 kg, ASA P2	Fospropofol 2.0 mg/kg (227.5 mg total) Fentanyl 50 mcg	Midazolam 3.5 mg	2	0	None
31, male, 68 kg, ASA P4	Fospropofol 2.0 mg/kg (157.5 mg total) Fentanyl 300 mcg	Midazolam 5 mg	52	0	Hypoxemia - moderate (Face mask; Increased oxygen flow; Jaw thrust)
75, male, 77 kg, ASA P2	Fospropofol 2.0 mg/kg (227.5 mg total) Fentanyl 100 mcg	Midazolam 4 mg	18	0	Hypoxemia - mild (Increased oxygen flow)
66, female, 43 kg, ASA P4	Fospropofol 2.0 mg/kg (140 mg total) Fentanyl 200 mcg	Midazolam 5 mg	8	0	None
43, female, 61 kg, ASA P2	Fospropofol 2.0 mg/kg (227.5 mg total) Fentanyl 150 mcg	Midazolam 3 mg	2	0	None

Table 41 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0524, Bronchoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
82, female, 71 kg, ASA P2	Fospropofol 2.0 mg/kg (210 mg total) Fentanyl 50 mcg	Midazolam 2 mg	12	0	Hypoxemia - moderate (Increased oxygen flow)
75, male, 60 kg, ASA P3	Fospropofol 2.0 mg/kg (157.5 mg total) Fentanyl 75 mcg	Midazolam 3 mg	2	0	None
48, female, 75 kg, ASA P2	Fospropofol 6.5 mg/kg (490 mg total) Fentanyl 50 mcg	None	6	0	Hypoxemia - severe (Increased oxygen flow; patient repositioning, suction, verbal stimulation)
39, female, 110 kg, ASA P2	Fospropofol 6.5 mg/kg (997.5 mg total) Fentanyl 50 mcg	Midazolam 2 mg	4	0	None
55, male, 88 kg, ASA P2	Fospropofol 6.5 mg/kg (717.5 mg total) Fentanyl 50 mcg	None	6	0	Hypotension - moderate (Chin lift; tactile stimulation; verbal stimulation)
57, male, 100 kg, ASA P2	Fospropofol 6.5 mg/kg (577.5 mg total) Fentanyl 50 mcg	None	4	0	Apnea - moderate; Hypoxemia - moderate; Hypotension - moderate (Chin lift; increased oxygen flow; tactile stimulation)
80, female, 55 kg, ASA P2	Fospropofol 6.5 mg/kg (280 mg total) Fentanyl 50 mcg	None	8	0	Hypoxemia - moderate (Increased oxygen flow)

Table 41 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0524, Bronchoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
78, male, 92 kg, ASA P3	Fospropofol 6.5 mg/kg (437.5 mg total) Fentanyl 50 mcg	None	2	2	Hypoxemia (SAE) - severe (Increased oxygen flow; Manual ventilation)
67, male, 59 kg ASA P3	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 50 mcg	None	6	0	None
68, male, 81 kg, ASA P2	Fospropofol 6.5 mg/kg (507.5 mg total) Fentanyl 50 mcg	None	0	2	None
64, male, 73 kg, ASA P3	Fospropofol 6.5 mg/kg (350 mg total) Fentanyl 50 mcg	None	4	0	None
65, female, 62 kg, ASA P3	Fospropofol 6.5 mg/kg (507.5 mg total) Fentanyl 75 mcg	None	2	0	Hypoxemia - mild (Increased oxygen flow)
58, male, 80 kg, ASA P3	Fospropofol 6.5 mg/kg (630 mg total) Fentanyl 50 mcg	None	6	0	None
44, male, 81 kg, ASA P2	Fospropofol 6.5 mg/kg (665 mg total) Fentanyl 50 mcg	None	8	0	Hypoxemia - mild (Increased oxygen flow; Jaw thrust; Patient repositioning)
72, male, 92 kg, ASA P3	Fospropofol 6.5 mg/kg (542.5 mg total) Fentanyl 100 mcg	None	2	0	None

Table 41 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0524, Bronchoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
75, female, 85 kg, ASA P4	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 50 mcg	None	4	0	None
46, male, 45 kg, ASA P2	Fospropofol 6.5 mg/kg (385 mg total) Fentanyl 50 mcg	None	20	0	None
45, male, 75 kg, ASA P4	Fospropofol 6.5 mg/kg (612.5 mg total) Fentanyl 50 mcg	None	6	10	None
63, male, 65 kg, ASA P3	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 50 mcg	None	0	0	Hypoxemia - moderate (Increased oxygen flow)
64, male, 90 kg, ASA P3	Fospropofol 6.5 mg/kg (437.5 mg total) Fentanyl 50 mcg	None	2	0	Hypoxemia - moderate (Increased oxygen flow; Jaw thrust)
64, male, 64 kg, ASA P2	Fospropofol 6.5 mg/kg (420 mg total) Fentanyl 50 mcg	None	6	0	None
52, female, 88 kg, ASA P2	Fospropofol 6.5 mg/kg (857.5 mg total) Fentanyl 50 mcg	None	8	0	None
70, male, 41 kg, ASA P3	Fospropofol 6.5 mg/kg (350 mg total) Fentanyl 50 mcg	None	2	0	No SRAE (Increased oxygen flow)
56, female, 75 kg, ASA P2	Fospropofol 6.5 mg/kg (735 mg total) Fentanyl 50 mcg	None	4	0	None

Table 41 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0524, Bronchoscopy)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
66, male, 81 kg, ASA P2	Fospropofol 6.5 mg/kg (612.5 mg total) Fentanyl 50 mcg	None	6	0	Hypotension - moderate
73, female, 55 kg, ASA P2	Fospropofol 6.5 mg/kg (280 mg total) Fentanyl 50 mcg	None	16	0	No SRAE (Increased oxygen flow)

Source: Study Report for 3000-0524, Listing 1.2, Listing 2.2, Listing 3.2.4, Listing 3.1, Listing 101

In study 3000-0523, 7 of 123 (5.7 %) reached a MOAA/S score of 1 or 0 ([Table 42](#)). One of these patients experienced a mild hypoxemia that resolved with chin lift and verbal stimulation.

Table 42 Patients with MOAA/S 0 or 1 at any time During the Procedure (Study 3000-0523, Minor Surgical Procedures)

Demographics (age, sex, weight, ASA)	Randomized dose Total dose	Alternative sedatives	Duration (min) at MOAA/S 1	Duration (min) at MOAA/S 0	SRAE (Airway Assistance)
60, female, 74 kg, ASA P2	Fospropofol 6.5 mg/kg (595 mg total) Fentanyl 50 mcg	None	4	0	None
47, male, 92 kg, ASA P1	Fospropofol 6.5 mg/kg (717.5 mg total) Fentanyl 50 mcg	None	2	0	None
46, female, 99 kg, ASA P2	Fospropofol 6.5 mg/kg (577.5 mg total) Fentanyl 50 mcg	None	0	14	None
52, female, 75 kg, ASA P2	Fospropofol 6.5 mg/kg (857.5 mg total) Fentanyl 50 mcg	None	4	2	None
54, female, 75 kg, ASA P2	Fospropofol 6.5 mg/kg (1225 mg total) Fentanyl 50 mcg	None	2	0	None
51, female, 83 kg, ASA P2	Fospropofol 6.5 mg/kg (822.5 mg total) Fentanyl 75 mcg	None	2	0	Hypoxemia – mild (chin lift, verbal stimulation)
41, female, 95 kg, ASA P2	Fospropofol 6.5 mg/kg (1137.5 mg total) Fentanyl 75 mcg	Midazolam 2.0 mg, Sevoflurane 1%	12	0	No SRAE (chin lift, oral airway)

Source: Study Report for 3000-0523, Listing 1.1, Listing 1.5, Listing 2.1, Listing 2.2.4, Listing 101

8.7.5 Clinical Laboratory Findings and Electrocardiogram Results

8.7.5.1 Clinical Laboratory Results

In the phase 3 studies utilizing the proposed dose titration regimen (3000-0522, 3000-0524), there were no findings of clinical concern in the results of clinical laboratory tests.

In the controlled studies utilizing the proposed dose titration regimen (3000-0522, 3000-0524), the most frequently experienced clinically significant changes from baseline laboratory test results for patients in the 2.0 mg/kg and 6.5 mg/kg groups included: (1) phosphate levels in 2/204 (1.0%), and 18/315 (5.7%); (2) total calcium levels in 9/218 (4.1%) and 9/327 (2.7%); and (3) albumin levels in 7/218 (3.2%) and 10/330 (3.0%), respectively ([Appendix A](#), Pooled data sets for 3000-0522 and

3000-0524 [Table 8-A](#)). With the exception of phosphate, the frequency of changes was similar in both dose groups.

Phosphate is distributed in extracellular water, thus a theoretical maximum change of phosphate in a 70 kg person, receiving the proposed standard dosing regimen and all supplements, would be less than 1 mg/dL. Reported changes in serum phosphate after bowel prep with sodium phosphate tablets range from 2.5 – 4.2 mg/dL ([Wruble L, 2007](#); [Rex D, 2006](#)).

The majority of significant elevations of phosphate (≥ 1 mg/dL) (15/20 patients) in the controlled studies (3000-0522, and 3000-0520, 3000-0524) occurred between screening (-14 to 0 days prior to procedure) and baseline (predosing period on the day of the procedure) in colonoscopy patients who had received a phosphate containing bowel preparation, but before receiving study drug ([Appendix A, Table 8-A](#)). These values often decreased between baseline and recovery (time period from end of the procedure to when the patient was discharged), as noted by the mean change of -0.05 (median 0.10) for those colonoscopy patients who received a phosphate bowel preparation and were randomized to the 6.5 mg/kg fospropofol disodium group.

Other changes in phosphate values between screening/baseline and baseline/recovery fall within the range reported for daily shifts in phosphate suggesting that the additional phosphate generated by fospropofol metabolism results in serum changes that are not clinically significant compared with daily dietary phosphate intake and that are comparable to normal diurnal variation ([Kemp, 1992](#)).

No laboratory findings were noted in the individual or combined analyses that require adjustment of dose or specific warnings or precautions.

8.7.5.2 Electrocardiograms

In the combined data sets from the fixed-dose and proposed dose titration studies and in patients who received fospropofol disodium in the prolonged duration study (3000-0413), there were no shifts from normal to clinically significant abnormal in ECG results for any patient. A thorough QT (time necessary for cardiac repolarization) study (3000-0521) was performed and a no subject had a QT interval corrected for heart rate (QT_c) > 480 milliseconds (ms) throughout the study, regardless of the QT correction formula used. No subject had an individually corrected QT interval (QT_{cI}), length of the QT interval corrected for heart rate by Fridericia's formula (QT_{cF}), or length of the QT interval corrected for heart rate by Studywise formula (QT_{cS}) change from Baseline that was > 60 ms.

8.7.5.3 Clinical Laboratory Results of Special Interest

Formaldehyde is generated as a normal product of cellular metabolism, and human exposure results from ingestion of food sources that contain formaldehyde or materials that can be metabolized to formaldehyde ([Dhareshwar, 2008](#)). As a product of the metabolism of fospropofol disodium, consideration was given to formate levels and the potential for formate toxicity. Assuming there was no elimination of formate, the expected mean change in formate levels for a 70 kg person, treated with the proposed standard dose titration regimen and all supplements, would be 3.6 mcg/mL. As background levels of formate are between 3 and 20 mcg/mL, and toxic levels are thought to be between 200 to 300 mcg/mL ([Hantson, 2005](#)), it is unlikely that bolus intermittent use of fospropofol disodium can affect formate levels.

Clinical indicators of possible formate toxicity (eg, abnormalities on ophthalmologic exams) were monitored in the development program. Formate levels were monitored in several studies (3000-0001, 3000-0102, 3000-0103, 3000-0104, 3000-0206, 3000-0207, 3000-0308, and 3000-0413) and did not increase above baseline levels after treatment with fospropofol disodium. In the prolonged infusion study, a single patient with renal and hepatic impairment who received 3987 mg fospropofol disodium over a 12 hour infusion demonstrated a formate level of 212 mcg/mL, which was above his elevated baseline level of 66.3 mcg/mL. There were no clinical findings consistent with formate toxicity, and fundoscopic examination at the conclusion of the infusion was normal.

8.7.5.4 Vital Signs

The average changes in vital signs (systolic BP, diastolic BP, heart rate, and respiration rate) for studies 3000-0522 and 3000-0524 from baseline to average during the procedure by initial dose in mg/kg are summarized in [Table 43](#).

Table 43 Average Changes in Vital Signs by Initial Dose (mg/kg) (Studies 3000 0522, and 3000-0524)

	3000-0522 (Colonoscopy)			3000-0524 (Bronchoscopy)	
	Fospropofol 2.0 mg/kg	Fospropofol 6.5 mg/kg	Midazolam 0.02 mg/kg	Fospropofol 2.0 mg/kg	Fospropofol 6.5 mg/kg
Change from baseline in systolic BP (mm Hg) to average during the procedure					
n=	102	158	52	102	147
Mean (± std deviation)	-10.7, (15.1)	-17.5 (14.5)	-11.0 (13.9)	-2.3 (15.6)	-12.5 (16.6)
Min, max	-51, 24	-55, 21	-58, 33	-52, 35	-76, 33
Change from baseline in diastolic BP (mm Hg) to average during the procedure					
n =	102	158	52	102	147
Mean (± std deviation)	-4.8 (9.5)	-8.7 (9.0)	-4.0 (6.9)	-0.4 (10.8)	-4.3 (12.5)
Min, max	-31, 15	-52, 20	-20, 18	-34, 53	-35, 34
Change from baseline in heart rate (bpm) to average during the procedure					
n =	102	158	52	102	148
Mean (± std deviation)	-1.4 (7.1)	-0.6 (7.3)	0.4 (6.5)	9.3 (11.6)	8.9 (10.3)
Min, max	-18, 17	-21, 21	-10, 17	-36, 50	-18, 38
Change from baseline in respiration rate (breaths per minute) to average during the procedure					
n =	102	158	52	100	148
Mean (± std deviation)	-0.3 (3.2)	-0.4 (3.0)	-0.5 (4.7)	0.8 (3.7)	-0.2 (3.9)
Min, max	-8, 10	-9, 9	-27, 5	-10, 11	-11, 12

Source data: Module 5.3.5.3, Table 201, Table 201b of the NDA

Although hypotension as an adverse event (defined as a systolic blood pressure <90 mm Hg and requiring medical intervention) was infrequently reported in the controlled pivotal trials, variability was observed in blood pressure responses. For example, the minimum and maximum changes in systolic blood pressure observed for the 6.5 mg/kg dose ranged from -52 mm Hg to + 35 mm Hg. Decreases in systolic and diastolic blood pressure appeared to be dose related. Changes in systolic and diastolic blood pressure were transient and usually returned to normal levels without medical intervention.

No dose-dependent changes in heart rate were observed.

No dose-dependent changes in respiration rates were observed.

8.7.6 Safety Analyses of Subpopulations

Sedation-related AEs requiring intervention in studies 3000-0522 and 3000-0524 are presented by age (Table 44), race (Table 45), weight (Table 46), sex (Table 47), ASA status (Table 48), and special populations (Table 49). There was a low frequency of SRAEs in study 3000-0522, and no specific statements regarding subpopulation related trends can be made. For all of the groups analyzed, and all of the subpopulations, hypoxemia was the most commonly reported SRAE.

Age

In study 3000-0524, the incidence of hypoxemia was similar for all 3 age groups in the 2.0 mg/kg group; however, for the 6.5 mg/kg group, the incidence of hypoxemia increased with age: 18-<65 (19.1%), ≥65 (26.2%), ≥75 (36.8%) (Table 44). The incidence of hypotension was similar between all groups for the 6.5 mg/kg arm: 18-<65 (6.7%), ≥65 (4.9%), ≥75 (5.3%).

Race

In study 3000-0524 the incidence of hypoxemia was somewhat lower in blacks compared to whites in the 2.0 mg/kg group (7.1% vs. 11.9%); and the 6.5 mg/kg group (12.5% vs. 17.7%). The incidence of hypotension was similar between whites (6.2%) and blacks (6.3%) in the 6.5 mg/kg group; hypotension was not reported for patients in the 2.0 mg/kg group. Too few patients were classified as “other” to make any specific statements related to SRAEs (Table 45).

Weight

In study 3000-0524, the incidence of hypoxemia was similar for all 3 weight groups in the 2.0 mg/kg study arm. In the 6.5 mg/kg group, the incidence of hypoxemia was

similar in patients who weighed <60 kg (22.2 %) and >90 kg (21.4%); whereas hypoxemia was reported in 12.3% of patients who weighed between 60 and 90 kg. Hypotension was reported for 3.7% (<60 kg), 7.4% (60-90 kg) and 4.8% (>90 kg) of patients in the 6.5 mg/kg arm and no patients in the 2.0 mg/kg arm (Table 46).

Sex

In study 3000-0524, hypoxemia was the most common SRAE for males and females. The incidence of hypoxemia was similar for males and females in the 2.0 mg/kg study arm; however, for the 6.5 mg/kg group, the incidence of hypoxemia was somewhat lower in males compared to females (14% vs. 20.3%) and the incidence of hypotension was somewhat higher in males compared to females (9.3% vs. 1.6%) (Table 47).

ASA Status

Overall, the percentage of ASA P3/4 patients in the controlled phase 3 studies was highest in the bronchoscopy studies, ASA P3 36.5%; ASA P4 6.0%, (Table 10 and Table 11). There were too few ASA P3 or P4 patients in the phase 3 colonoscopy study to draw any conclusions regarding the effect of ASA status on SRAE requiring airway assistance. Patient incidence in the bronchoscopy study 3000-0524 (Table 48) for SRAEs requiring intervention in patients receiving 6.5 mg/kg fospropofol disodium was: 19 of 81 (23.5%) ASA P1/P2 patients, 13 of 61 (21.3%) ASA P3 patients and 1 of 7 (14.3%) ASA P4 patients. For patients in this study receiving 2.0 mg/kg fospropofol disodium the incidence was: 6 of 64 (9.4%) ASA P1/P2 patients and 3 of 31 (9.7%) ASA P3 patients, and 2 of 8 (25.0%) ASA P4 patients.

Renal and Hepatic Impairment

Patients were considered to have moderate renal impairment if their creatinine clearance was < 50 mL/min. There were a total of 43 patients with moderate renal impairment. Of those, 6 patients experienced an SAE, all were considered unrelated to study drug, and no deaths occurred in patients with moderate hepatic impairment. Five patients experienced an SRAE (4 patients with hypoxemia and 1 patient with hypotension). Patients with a creatinine clearance <30 mL/min were considered to have severe renal impairment. Of the 7 patients with severe renal impairment, all received the reduced dose based on their age or ASA status. One of the 7 patients with severe renal impairment experienced an SAE that was considered unrelated to study drug. No deaths occurred in patients with severe renal impairment. One patient experienced an SRAE of hypoxemia that was treated with increased oxygen flow. The number of patients with severe renal impairment is too small to draw any conclusions about the influence of renal impairment on the potential occurrence of SRAEs (Table 49).

Patients were considered to have moderate to severe hepatic impairment based the Child-Pugh scale and a complete review of their medical history (*Guidance for Industry, 2003*).

Of the 8 patients with moderate to severe hepatic impairment, 5 received the reduced dose based on their age or ASA status. Two patients with moderate to severe hepatic impairment experienced an SAE, both were considered unrelated to study drug, and one death occurred in patients with hepatic impairment (study 3000-0524 bronchoscopy). One patient experienced an SRAE of hypotension. The number of patients with moderate to severe hepatic impairment is too small to draw any conclusions about the influence of hepatic impairment on the potential occurrence of SRAEs.

Table 44 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by Age

Type of Event	Study 3000-0522 Colonoscopy									Study 3000-0524 Bronchoscopy					
	Fospropofol 2.0 mg/kg N = 102			Fospropofol 6.5 mg/kg N = 158			Midazolam 0.02 mg/kg N = 52			Fospropofol 2.0 mg/kg N = 103			Fospropofol 6.5 mg/kg N = 149		
Age in years	18-<65 m = 88	65+ m = 14	75+ m = 1	18-<65 m = 137	65+ m = 21	75+ m = 4	18-<65 m = 42	65+ m = 10	75+ m = 1	18-<65 m = 60	65+ m = 42	75+ m = 18	18-<65 m = 89	65+ m = 61	75+ m = 19
Sedation-related AE requiring intervention n (%)	1 (1.1)	1 (7.1)	0	4 (2.9)	0	0	0	1 (10.0)	0	8 (13.3)	3 (7.1)	2 (11.1)	17 (19.1)	16 (26.2)	7 (36.8)
Apnea	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.1)	0	0
Bradycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	1 (1.1)	1 (7.1)	0	3 (2.2)	0	0	0	1 (10.0)	0	0	0	0	6 (6.7)	3 (4.9)	1 (5.3)
Hypoxemia	0	0	0	1 (0.7)	0	0	0	0	0	8 (13.3)	3 (7.1)	2 (11.1)	12 (13.5)	13 (21.3)	6 (31.6)
Airway Management n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	1 (5.3)
Manual Ventilation	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	1 (5.3)

Source: Table 184 a

Table 45 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by Race

Type of Event	Study 3000-0522 Colonoscopy									Study 3000-0524 Bronchoscopy					
	Fospropofol 2.0 mg/kg N = 102			Fospropofol 6.5 mg/kg N = 158			Midazolam 0.02 mg/kg N = 52			Fospropofol 2.0 mg/kg N = 103			Fospropofol 6.5 mg/kg N = 149		
Race	W m = 69	B m = 20	O m = 13	W m = 133	B m = 11	O m = 14	W m = 43	B m = 6	O m = 3	W m = 84	B m = 14	O m = 4	W m = 130	B m = 16	O m = 4
Sedation-related AE requiring intervention n (%)	2 (2.9)	0	0	3 (2.3)	0	1 (7.1)	1 (2.3)	0	0	10 (11.9)	1 (1.7)	0	31 (23.8)	2 (12.5)	0
Apnea	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (6.3)	0
Bradycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	2 (2.9)	0	0	2 (1.5)	0	1 (7.1)	1 (2.3)	0	0	0	0	0	8 (6.2)	1 (6.3)	0
Hypoxemia	0	0	0	1 (0.8)	0	0	0	0	0	10 (11.9)	1 (7.1)	0	23 (17.7)	2 (12.5)	0
Airway Management n (%)	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0	0
Manual Ventilation	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0	0

W=White; B=Black; O=Other, m=the number of patients included in the noted subpopulation for a given study arm

Source: Table 186a

Table 46 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by Weight

Type of Event	Study 3000-0522									Study 3000-0524					
	Fospropofol 2.0 mg/kg N = 102			Colonoscopy Fospropofol 6.5 mg/kg N = 158			Midazolam 0.02 mg/kg N = 52			Fospropofol 2.0 mg/kg N = 103			Fospropofol 6.5 mg/kg N = 149		
Weight in kg	<60 m = 13	60-<90 m = 56	90 + m = 33	<60 m = 9	60-<90 m = 86	90 + m = 63	<60 m = 4	60-<90 m = 31	90 + m = 17	<60 m = 19	60-<90 m = 51	90 + m = 32	<60 m = 27	60-<90 m = 81	90 + m = 42
Sedation-related AE requiring intervention n (%)	1 (7.7)	1 (1.8)	0	1 (11.1)	2 (2.3)	1 (1.6)	0	1 (3.2)	0	2 (10.5)	6 (11.8)	3 (9.4)	7 (25.9)	16 (19.8)	10 (23.8)
Apnea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (2.4)
Bradycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	1 (7.7)	1 (1.8)	0	1 (11.1)	1 (1.2)	1 (1.6)	0	1 (3.2)	0	0	0	0	1 (3.7)	6 (7.4)	2 (4.8)
Hypoxemia	0	0	0	0	1 (1.2)	0	0	0	0	2 (10.5)	6 (11.8)	3 (9.4)	6 (22.2)	10 (12.3)	9 (21.4)
Airway Management n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (2.4)
Manual Ventilation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (2.4)

m = the number of patients included in the noted subpopulation for a given study arm

Source: Table 187a

Table 47 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by Sex

Type of Event	Study 3000-0522						Study 3000-0524			
	Fospropofol 2.0 mg/kg N = 102		Colonoscopy Fospropofol 6.5 mg/kg N = 158		Midazolam 0.02 mg/kg N = 52		Bronchoscopy Fospropofol 2.0 mg/kg N = 103		Fospropofol 6.5 mg/kg N = 149	
Sex	M m = 46	F m = 56	M m = 76	F m = 82	M m = 34	F m = 18	M m = 54	F m = 48	M m = 86	F m = 64
Sedation-related AE requiring intervention n (%)	0	2 (3.6)	1 (1.3)	3 (3.7)	1 (2.9)	0	6 (11.1)	5 (10.4)	19 (22.1)	14 (21.9)
Apnea	0	0	0	0	0	0	0	0	1 (1.2)	0
Bradycardia	0	0	0	0	0	0	0	0	0	0
Hypotension	0	2 (3.6)	0	3 (3.7)	1 (2.9)	0	0	0	8 (9.3)	1 (1.6)
Hypoxemia	0	0	1 (1.3)	0	0	0	6 (11.1)	5 (10.4)	12 (14.0)	13 (20.3)
Airway Management n (%)	0	0	0	0	0	0	0	0	1 (1.2)	0
Manual Ventilation	0	0	0	0	0	0	0	0	1 (1.2)	0

M=Male; F=Female; m = the number of patients included in the noted subpopulation for a given study arm

Source Table 185a:

Table 48 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by ASA Status

Type of Event	Study 3000-0522 Colonoscopy									Study 3000-0524 Bronchoscopy					
	Fospropofol 2.0 mg/kg N = 102			Fospropofol 6.5 mg/kg N = 158			Midazolam 0.02 mg/kg N = 52			Fospropofol 2.0 mg/kg N = 103			Fospropofol 6.5 mg/kg N = 149		
ASA Status	P1/P2 m = 98	P3 m = 4	P4 m = 0	P1/P2 m = 153	P3 m = 5	P4 m = 0	P1/P2 m = 49	P3 m = 3	P4 m = 0	P1/P2 m = 64	P3 m = 31	P4 m = 8	P1/P2 m = 81	P3 m = 61	P4 m = 7
Sedation-related AE requiring intervention n (%)	2 (2.0)	0	0	3 (2.0)	1 (20.0)	0	1 (2.0)	0	0	6 (9.4)	3 (9.7)	2 (25.0)	19 (23.5)	13 (21.3)	1 (14.3)
Apnea	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.2)	0	0
Bradycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	2 (2.0)	0	0	2 (1.3)	1 (20.0)	0	1 (2.0)	0	0	0	0	0	7 (8.6)	2 (3.3)	0
Hypoxemia	0	0	0	1 (0.7)	0	0	0	0	0	6 (9.4)	3 (9.7)	2 (25.0)	13 (16.0)	11 (18.0)	1 (14.3)
Airway Management n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	0
Manual Ventilation	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	0

m = the number of patients included in the noted subpopulation for a given study arm

Source: Table 188f

Table 49 Number (%) of Patients with Sedation-related Adverse Events and Airway Management by Special Disease Population

Type of Event	Study 3000-0522 Colonoscopy						Study 3000-0524 Bronchoscopy			
	Fospropofol 2.0 mg/kg N = 102		Fospropofol 6.5 mg/kg N = 158		Midazolam 0.02 mg/kg N = 52		Fospropofol 2.0 mg/kg N = 103		Fospropofol 6.5 mg/kg N = 149	
Disease Population	Hepatic impair. m = 0	Renal impair. m = 0	Hepatic impair. m = 0	Renal impair. m = 2	Hepatic impair. m = 0	Renal impair. m = 1	Hepatic impair. m = 0	Renal impair. m = 10	Hepatic impair. m = 0	Renal impair. m = 17
Sedation-related AE requiring intervention n (%)	0	0	0	0	0	0	0	1 (10.0)	0	4 (23.5)
Apnea	0	0	0	0	0	0	0	0	0	0
Bradycardia	0	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0	0	0	1 (5.9)
Hypoxemia	0	0	0	0	0	0	0	1 (10.0)	0	3 (17.6)
Airway Management n (%)	0	0	0	0	0	0	0	0	0	0
Manual Ventilation	0	0	0	0	0	0	0	0	0	0

Hepatic impair.=Hepatic impairment, based on the Child-Pugh score and a complete review of medical history; Renal impair.= Moderate Renal impairment i.e., creatinine clearance <50 mL/min; m = the number of patients included in the noted subpopulation for a given study arm

Source Table 188b:

8.8 Summary of Safety from Fixed Dose studies

In the early development of fospropofol disodium (Studies 3000-0207, 3000-0409, 3000-410, 3000-0411, 3000-0412, 3000-0415), the development strategy was to identify a dose at which a single bolus administration could achieve and maintain the desired level of sedation. Thus, studies conducted in the initial clinical development used a fixed dose regimen in which the same dose, in milligrams (mg) was administered to all patients who fell within a broad weight range. A greater percentage of patients in the fixed dose studies than in the dose titration studies received initial doses of fospropofol >8mg/kg (Table 19).

The dosing regimen was successful in sedating patients, a single dose of between 10 and 12.5 mg/kg sedated the majority of patients. However, data from subsequent series of studies indicated that this regimen led a high percentage of patients into levels of sedation not necessary for diagnostic and therapeutic procedures (Table 50).

8.8.1 Summary of Adverse Events in Fixed Dose Studies

Studies conducted in initial clinical development used a relatively high, fixed dose regimen in which the same dose, in milligrams was administered to all patients who fell within broad weight ranges. In colonoscopy study 3000-0410 108/210 (51.4%) patients were sedated to MOAA/S scores of 1 or 0; and therefore, studies 3000-0409, 3000-0411, 3000-0412, 3000-0415 were terminated prior to completion of enrollment.

In these studies, most patients experienced TEAEs of paresthesia (burning, stinging, tingling, prickling) or pruritus (itching). Two related SAEs were reported for patients receiving fospropofol disodium and no related deaths occurred in these studies (Appendix C). A single patient was discontinued from the study drug and no patient was discontinued from the study or a procedure.

In studies Studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415, the definition of hypoxemia was O₂ saturation <90% or a 3% decrease from baseline sustained for more than 2 minutes. Apnea was defined as lack of spontaneous breathing ≥60 seconds, and hypopnea was defined as lack of spontaneous breathing >30 to 59 seconds. Hypotension was defined as systolic blood pressure <90mm Hg and requiring medical intervention. Bradycardia was defined as heart rate <50 bpm and requiring medical intervention.

The frequency of SRAEs in these studies (Table 50) were much higher than that of the phase 3 studies conducted with the proposed dose titration regimen (Table 37). This was likely due to the higher level of drug exposure in the fixed dose studies and the deeper

level of sedation achieved with this regimen (Section 7.1.7.2). Despite the increased frequency of advanced airway maneuvers provided for SRAEs, the events were generally transient, rarely treatment limiting, and resolved without clinical sequelae.

Table 50 Patient Incidence of Sedation-Related Adverse Events (Studies 3000-0409, 3000-0410, and 3000-0411, 3000-0412, 3000-0415)

	Study 3000-0409	Study 3000-0410	Study 3000-0411	Study 3000-0412	Study 3000-0415
Sedation- Related AE	Fospropofol N = 40 n (%)	Fospropofol N = 210 n (%)	Fospropofol N = 6 n (%)	Fospropofol N = 121 n (%)	Fospropofol N = 15 n (%)
Patients with any SRAE	18 (45.0)	83 (39.5)	4 (66.7)	24 (19.8)	6 (40.0)
Hypopnea ¹	0	1 (0.5)	0	1 (0.8)	0
Apnea	1 (2.5)	1 (0.5)	1 (16.7)	1 (0.8)	0
Hypoxemia	17 (42.5)	69 (32.9)	3 (50.0)	23 (19.0)	6 (40.0)
Hypotension	2 (5.0)	14 (6.7)	0	4 (3.3)	0
Bradycardia	0	0	0	0	1 (6.7)

¹ Hypopnea was defined as the lack of spontaneous breathing >30 to 59 seconds and apnea was defined as the lack of spontaneous breathing ≥60 seconds.

Source: Study Reports for 3000-0409, Table 30; 3000-0410, Table 29; 3000-0411, Table 20; 3000-0412, Table 31; 3000-0415 Table 20

8.9 Safety Conclusions

Data from the phase 3 program provide strong evidence to suggest that the titration-based, individualized dosing regimen results in effective sedation, clinical benefit, and an acceptable and expected safety profile for patients.

Patients who received fixed-doses of fospropofol disodium in the early clinical studies received higher doses of fospropofol, reached deeper levels of sedation and had a higher frequency of SRAEs requiring more advanced forms of airway management in comparison to patients treated in clinical studies performed with the proposed fospropofol disodium dose titration regimen.

In addition, SRAE data from the fospropofol disodium controlled studies (3000-0522, and 3000-0524) compare favorably with the published literature (Section 8.6.1) and support the following conclusions related to the proposed dose titration regimen:

- Administration results in a manageable safety profile in patients with a wide range of baseline physical conditions, age, and ASA status.
- Administration by a non-anesthesiologist provides for safe and effective sedation when patients are concomitantly monitored for sedation related complications during and after the procedure by a health care professional not performing the procedure.
- The most frequent adverse events included paresthesia, pruritus, and procedural pain that were generally mild to moderate in severity.
- The incidence of SRAEs, including, apnea, hypoxemia, hypotension, and bradycardia is low and the events that occur are generally manageable with basic, non-invasive maneuvers.
- Hypoxemia is the most prevalent SRAE, is usually managed by increased oxygen flow, and occurs most frequently in patients undergoing bronchoscopy.
- Serious drug related adverse events were experienced by 6 of 1,611 individuals.
- No drug related patient deaths occurred during the clinical program.

The frequency of Sedation-Related Adverse Events (SRAEs) in the phase 3 studies was determined in a subgroup analysis by age, race, weight, sex, ASA status and renal or hepatic insufficiency. SRAEs were too rare in the pivotal colonoscopy study (3000-0522) to draw conclusions, and none required manual or mechanical ventilatory assistance. In the pivotal bronchoscopy study (3000-0524), hypoxemia was the only SRAE of sufficient frequency to support any conclusions. In study 3000-0524, only advanced age (>65, >75) seemed to be associated with the frequency of hypoxemia.

9. OVERDOSE AND ABUSE POTENTIAL

9.1 Overdose

There is no specific antidote for an overdose of propofol, the active metabolite of fospropofol disodium. Some patients receiving high doses of fospropofol disodium (in the presence of concomitant medication including opioids and other sedatives) experienced sedation-related adverse events, including cardiorespiratory depression. If over dosage occurs, fospropofol disodium administration should be discontinued immediately. Respiratory depression may require manual or mechanical ventilation, and cardiovascular depression may require elevation of lower extremities, intravascular volume replacement, and/or pharmacological management. Clinicians who use fospropofol disodium must be prepared to provide general support for respiratory depression, apnea, hypoxemia, and hypotension.

Formate and phosphate are metabolites of fospropofol disodium and may contribute to signs of toxicity following over dosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with anion-gap metabolic acidosis (*Hantson, 2005*). Large amounts of phosphate, delivered rapidly, could potentially cause hypocalcemia (*Hebert, 1966*) with paresthesia, muscle spasms, and seizures.

9.2 Drug Abuse

Propofol, approved in the United States under the tradename DIPRIVAN® (propofol) Injectable Emulsion is not regulated under the Controlled Substances Act (CSA). Although propofol has been available in the United States since 1989, the scientific literature contains only a few case reports of propofol abuse and those were largely limited to health care professionals (*Odell, 1999; Schneider, 2001; Kranioti, 2007*).

No formal studies of the abuse potential of fospropofol disodium have been conducted. Fospropofol disodium has been associated with descriptions of euphoria in a small number of subjects who have received intravenous or oral dosing.

9.3 Dependence

No formal studies of dependence have been performed.

9.4 Withdrawal and Rebound

Fospropofol disodium is intended for short-term, episodic use, withdrawal or rebound effects are not expected if used as labeled. No formal studies of withdrawal and rebound have been completed.

10. RISK MANAGEMENT

10.1 Safety Risks Associated with Sedation by Fospropofol Disodium

As with any sedative/hypnotic agent, risks associated with the use of fospropofol disodium can be minimized by implementing the following recommendations:

- Pre-procedure assessment of patients. Sedative-hypnotic agents should be used with caution in patients in whom management of the airway is judged to be difficult due to obesity, short thyro-mental distance (“short neck”), or Mallampati score.
- Patients should be managed during sedation and through the recovery process until clinical discharge criteria are met in facilities appropriately staffed and equipped for detection and management of hypotension, hypoxemia, hypoventilation, airway obstruction, and/or apnea.
- A health care professional not performing the procedure should monitor patients during sedation, paying particular attention to the adequacy of spontaneous respirations, lack of response to verbal stimuli, lack of purposeful movement, hypoxemia, hypotension, bradycardia, or other cardiac arrhythmias.
- Supplemental doses of fospropofol disodium should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.
- Supplemental oxygen should be administered to all patients.
- Concomitant use of opioids should be minimized

The fospropofol disodium dose titration regimen was selected so as to allow clinicians to easily individualize sedation across a broad range of patients, including the ill and elderly. The recommended fospropofol disodium dose titration regimen is an initial dose of 6.5 mg/kg with supplemental doses (1.6 mg/kg) provided at four minute intervals, as needed, to achieve and maintain the desired level of sedation. The dosing regimen includes upper (90 kg) and lower (60 kg) weight bounds and dosing adjustments to 75% of the dose for persons ≥ 65 years of age and ASA P3 and P4 patients in order to provide the optimum balance between efficacy of sedation, ease of use, and acceptable safety. This dosing regimen has been summarized in the proposed product labeling in two easy to follow tables ([Table 51](#) and [Table 52](#)).

Table 51 Standard Dosing Regimen, Adults 18 to <65 Years of Age Who are Healthy or Have Mild Systemic Disease (ASA P1 or P2)

Weight (kg)	Initial Dose		Supplemental Dose (No more frequently than every 4 min)	
	mg	mL	mg	mL
≤60	385.0	11.0	105.0	3.0
61 to 63	402.5	11.5	105.0	3.0
64 to 65	420.0	12.0	105.0	3.0
66 to 68	437.5	12.5	105.0	3.0
69 to 71	455.0	13.0	105.0	3.0
72 to 74	472.5	13.5	122.5	3.5
75 to 76	490.0	14.0	122.5	3.5
77 to 79	507.5	14.5	122.5	3.5
80 to 82	525.0	15.0	140.0	4.0
83 to 84	542.5	15.5	140.0	4.0
85 to 87	560.0	16.0	140.0	4.0
88 to 89	577.5	16.5	140.0	4.0
≥90	577.5	16.5	140.0	4.0

Source: Draft label for fospropofol disodium, NDA 22-244

Note: Doses are rounded to the nearest half-milliliter volume. Actual mg/kg may vary slightly due to the rounding effect.

Table 52 Modified Dosing Regimen, Ages ≥ 65 Years Or Those with Severe Systemic Disease (ASA P3 or P4)

Weight (kg)	Initial Dose		Supplemental Dose (No more frequently than every 4 min)	
	mg	mL	mg	mL
≤60	297.5	8.5	70.0	2.0
61 to 62	297.5	8.5	70.0	2.0
63 to 64	315.0	9.0	87.5	2.5
65 to 66	315.0	9.0	87.5	2.5
67 to 69	332.5	9.5	87.5	2.5
70 to 73	350.0	10.0	87.5	2.5
74 to 77	367.5	10.5	87.5	2.5
78 to 80	385.0	11.0	105.0	3.0
81 to 84	402.5	11.5	105.0	3.0
85 to 87	420.0	12.0	105.0	3.0
88 to 89	437.5	12.5	105.0	3.0
≥90	437.5	12.5	105.0	3.0

Source: Draft label for fospropofol disodium, NDA 22-244

Note: Doses are rounded to the nearest half-milliliter volume. Actual mg/kg may vary slightly due to the rounding effect.

All education of healthcare professionals in support of proper use of fospropofol disodium will have a foundation based upon the communication and reinforcement of appropriate patient selection, correct dose and administration, adequate patient monitoring, and treatment in an appropriate setting with the necessary staff and training in airway management. Educational tools will be developed with the input of likely fospropofol disodium users and field tested. Examples of tools expected to be created and in place concurrent with marketing of fospropofol disodium include pre-sedation patient assessment tools, dosing and administration aids, in-service training kits, sedation related Continuing Medical Education sponsorship and support of sedation related activities conducted by certain national and state medical societies and associations.

All sales and medical employees fielded in support of fospropofol disodium will undergo extensive training on the goals and risks associated with the use of sedatives generally, and in depth instruction on the proper use of fospropofol disodium consistent with its final approved labeling. The preparation provided to these employees will consist of both internal and external third party education, culminating in an internal certification of preparedness for Sponsor's sales and medical employees fielded to appropriately and adequately support proper use of fospropofol disodium.

Additional clinical trials, along with support of appropriate investigator initiated research proposals, are expected to augment the current safety database for fospropofol disodium, particularly in real world clinical use settings.

10.2 Risk for Abuse

Propofol, approved in the United States under the tradename DIPRIVAN® (propofol) Injectable Emulsion is not regulated under the Controlled Substances Act. Propofol has been available in the United States since 1989, and the scientific literature contains a small number of case reports of propofol abuse and those were largely limited to health care professionals (*Odell, 1999; Schneider, 2001; Kranioti, 2007*).

As a prodrug, fospropofol disodium exhibits a slower time to onset of active drug effect and reduced C_{max}. It is recognized that the more rapidly potential drugs of abuse reach the brain, the greater their potential for addiction. The PK-PD profile of fospropofol disodium, characterized by a delayed onset of effect and more gradual rise to peak effect should discourage the potential for abuse in comparison to that of propofol lipid emulsion (*Samaha, 2005; Farre, 1991*).

10.3 Pharmacovigilance

The Sponsor will collect, process and report all Individual Case Safety Reports from post-marketing sources in a manner that is in accordance with applicable local/regional regulations and guidelines

The Sponsor will continually assess whether the risk-benefit profile of fospropofol disodium that was established during the clinical development program changes with increased experience. This review will include regular analysis of spontaneous reports, literature searches, and review of reports from the Drug Abuse Warning Network database provided by the Substance Abuse and Mental Health Services Administration and the National Forensic Laboratory Information System sponsored by the Drug Enforcement Administration during its marketed life. In addition, during the execution of post-marketing clinical trials, risk and benefit of fospropofol disodium will continue to be measured.

11. BENEFIT/RISK SUMMARY

11.1 Overview

Patients undergoing diagnostic or minor surgical procedures often require minimal to moderate sedation to relieve anxiety, discomfort and pain (*Gross, 2002*). The goals of sedation in these settings include providing adequate analgesia, sedation, anxiolysis and amnesia during the performance of the procedure; to control unwanted behavior that inhibits the performance of the procedure; to rapidly return the patient to a state of consciousness; and to minimize the risk of adverse events (*Amer. Acad. Ped. Comm. Drug, 1992; Cote, 2006; Ghisi, 2005; Bahn, 2005; Martin G, 2003*). By providing sedation, patient tolerance of unpleasant procedures is improved (*Gross, 2002*).

Minimal to moderate sedation is used in a variety of procedures including upper and lower gastrointestinal endoscopy, bronchoscopy, minor surgery, diagnostic magnetic resonance imaging (MRI) and interventional radiology. These procedures are performed in a variety of settings including ambulatory surgical centers (ASC), hospital outpatient departments (HOPD), physician offices, emergency rooms and radiology departments (*Gross, 2002; Amer. Acad. Ped. Comm. Drug, 1992; Martin ML, 2003; Cohen, 2007; Waring, 2003; Aisenberg, 2006; Cohen, 2006; Prakash, 1991; Matot, 2000; Vincent, 2007; Dolk, 2002; Tang, 1999; Pellicano, 2000; Moscona, 1995; Avramov, 1997; Kinirons, 2000; Li, 2000; Christian, 2000; Pershad, 2006; Bluemke, 2000; Mueller, 1997; Kwak, 2006; Leitch, 2004; Parworth, 1998; Averley, 2004; Dionne, 2001; Biswas, 1999; Yee, 1996; Frey, 1999; Sherry, 1992; Kwan, 2006*). The volume of procedures performed in the outpatient setting has steadily increased since the first ambulatory

surgery centers were opened in 1970 (*Amer. Hosp Assoc., 2006; Manchikanti, 2007*). Since 1989, the number of surgeries performed on an outpatient basis has exceeded the number performed on an inpatient basis (*Manchikanti, 2007; Hall, 1998*). In 2006 there were an estimated 40 million procedures performed in the outpatient setting compared to 10 million conducted in the inpatient setting (*Amer. Hosp Assoc., 2006*). In 1981, the majority of these procedures occurred in HOPD (> 90%) but this declined to approximately 45% by 2005 while the proportion of procedures performed in ASC and physician's offices has increased to 38% and 17%, respectively (*Amer. Hosp Assoc., 2006; Manchikanti, 2007*). The projected number of outpatient gastrointestinal endoscopic procedures performed in 2005 was estimated to be between 20.4 to 22.3 million (*Bramley, 2005*). In addition there were approximately 150,000 flexible bronchoscopies performed in 2004 (*Vincent, 2007*).

Desirable characteristics of agents for minimal to moderate sedation include rapid onset, rapid recovery without residual side effects, and a consistent and predictable safety profile with side effects that are understood by, and are familiar to practitioners who use sedative agents. Benzodiazepines, used alone or in combination with an opioid analgesic, are often used to provide sedation in patients undergoing diagnostic or minor surgical procedures (*Niemann, 2001; Gan, 2006*). In the majority of gastrointestinal endoscopy and bronchoscopy procedures, midazolam is used in combination with either fentanyl or meperidine (*Cohen, 2006; Waring, 2003; Vincent, 2007; Matot, 2000; Prakash, 1991*). The desired therapeutic effects of midazolam and other benzodiazepines include anxiolysis, sedation and amnesia (*Niemann, 2001; Cohen, 2006*). Adverse events that occur with midazolam include hypotension, respiratory depression and apnea (*Niemann, 2001; Cohen, 2006; Waring, 2003*). Midazolam is also associated with variability in patient response and a relatively slow time to clear headed recovery.

Propofol is a rapid acting agent used in diagnostic and surgical procedures (*Niemann, 2001; Gan, 2006; Cohen, 2006; Vincent, 2007; Steinbacher, 2001*). Its attributes include rapid onset, short duration and rapid recovery (*Gan, 2006; Steinbacher, 2001; Lubarsky, 2007; Cohen, 2007*). At lower doses propofol produces moderate sedation while at higher doses it can produce general anesthesia (*Gan, 2006*). Serious adverse events including hypotension, decreased cardiac output, respiratory depression and hypoxemia can occur, and are more common when propofol is used in conjunction with opioid analgesics (*Gan, 2006; Lubarsky, 2007; Cohen, 2007*). Further disadvantages of propofol lipid emulsion include pain on injection, and drawbacks inherent to a lipid emulsion formulation including emulsion instability, potential microbial contamination, allergic reactions and hyperlipidemia-related side effects (*Baker, 2005*). Although the attributes of propofol are desired by patients and physicians, its use is mostly limited to monitored anesthesia care settings where an anesthesiologist or registered nurse anesthetist is present.

Product labeling and a joint position statement from the ASA and the American Association of Nurse Anesthetists (AANA) have limited the use of propofol by proceduralists (*Lubarsky, 2007; Cohen, 2007; DIPRIVAN Injectable Emulsion package insert, 2005; ANA-ASA joint statement regarding propofol administration 2008; Gross, 2002; Rex, 2004; Aisenberg, 2006*). Propofol lipid emulsion (Diprivan[®]) contains a bolded warning that propofol should only be administered by persons trained in the administration of general anesthesia (*DIPRIVAN Injectable Emulsion package insert, 2005*). In guidelines developed by ASA, proceduralists using propofol for moderate sedation including fospropofol should be able to rescue a patient from any level of sedation including general anesthesia (*Gross, 2002*).

Sedation induced by pharmacologic agents occurs in a continuum that ranges from minimal and moderate sedation, to deep sedation and general anesthesia. The desired risk benefit ratio for a sedative agent intended for use in patients undergoing diagnostic and therapeutic procedures can be achieved if patients are maintained in the range of minimal to moderate sedation for the majority of time they undergo these procedures.

11.2 Benefits of Fospropofol Disodium

Fospropofol disodium is a water-soluble prodrug form of propofol intended for use as an IV sedative-hypnotic agent for adult patients undergoing diagnostic or therapeutic procedures. The benefits and risks of fospropofol used in combination with an analgesic for minimal to moderate sedation were characterized in a comprehensive clinical development program. This program evaluated fospropofol disodium in a variety of populations and procedures and has allowed for an appropriate characterization of the efficacy and safety profile, leading to a dose titration regimen that provides a favorable benefit to risk profile.

The recommended fospropofol disodium dose titration regimen is an initial dose of 6.5 mg/kg with supplemental doses (1.6 mg/kg) provided at four minute intervals, as needed, to achieve the desired level of sedation. The dosing regimen includes upper (90 kg) and lower (60 kg) weight bounds and dosing adjustments to 75% of the dose for persons ≥ 65 years of age and ASA P3 and P4 patients in order to provide the optimum balance between efficacy of sedation, ease of use, and acceptable safety.

Fospropofol disodium is a pharmacologically inactive compound that is metabolized to propofol, resulting in a smooth and gradual increase to a therapeutic plasma propofol concentration that is followed by a gradual decrease over time (lower C_{max} and later T_{max} for fospropofol disodium in comparison to propofol lipid emulsion). As a water-soluble prodrug in aqueous formulation, the complications of a lipid based formulation such as pain on injection, bacterial contamination and hyperlipidemia are avoided.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Fospropofol disodium provides the desirable attributes of propofol without the potential complications of the available lipid-emulsion formulation.

The clinical trials of the fospropofol disodium dose titration regimen (3000-0520, 3000-0522, 3000-0524, 3000-0523), incorporated measures of the clinical benefit provided by sedation. Endpoints were selected based on discussion with the FDA and included the ability to complete the procedure, a reduction in the use of alternative sedative medication and opioids, reduced recall of the procedure, recovery, and patient and physician satisfaction. The recommended fospropofol disodium dose titration regimen provides effective sedation without a need for advanced airway maneuvers such as manual or mechanical ventilation in patients undergoing a variety of procedures. In comparison to the control group, the majority of patients receiving the recommended fospropofol disodium dose titration regimen were able to complete the procedure without an alternative sedative agent (Table 12, Table 13).

Effective levels of sedation were maintained with the recommended fospropofol disodium dose titration regimen so that in comparison to the control group, fewer patients required supplemental analgesic to manage pain or discomfort associated with the procedure (Table 14); and fewer doses of analgesics were administered overall (Table 15). Certain effects of opioids, such as cardio-respiratory depression, may outlast the analgesic effects (Bailey, 1990a); therefore, reduced use of opioids may decrease the risk of cardio-respiratory depression, resulting in a potential clinical benefit to patients.

Patients who recall disagreeable aspects of their procedure, including pain and discomfort are less likely to return for necessary repeat procedures or other procedures. In addition, patients who are awake during the procedure are more likely to feel pain and receive additional analgesic, and are a greater distraction to the clinician due to the need for re-dosing and the longer time required to administer additional doses of sedative to achieve an acceptable level of sedation.

Patients treated with the recommended fospropofol disodium dose titration regimen were less likely to recall being awake during the procedure (Table 14) and were more highly satisfied with their overall experience than those in the control group. The proportion of patients willing to be treated again with the same study medication was higher with the recommended fospropofol disodium dose titration regimen in Study 3000-0522 (colonoscopy) and Study 3000-0524 (bronchoscopy) (Table 14).

Physicians were also highly satisfied with the recommended fospropofol disodium dose titration regimen and more Investigators preferred this dosing regimen to the lower dose of fospropofol disodium used in the control group.

Rapid recovery is a benefit to both patients and providers of diagnostic and minor surgical procedures. The median time to alertness for patients in the controlled studies 3000-0522 (colonoscopy) and 3000-0524 (bronchoscopy) was 5.0 minutes (range = 0-47 minutes) and 5.5 minutes (range = 0-61 minutes), respectively. The median time to discharge for patients in the controlled studies 3000-0522 (colonoscopy) and 3000-0524 (bronchoscopy) was 7.0 minutes (range = 0-47 minutes) and 8.5 minutes (range = 0-66 minutes), respectively.

11.3 Risks of Fospropofol Disodium

The fospropofol disodium safety profile in the patient population studied is consistent with that of other commonly used sedating agents (*Ulmer, 2003; Casey, 2007*). Risks of fospropofol disodium are predictable, are known to the practitioners who use sedatives, and include a low incidence of bradycardia, hypoxemia, and hypotension that are comparable to expected findings during sedation (*Bailey, 1990b*).

Events of hypoxemia experienced by patients treated with the proposed fospropofol disodium dose titration regimen were generally mild and transient and could be expected in patients who are sleeping or sedated, particularly if the patient is in the supine or lateral decubitus positions. Hypoxemia was typically managed with increased oxygen flow or verbal/tactile stimulation and maneuvers such as chin lifts. Events of hypotension were most often mild to moderate and resolved with the administration of fluids. The single observed apnea episode reported in the phase 3 studies was of short duration and consistent with respiratory patterns known to exist during sleep.

The compound-associated sensory findings of transient pruritus and paresthesia are typically minor to moderate in severity, are self-limiting and of short duration and should not restrict the use of fospropofol disodium.

As would be good clinical practice with the use of any sedative-hypnotic agent, when fospropofol disodium is being used, a health care professional not performing the procedure should monitor patients, paying particular attention to the adequacy of spontaneous respirations, lack of response to verbal stimuli, lack of purposeful movement, hypoxemia, hypotension, bradycardia, or other cardiac arrhythmias. Patients should be managed during sedation and through the recovery process until clinical discharge criteria are met in facilities appropriately staffed and equipped for detection and management of hypotension, hypoxemia, hypoventilation, airway obstruction, and/or apnea.

12. CONCLUSION

Fospropofol disodium is a prodrug of propofol. The pharmacological activity of fospropofol disodium results from the alkaline phosphatase-mediated liberation of propofol, the active sedative agent. The PK-PD profile of fospropofol disodium demonstrates a more gradual and measured onset of sedation than occurs with an IV bolus administration of propofol; while enabling a patient to experience the pharmacologic benefits associated with propofol.

The administration of fospropofol disodium by non-anesthesiologists following the instructions established by the Sponsor, which are consistent with the ASA guidelines for minimal to moderate sedation practices, demonstrated the safety and efficacy of the dose titration regimen in two phase 3 clinical studies of diagnostic/therapeutic procedures (study 3000-0522, colonoscopy and study 3000-0524, bronchoscopy). These controlled phase 3 studies, and the supportive study in the minor surgery setting (study 3000-0523), provided for the investigation of a wide range of patient populations (ASA P1 to P4, ≥ 65 years of age). Hypoxemia was the most common sedation-related adverse event experienced by patients in the study population as a whole and in each of the subpopulations and was typically managed with increased oxygen flow, verbal/tactile stimulation or basic maneuvers such as chin lifts.

The benefits of the recommended fospropofol disodium dose titration regimen include effective sedation, enabling completion of unpleasant diagnostic/therapeutic procedures while reducing the need for alternative sedative medication and opioids, reduced recall of the procedure, rapid recovery, and patient and physician satisfaction.

As with any sedative/hypnotic agent, risks associated with the use of fospropofol disodium can be minimized by implementing the following recommendations:

- Appropriate patient selection with pre-procedure assessment. Sedative-hypnotic agents should be used with caution in patients in whom management of the airway is judged to be difficult due to obesity, short thyro-mental distance (“short neck”), or Mallampati score.
- Patients should be managed during sedation and through the recovery process until clinical discharge criteria are met in facilities appropriately staffed and equipped for detection and management of hypotension, hypoxemia, hypoventilation, airway obstruction, and/or apnea.
- A health care professional not performing the procedure should monitor patients during sedation, paying particular attention to the adequacy of spontaneous respirations, lack of response to verbal stimuli, lack of purposeful movement, hypoxemia, hypotension, bradycardia, or other cardiac arrhythmias.
- Supplemental doses of fospropofol disodium should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.
- Supplemental oxygen should be administered to all patients.
- Concomitant use of opioids should be minimized

With appropriate care in patient selection, dosing, and monitoring, fospropofol disodium can be safely administered for use as a sedative/hypnotic agent for diagnostic and therapeutic procedures.

13. REFERENCES

American Gastroenterological Association. AGA Institute review of endoscopic sedation. *Gastroenterology*. 2007 Aug;133(2):675-701.

Aisenberg J, Cohen LB. Sedation in endoscopic practice. *Gastrointest Endoscopy Clin N Am* 2006;16:695-708.

Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg*. 1970;49(6):924-34.

American Academy of Pediatrics Committee on Drugs. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 1992;89:1110-1115.

American Cancer Society. *Facts and Figures 2007*. Atlanta: American Cancer Society; 2007

American Hospital Association. The migration of care to non-hospital settings: Have regulatory structures kept pace with care delivery? *Trendwatch* July 2006;1-12. <http://www.aha.org/aha/trendwatch/2006/twjuly2006migration.pdf>. Accessed January 11, 2008.

American Association of Nurse Anesthetists (AANA), & American Society of Anesthesiologists (ASA). AANA-ASA Joint Statement Regarding Propofol Administration. American Society of Anesthesiologists. Available at <http://www.asahq.org/news/propofolstatement.htm>. Accessed March 24, 2008.

American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002;96(4):1004-17.

ASA Relative Value Guide, American Society of Anesthesiologists, 1999, updated in 2001

ASA News Release: PR Newswire. Nationwide Anesthesiologist Shortage Delays Patients' Surgery; Declining Anesthesia Medicare Reimbursement Cited As Major Factor For Shortage. July 30, 2002.

Averley PA, Lane I, Sykes J, Girdler NM, Steen N, Bond S. An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment – an alternative to general anesthesia. *Br Dent J* 2004;197:553-558.

Avramov MN, White PF. Use of alfentanil and propofol for outpatient monitored anesthesia care: determining the optimal dosing regimen. *Anesth Analg* 1997;85:566-572.

Bahn EL, Holt KR. Procedural sedation and analgesia: A review and new concepts. *Emerg Med Clin N Am* 2005;23:503-517.

Bailey PL, Pace NL, Ashburn MA, Moll JWB, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. *Anesthesiology*. 1990b;73(5):826-30.

Bailey PL, Streisand JB, East KA, East TD, Isern S, Hansen TW, et al. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. *Anesth Analg*. 1990a;70(1):8-15.

Baker MT, Naguib M. Propofol: the challenges of formulation. *Anesthesiology*. 2005;103(4):860-76.

Bali M, Akabas MH. Defining the propofol binding site location on the GABAA receptor. *Mol Pharmacol* 2004;65(1):68-76.

Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test - Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *Clin Neuropsychol*. 1998;12(1):43-55.

Biswas S, Bhatnagar M, Rhatigan M, Kincey J, Slater R, Leatherbarrow B. Low-dose midazolam infusion for oculoplastic surgery under local anesthesia. *Eye* 1999;13:537-540.

Bluemke DA, Breiter SN. Sedation procedures in MR imaging: safety, effectiveness, and nursing effect on examinations. *Radiology* 2000;216:645-652.

Boeniger MF. Formate in urine as a biological indicator of formaldehyde exposure: a review. *Am Ind Hyg Assoc J*. 1987;48(11):900-8.

Bramley TJ, Meyer KL, Grogg AL, Rex DK. Economic impact of anesthetist-administered sedation in outpatient gastrointestinal endoscopy. *Am J Gastroenterol* 2005;100:S368. Bramley

Campbell SG, Magee KD, Kovacs GJ, Petrie DA, Tallon JM, McKinley R, et al. Procedural sedation and analgesia in a Canadian adult tertiary care emergency department: a case series. *CJEM*. 2006;8(2):85-93.

Casey KR, Cantillo KO, Brown LK. Sleep-related hypoventilation/hypoxemic syndromes. *Chest*. 2007;131(6):1936-48.

Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244-51.

Christian M, Yeung L, Williams R, Lapinski P, Moy R. Conscious sedation in dermatologic surgery. *Dermatol Surg* 2000;26:923-928.

Clarkson K, Power CK, O'Connell F, Pathmakanthan S, Burke CM. A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest*. 1993;104(4):1029-31.

Cohen LB, Delegge MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, Piorowski JD Jr; AGA Institute. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007 Aug;133(2):675-701.

Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level of sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004;59(7):795-803.

Cohen LB, Wechsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006;101(5):967-74.

Cote CJ, Wilson S, and the Working Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. *Pediatrics* 2006;118:2587-2602.

Dhareshwar SS, Stella VJ. Your prodrug releases formaldehyde: Should you be concerned? No! *J Pharm Sci* 2008.

Dionne RA, Yagiela JA, Moore PA, Gonty A, Zuniga J, Beirne OR. For the Collaborative Sedation Study Group. Comparing efficacy and safety of four intravenous sedation regimens in dental outpatients. *J Am Dent Assoc* 2001;132:740-751.

DIPRIVAN® injectable emulsion (propofol) for i.v. administration (professional information brochure). [Publication on the Internet] Wilmington, DE: AstraZeneca Pharmaceuticals, 2005; Available from: <http://www.astrazeneca-us.com/pi/diprivan.pdf>. Accessed March 24, 2008.

Dolk A, Cannerfelt R, Anderson RE, Jakobsson J. Inhalation anaesthesia is cost-effective for ambulatory surgery: a clinical comparison with propofol during elective knee arthroscopy. *Eur J Anaesthesiol.* 2002;19(2):88-92.

Degoute, CS, EEG bispectral index and hypnotic component of anesthesia induced by sevoflurane comparison between children and adults, *Brit. J Anesthesia*, 2001;82(2):210-212

Farré M, Camí J. Pharmacokinetic considerations in abuse liability evaluation. *Br J Addict.* 1991 Dec;86(12):1601-6. Review.

Favetta P, Degoute CS, Perdrix JP, Dufresne C, Bouliou R, Guitton J. Propofol metabolites in man following propofol induction and maintenance. *Br J Anaesth* 2002;88(5):653-8.

Forster A, Gardaz J-P, Suter PM, Gemperle M. Comparative respiratory effects of midazolam and diazepam. *Anesthesiology.* 1979;51(3):S383.

Forster A, Morel D, Bachmann M, Gemperle M. Ventilatory effects of various doses of IV midazolam assessed by a non-invasive method in healthy volunteers [abstract]. *Anesthesiology*; 1982. Abstract A480.

Frey K, Sukhani R, Pawlowski J, Pappas AL, Mikat-Stevens M, Slogoff S. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: Comparison of sedation quality, intraocular pressure changes, and recovery profiles. *Anesth Analg* 1999;89:317-321.

Gan TJ. Pharmacokinetic and pharmacodynamic characteristics of medications used for moderate sedation. *Clin Pharmacokinet.* 2006; 45: 855-869.

Ghisi D, Fanelli A, Tosi M, Nuzzi M, Fanelli G. Monitored anesthesia care. *Minerva Anesthesiol* 2005;71:533-538.

Grogono AW. Resident Numbers and Graduation Rate From Residencies. ASA Newsletter. 2005. Vol 69.

Gross JB, Bailey PL, Connis RT, et al. Practice guidelines for sedation and analgesia by non-anesthesiologists. An updated report by the American Society of Anesthesiologists Task Force on sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002;96:1004-1017.

Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, May 2003.

Hales TG, Lambert JJ. The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones. *Br J Pharmacol* 1991;104(3):619-28.

Hall MJ, Lawrence L. Ambulatory surgery in the United States, 1996. *Adv Data* 1998;300:1-16.

Hantson P, Haufroid V, Wallemacq P. Formate kinetics in methanol poisoning. *Hum Exp Toxicol.* 2005;24(2):55-9.

Harper MH, Hickey RF, Cromwell TH, Linwood S. The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. *J Pharmacol Exp Ther* 1976;199(2):464-8.

Hebert LA, Lemann J Jr, Petersen JR, Lennon EJ. Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. *J Clin Invest.* 1966 Dec;45(12):1886-94.

Kemp GJ, Blumsohn A, Morris BW. Circadian changes in plasma phosphate concentration, urinary phosphate excretion, and cellular phosphate shifts. *Clin Chem.* 1992;38(3):400-2.

Kinirons BP, Bouaziz H, Paqueron X, et al. Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerve block. *Anesth Analg* 2000;90:1118-1121.

Kranioti EF, Mavroforou A, Mylonakis P, Michalodimitrakis M. Lethal self administration of propofol (Diprivan). A case report and review of the literature. *Forensic Sci Int.* 2007 Mar 22;167(1):56-8. Epub 2006 Jan 23.

Kuznets N. Diagnostic colonoscopy: performance measurement study. *J Ambul Care Manage.* 2002 Jul;25(3):41-55.

Kwak HJ, Kim JY, Kwak YL, Park WS, Lee KC. Comparison of a bolus of fentanyl with an infusion of alfentanil during target-controlled propofol infusion in third molar extraction under conscious sedation. *J Oral Maxillofac Surg* 2006;64:1577-1582.

Kwan I, Bhattacharya S, Knox F, McNeil A. Conscious sedation and analgesia for oocyte retrieval during IVF procedures: a Cochrane review. *Hum Reprod* 2006;21:1672-1679.

Lechtzin N, Rubin HR, Jenckes M, White P Jr, Zhou L, Thompson DA, Diette GB. Predictors of Pain Control in Patients Undergoing Flexible Bronchoscopy. *Am J Respir Crit Care Med.* 2000; 162; 440-45

Leitch JA, Anderson K, Gambhir S, et al. A partially blinded randomised controlled trial of patient-maintained propofol sedation and operator controlled midazolam sedation in third molar extractions. *Anaesthesia* 2004;59:853-860.

Li S, Coloma M, White PF, et al. Comparison of the costs and recovery profiles of three anesthetic techniques for ambulatory anorectal surgery. *Anesthesiology* 2000;93:1225-1230.

Lubarsky DA, Candiotti K, Harris E. Understanding modes of moderate sedation during gastrointestinal procedures: a current review of the literature. *J Clin Anesth.* 2007 Aug;19(5):397-404. Review

Manchikanti L, Boswell MV. Interventional techniques in ambulatory surgery centers: A look at the new payment system. *Pain Physician* 2007;10:627-650.

Martin G, Glass PS, Breslin DS, MacLeod DB, Sanderson IC, Lubarsky DA, Reves JG, Gan TJ. A Study of Anesthetic Drug Utilization in Different Age Groups. *Journal of Clinical Anesthesia.* 2003;15:194 –200.

Martin ML, Lennox PH. Sedation and analgesia in the interventional radiology department. *J Vasc Interv Radiol* 2003;14:1119-1128.

Matot I, Kramer MR. Sedation in outpatient bronchoscopy. *Respir Med* 2000;94:1145-1153.

Michalodimitrakis M, Christodoulou P, Tsatsakis AM, Askoxilakis I, Stiakakis I, Mouzas I. Death related to midazolam overdose during endoscopic retrograde cholangiopancreatography. *Am J Forensic Med Pathol.* 1999;20(1):93-7.

Morel D, Forster A, Bachmann M, Suter PM. Changes in breathing pattern induced by midazolam in normal subjects [abstract]. *Anesthesiology*; 1982. Abstract A481.

Moscona RA, Ramon I, Ben-David B, Isserles S. A comparison of sedation techniques for outpatient rhinoplasty: midazolam versus midazolam plus ketamine. *Plast Reconstr Surg* 1995;96:1066-1074.

Mueller PR, Wittenberg KH, Kaufman JA, Lee MJ. Patterns of anesthesia and nursing care for interventional radiology procedures: A national survey of physician practices and preferences. *Radiology* 1997;202:339-343.

Niemann C, Gropper MA. Pharmacology of conscious sedation. In: Wiener-Kronish JP, Gropper MA, eds. *Conscious Sedation*. Philadelphia, PA: Hanley & Belfus, Inc.; 2001:1-16.

Odell M. Propofol abuse. *Anaesth Intensive Care.* 1999; Oct;27(5):539.

Ozturk T, Tuncok Y, Kalkan S, Guven H, Aran G. Midazolams cardiac depressant effects and their lack of reversal by flumazenil in isolated rabbit hearts. *Pharmacol Res.* 1999;39(4):283-7.

Pandey CK, Agarwal A, Baronia A, Singh N. Toxicity of ingested formalin and its management. *Hum Exp Toxicol.* 2000;19(6):360-6.

Parworth LP, Frost DE, Zuniga JR, Bennett T. Propofol and fentanyl compared with midazolam and fentanyl during third molar surgery. *J Oral Maxillofac Surg* 1998;56:447-453.

Patten D, Foxon GR, Martin KF, Halliwell RF. An electrophysiological study of the effects of propofol on native neuronal ligand-gated ion channels. *Clin Exp Pharmacol Physiol* 2001;28(5-6):451-8.

Pellicano M, Zullo F, Cappiello F, Di Carlo DI, Cirillo D, Nappi C. Minilaparoscopic ovarian biopsy performed under conscious sedation in women with premature ovarian failure. *J Reprod Med* 2000;45:817-822.

Pershad J, Gilmore B. Successful implementation of a radiology sedation service staffed exclusively by pediatric emergency physicians. *Pediatrics* 2006;117:e413-e422.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Pollak MR. Chapter 22: Disturbances of Calcium, Magnesium and Phosphate Metabolism. In: Brenner BM, editor. Brenner & Rector's The Kidney. 7th ed: Saunders; 2004.

Prakash UBS, Offord KP, Stubbs SE. Bronchoscopy in North America: The ACCP survey. Chest 1991;100:1668-1675.

Pratilla MG, Fischer ME, Alagesan R, Alagesan R, Reinsel RA, Pratilas D. Propofol versus midazolam for monitored sedation: a comparison of intraoperative and recovery parameters. Journal of Clinical Anesthesia. 1993;5(4):268-274

PR Newswire. Nationwide Anesthesiologist Shortage Delays Patients' Surgery; Declining Anesthesia Medicare Reimbursement Cited As Major Factor For Shortage. July 30, 2002.

Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology. 1985;62(3):310-24.

Rex DK. The science and politics of propofol. American Journal of Gastroenterology. 2004;99:2080-2083.

Rex D, Schwartz, H, Goldstein, M, et al. Safety and Colon-Cleansing Efficacy of a New Residue-Free Formulation of Sodium Phosphate Tablets. Am J Gastroenterol 2006; 101:2594-2604.

Rex, DK, Heuss, LT, Walker, JA, Rong, QI, Trained Registered Nurses/Endoscopy Teams can administer propofol safely for Endoscopy. Gastroenterology 2005; 129:1384-1391

Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol Sci. 2005 Feb;26(2):82-7.

Schneider U, Rada D, Rollnik JD, Passie T, Emrich HM. Propofol dependency after treatment of tension headache. Addict Biol. 2001 Jul;6(3):263-265.

Sherry E. Admixture of propofol and alfentanil. Use for intravenous sedation and analgesia during transvaginal oocyte retrieval. Anaesthesia 1992;47:477-479.

Sieg A. Propofol Sedation in Outpatient Colonoscopy by Trained Practice Nurses Supervised by the Gastroenterologist: a Prospective Evaluation of over 3000 Cases. *Z Gastroenterol.* 2007;45(8):697-701.

Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of 14C-propofol. *Xenobiotica.* 1988 Apr;18(4):429-40.

Sipe BW, Rex DK, Latinovich D, Overley C, Kinser K, Bratcher L, et al. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc.* 2002;55(7):815-25.

Steinbacher DM. Propofol: a sedative-hypnotic anesthetic agent for use in ambulatory procedures. *Anesth Prog.* 2001 Spring;48(2):66-71. Review

Tang J, Chen L, White PF, et al. Recovery profile, costs, and patient satisfaction with propofol and sevoflurane for fast-track office-based anesthesia. *Anesthesiology* 1999;91:253-261.

Thompson KA, Goodale DB. The recent development of propofol (DIPRIVAN). *Intensive Care Med.* 2000;26 Suppl 4:S400-4.

Tohda G, Higashi S, Wakahara S, Morikawa M, Sakumoto H, Kane T. Propofol sedation during endoscopic procedures: safe and effective administration by registered nurses supervised by endoscopists. *Endoscopy.* 2006;38(4):360-7.

Ulmer BJ, Hansen JJ, Overley CA, Symms MR, Chadalawada V, Liangpunsakul S, et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol.* 2003;1(6):425-32.

Vargo JJ, Zuccaro G, Jr., Dumot JA, Shermock KM, Morrow JB, Conwell DL, Trolli PA, Maurer WG. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology* 2002;123(1):8-16.

Vicari JJ. Sedation and analgesia. *Gastrointest Endosc Clin N Am.* 2002;12(2):297-311, viii.

Vincent B, Silvestri G. An Update on Sedation and Analgesia During Flexible Bronchoscopy. *J Bronchol.* 2007;14:173-180.

Waring JP, Baron TH, Hirota WK, et al. Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. *Gastrointest Endosc* 2003;58:317-322.

Weston BR, Chadalawada V, Chalasani N, Kwo P, Overley CA, Symms M, Strahl E, Rex DK. Nurse-administered propofol versus midazolam and meperidine for upper endoscopy in cirrhotic patients. *Am J Gastroenterol* 2003;98(11):2440-7.

Wruble L, DeMicco M, Medoff J, et al. Residue-free sodium phosphatets (OsmoPrep) versus Visicol for colon cleansing: a randomized, investigator-blinded trial. *Gastrointest Endosc* 2007; 65:660-70.

Yee JB, Burns TA, Mann JM, Crandall AS. Propofol and alfentanil for sedation during placement of retrobulbar block for cataract surgery. *J Clin Anesth* 1996;8:623-626.

14. APPENDICES

Appendix A Tables and Figures Referred to But Not Included In Text

Table 1-A Extent of Fospropofol Disodium Exposure by Procedure and Study – Total Fospropofol Disodium Dose (mg) Received

Population/ procedure	Study	Median duration (Min) of procedure (min, max)	Total fospropofol dose (mg) received				
			≤450 n (%)	>450-700 n (%)	>700-950 n (%)	>950-1200 n (%)	>1200 n (%)
Pivotal, Adequate, Well-controlled, Double-Blind, studies							
Colonoscopy	3000-0520 (N=101)	12 (3, 32)	39 (38.6)	32 (31.7)	24 (23.8)	4 (4.0)	2 (2.0)
Colonoscopy	3000-0522 (N=260)	11 (4, 60)	112 (43.1)	39 (15.0)	68 (26.2)	36 (13.8)	5 (1.9)
Bronchoscopy	3000-0524 (N=252)	10 (1, 62)	143 (56.7)	62 (24.6)	31 (12.3)	11 (4.4)	5 (2.0)
	Total N = 613	NA	294 (47.9)	133 (21.7)	123 (20.1)	51 (8.3)	12 (1.9)
Open-label Supportive							
Colonoscopy	3000-0207 (N=164)	10 (2, 50)	0 (0.0)	23 (14.0)	61 (37.2)	55 (33.5)	25 (15.2)
Minor procedures	3000-0523 (N=123)	17 (2, 110)	12 (9.8)	43 (35.0)	47 (38.2)	15 (12.2)	6 (4.9)
	Total N = 287	NA	12 (4.2)	66 (22.9)	108 (37.6)	70 (24.4)	31 (10.8)
Open-label, Fixed-dose, Supportive							
Bronchoscopy	3000-0409 (N=40)	10 (3, 34)	1 (2.5)	11 (27.5)	19 (47.5)	8 (20.0)	1 (2.5)
Colonoscopy	3000-0410 (N=210)	11 (2, 54)	0 (0.0)	13 (6.2)	83 (39.5)	99 (47.1)	15 (7.1)
Minor procedures	3000-0411 (N=6)	26 (13, 41)	0 (0.0)	1 (16.7)	5 (83.3)	0 (0.0)	0 (0.0)
Minor procedures	3000-0412 (N=121)	18 (2, 102)	0 (0.0)	7 (5.8)	36 (29.8)	60 (49.6)	18 (14.9)
Colonoscopy	3000-0415 (N=15)	14 (5, 28)	0 (0.0)	9 (60.0)	6 (40.0)	0 (0.0)	0 (0.0)
	Total N= 392	NA	1 (0.3)	41 (10.5)	149 (38.0)	167 (42.6)	34 (8.7)
Prolonged exposure (ICU/CABG)							
Prolonged Exposure	3000-0104 (N=8)	405 (369, 540)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100.0)
Prolonged Exposure	3000-0413 (N=38)	223 (90, 733)	10 (26.3)	5 (13.2)	2 (5.3)	3 (7.9)	18 (47.4)
	Total N=46	389 (90, 733)	10 (21.7)	5 (10.9)	2 (4.3)	3 (6.5)	26 (56.5)
Healthy subjects¹							
Healthy subjects	3000-0001 (N=12)	N/A	1 (8.3)	1 (8.3)	0 (0.0)	1 (8.3)	9 (75.0)
Healthy subjects	3000-0102 (N=12)	N/A	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)
Healthy subjects	3000-0103 (N=36)	N/A	6 (16.7)	3 (8.3)	5 (13.9)	6 (16.7)	16 (44.4)
Healthy subjects	3000-0205 (N=8)	N/A	8 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Healthy subjects	3000-0206 (N=54)	N/A	53 (98.1)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Healthy subjects	3000-0308 (N=10)	N/A	0 (0.0)	2 (20.0)	4 (40.0)	3 (30.0)	1 (10.0)
Healthy subjects	3000-0414 (N=60)	N/A	1 (1.7)	24 (40.0)	31 (51.7)	4 (6.7)	0 (0.0)
Healthy subjects	3000-0521 (N=69)	N/A	1 (1.4)	0 (0.0)	0 (0.0)	22 (31.9)	46 (66.7)
Healthy subjects	3000-0625 (N=12)	N/A	0 (0.0)	7 (58.3)	5 (41.7)	0 (0.0)	0 (0.0)
Healthy subjects	Total (N=273)	N/A	70 (25.6)	38 (13.9)	45 (16.5)	36 (13.2)	84 (30.8)
Grand Total	Overall (N=1611)	12 (1,733)	387 (24.0)	283 (17.6)	427 (26.5)	327 (20.3)	187 (11.6)

Source data: Module 5.3.5.3, Table 71 of the NDA

¹ Patients in the crossover design are counted in the dose group for which they received the highest dose.

Table 2-A Extent of Fentanyl Exposure by Population and Study – Total Fentanyl Dose (µg) Received

Population/ Procedure	Study	Median duration (minutes) of procedure (min, max)	0-<50 n (%)	50-<100 n (%)	100-<150 n (%)	≥150 n (%)
Colonoscopy	3000-0207 (N=164)	10 (2, 50)	25 (15.2)	82 (50.0)	46 (28.0)	11 (6.7)
	3000-0410 (N=210)	11 (2, 54)	5 (2.4)	111 (52.9)	81 (38.6)	13 (6.2)
	3000-0415 (N=15)	14 (5, 28)	12 (80.0)	3 (20.0)	0 (0.0)	0 (0.0)
	3000-0520 (N=101)	12 (3, 32)	0 (0.0)	76 (75.2)	20 (19.8)	5 (5.0)
	3000-0522 (N=260)	11 (4, 60)	0 (0.0)	195 (75.0)	52 (20.0)	13 (5.0)
	Total (N=750)	11 (2, 60)	42 (5.6)	467 (62.3)	199 (26.5)	42 (5.6)
Bronchoscopy	3000-0409 (N=40)	10 (3, 34)	11 (27.5)	22 (55.0)	7 (17.5)	0 (0.0)
	3000-0524 (N=252)	10 (1, 62)	2 (0.8)	219 (86.9)	18 (7.1)	13 (5.2)
	Total (N=292)	10 (1, 62)	13 (4.5)	241 (82.5)	25 (8.6)	13 (4.5)
Minor procedures	3000-0411 (N=6)	26 (13, 41)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
	3000-0412 (N=121)	18 (2, 102)	3 (2.5)	37 (30.6)	67 (55.4)	14 (11.6)
	3000-0523 (N=123)	17 (2, 110)	2 (1.6)	116 (94.3)	5 (4.1)	0 (0.0)
	Total (N=250)	18 (2, 110)	7 (2.8)	155 (62.0)	73 (29.2)	15 (6.0)
Grand Total	Overall (N=1292)	11 (1, 110)	62 (4.8)	863 (66.8)	297 (23.0)	70 (5.4)

Source data: Module 5.3.5.3, Table 74

Table 3-A Age (years) Distribution in Studies of Brief Therapeutic and/or Diagnostic Procedures by Initial Dose Randomized (3000-0520, 3000-0522, 3000-0523, and 3000-0524) or by Initial Dose Received (3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Procedure Study	Fospropofol ≤5 mg/kg ¹				Fospropofol >5-<8 mg/kg ¹				Fospropofol ≥8 mg/kg ¹				Midazolam			
	Total N	18-<65 n (%)	≥65 n (%)	≥75 n (%)	Total N	18-<65 n (%)	≥65 n (%)	≥75 n (%)	Total N	18-<65 n (%)	≥65 n (%)	≥75 n (%)	Total N	18-<65 n (%)	≥65 n (%)	≥75 n (%)
Colonoscopy																
3000-0207	1	1 (100)	0	0	23	23 (100)	0	0	140	121 (86)	19 (14)	5 (4)	0	0	0	0
3000-0410	0	0	0	0	7	7 (100)	0	0	203	199 (98)	4 (2)	0	68	65 (96)	3 (4)	0
3000-0415	0	0	0	0	0	0	0	0	15	0	15 (100)	2 (13)	5	0	5 (100)	0
3000-0520	51	42 (82)	9 (18)	2 (4)	26	21 (81)	5 (19)	2 (8)	24	20 (83)	4 (17)	1 (4)	26	22 (85)	4 (15)	1 (4)
3000-0522	102	88 (86)	14 (14)	1 (1)	158	137 (87)	21 (13)	4 (3)	0	0	0	0	52	42 (81)	10 (19)	1 (2)
Total	154	131 (85)	23 (15)	3 (2)	214	188 (88)	26 (12)	6 (3)	382	340 (89)	42 (11)	8 (2)	151	129 (85)	22 (15)	2 (1)
Bronchoscopy																
3000-0409	0	0	0	0	11	11 (100)	0	0	29	26 (90)	3 (10)	0	15	13 (87)	2 (13)	0
3000-0524	102	60 (59)	42 (41)	18 (18)	150	89 (59)	61 (41)	19 (13)	0	0	0	0	0	0	0	0
Total	102	60 (59)	42 (41)	18 (18)	161	100 (62)	61 (38)	19 (12)	29	26 (90)	3 (10)	0	15	13 (87)	2 (13)	0
Minor procedures																
3000-0411	0	0	0	0	4	4 (100)	0	0	2	2 (100)	0	0	1	0	1 (100)	0
3000-0412	0	0	0	0	7	7 (100)	0	0	114	113 (99)	1 (1)	0	42	40 (95)	2 (5)	0
3000-0523	0	0	0	0	123	99 (80)	24 (20)	11 (9)	0	0	0	0	0	0	0	0
Total	0	0	0	0	134	110 (82)	24 (18)	11 (8)	116	115 (99)	1 (1)	0	43	40 (93)	3 (7)	0
Grand Total	256	191 (75)	65 (25)	21 (8)	509	398 (78)	111 (22)	36 (7)	527	481 (91)	46 (9)	8 (2)	209	182 (87)	27 (13)	2 (1)

Source data: Module 5.3.5.3, Table 79

Note: Patients in studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415 were randomized to receive a fixed dose (mg) of fospropofol, and patients in study 3000-0207 were randomized to receive weight-adjusted (mg/kg) (Part 1a) and fixed doses (mg) (Part 1b) of fospropofol.

¹ Patients who were randomized to initial bolus doses of ≤5 mg/kg, >5-<8 mg/kg, and ≥8 mg/kg for 3000-0520, 3000-0522, 3000-0523 and 3000-0524 or patients who received these doses for 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415.

Table 4-A Sex Distribution in Studies of Brief Therapeutic and/or Diagnostic Procedures by Initial Dose Randomized (3000-0520, 3000-0522, 3000-0523, and 3000-0524) or by Initial Dose Received (3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Procedure Study	Fospropofol ≤ 5.0 mg/kg ¹			Fospropofol >5.0 - <8.0 mg/kg ¹			Fospropofol ≥ 8.0 mg/kg ¹			Midazolam		
	Total N	Male n (%)	Female n (%)	Total N	Male n (%)	Female n (%)	Total N	Male n (%)	Female n (%)	Total N	Male n (%)	Female n (%)
Colonoscopy												
3000-0207	1	0	1 (100)	23	10 (43)	13 (57)	140	62 (44)	78 (56)	0	0	0
3000-0410	0	0	0	7	3 (43)	4 (57)	203	78 (38)	125 (62)	68	32 (47)	36 (53)
3000-0415	0	0	0	0	0	0	15	5 (33)	10 (67)	5	3 (60)	2 (40)
3000-0520	51	26 (51)	25 (49)	26	11 (42)	15 (58)	24	11 (46)	13 (54)	26	10 (38)	16 (62)
3000-0522	102	46 (45)	56 (55)	158	76 (48)	82 (52)	0	0	0	52	34 (65)	18 (35)
Total	154	72 (47)	82 (53)	214	100 (47)	114 (53)	382	156 (41)	226 (59)	151	79 (52)	72 (48)
Bronchoscopy												
3000-0409	0	0	0	11	8 (73)	3 (27)	29	14 (48)	15 (52)	15	6 (40)	9 (60)
3000-0524	102	54 (53)	48 (47)	150	86 (57)	64 (43)	0	0	0	0	0	0
Total	102	54 (53)	48 (47)	161	94 (58)	67 (42)	29	14 (48)	15 (52)	15	6 (40)	9 (60)
Minor procedures												
3000-0411	0	0	0	4	2 (50)	2 (50)	2	0	2 (100)	1	1 (100)	0
3000-0412	0	0	0	7	2 (29)	5 (71)	114	35 (31)	79 (69)	42	18 (43)	24 (57)
3000-0523	0	0	0	123	56 (46)	67 (54)	0	0	0	0	0	0
Total	0	0	0	134	60 (45)	74 (55)	116	35 (30)	81 (70)	43	19 (44)	24 (56)
Grand Total	256	126 (49)	130 (51)	509	254 (50)	255 (50)	527	205 (39)	322 (61)	209	104 (50)	105 (50)

Source data: Module 5.3.5.3, Table 82

Note: Patients in studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415 were randomized to receive a fixed dose (mg) of fospropofol, and patients in study 3000-0207 were randomized to receive weight-adjusted (mg/kg) (Part 1a) and fixed doses (mg) (Part 1b) of fospropofol.

¹ Patients who were randomized to initial bolus doses of ≤ 5 mg/kg, >5 - <8 mg/kg, and ≥ 8 mg/kg for 3000-0520, 3000-0522, 3000-0523 and 3000-0524 or patients who received these doses for 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415.

Table 5-A Race Distribution in Studies of Brief Therapeutic and/or Diagnostic Procedures by Initial Dose Randomized (3000-0520, 3000-0522, 3000-0523, and 3000-0524) or by Initial Dose Received (3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Population Study	Fospropofol ≤ 5.0 mg/kg ¹				Fospropofol >5.0 - <8.0 mg/kg ¹				Fospropofol ≥ 8.0 mg/kg ¹				Midazolam			
	Total N	White n (%)	Black n (%)	Other n (%)	Total N	White n (%)	Black n (%)	Other n (%)	Total N	White n (%)	Black n (%)	Other n (%)	Total N	White n (%)	Black n (%)	Other n (%)
Colonoscopy																
3000-0207	1	1 (100)	0	0	23	16 (70)	2 (9)	5 (22)	140	110 (79)	13 (9)	17 (12)	0	0	0	0
3000-0410	0	0	0	0	7	5 (71)	2 (29)	0	203	169 (83)	28 (14)	6 (3)	68	59 (87)	6 (9)	3 (4)
3000-0415	0	0	0	0	0	0	0	0	15	14 (93)	1 (7)	0	5	5 (100)	0	0
3000-0520	51	41 (80)	5 (10)	5 (10)	26	21 (81)	4 (15)	1 (4)	24	22 (92)	2 (8)	0	26	20 (77)	3 (12)	3 (12)
3000-0522	102	69 (68)	20 (20)	13 (13)	158	133 (84)	11 (7)	14 (9)	0	0	0	0	52	43 (83)	6 (12)	3 (6)
Total	154	111 (72)	25 (16)	18 (12)	214	175 (82)	19 (9)	20 (9)	382	315 (82)	44 (12)	23 (6)	151	127 (84)	15 (10)	9 (6)
Bronchoscopy																
3000-0409	0	0	0	0	11	10 (91)	1 (9)	0	29	24 (83)	1 (3)	4 (14)	15	11 (73)	4 (27)	0
3000-0524	102	84 (82)	14 (14)	4 (4)	150	130 (87)	16 (11)	4 (3)	0	0	0	0	0	0	0	0
Total	102	84 (82)	14 (14)	4 (4)	161	140 (87)	17 (11)	4 (2)	29	24 (83)	1 (3)	4 (14)	15	11 (73)	4 (27)	0
Minor procedures																
3000-0411	0	0	0	0	4	4 (100)	0	0	2	0	1 (50)	1 (50)	1	1 (100)	0	0
3000-0412	0	0	0	0	7	5 (71)	1 (14)	1 (14)	114	82 (72)	18 (16)	14 (12)	42	28 (67)	10 (24)	4 (10)
3000-0523	0	0	0	0	123	109 (89)	9 (7)	5 (4)	0	0	0	0	0	0	0	0
Total	0	0	0	0	134	118 (88)	10 (7)	6 (4)	116	82 (71)	19 (16)	15 (13)	43	29 (67)	10 (23)	4 (9)
Grand Total	256	195 (76)	39 (15)	22 (9)	509	433 (85)	46 (9)	30 (6)	527	421 (80)	64 (12)	42 (8)	209	167 (80)	29 (14)	13 (6)

Source data: Module 5.3.5.3, Table 85

Note: Patients in studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415 were randomized to receive a fixed dose (mg) of fospropofol, and patients in study 3000-0207 were randomized to receive weight-adjusted (mg/kg) (Part 1a) and fixed doses (mg) (Part 1b) of fospropofol.

¹ Patients who were randomized to initial bolus doses of ≤ 5 mg/kg, >5 - <8 mg/kg, and ≥ 8 mg/kg for 3000-0520, 3000-0522, 3000-0523 and 3000-0524 or patients who received these doses for 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415.

Table 6-A Body Weight (kg) Distribution in Studies of Brief Therapeutic and/or Diagnostic Procedures by Initial Dose Randomized (3000-0520, 3000-0522, 3000-0523, and 3000-0524) or by Initial Dose Received (3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Population Study	Fospropofol ≤5.0 mg/kg ¹				Fospropofol >5.0-<8.0 mg/kg ¹				Fospropofol ≥8.0 mg/kg ¹				Midazolam			
	Total N	<60 n (%)	60-<90 n (%)	≥90 n (%)	Total N	<60 n (%)	60-<90 n (%)	≥90 n (%)	Total N	<60 n (%)	60-<90 n (%)	≥90 n (%)	Total N	<60 n (%)	60-<90 n (%)	≥90 n (%)
Colonoscopy																
3000-0207	1	0	1 (100)	0	23	2 (9)	12 (52)	9 (39)	140	26 (19)	72 (51)	42 (30)	0	0	0	0
3000-0410	0	0	0	0	7	0	0	7 (100)	203	28 (14)	116 (57)	59 (29)	68	3 (4)	38 (56)	27 (40)
3000-0415	0	0	0	0	0	0	0	0	15	3 (20)	9 (60)	3 (20)	5	1 (20)	3 (60)	1 (20)
3000-0520	51	7 (14)	31 (61)	13 (25)	26	6 (23)	13 (50)	7 (27)	24	4 (17)	10 (42)	10 (42)	26	1 (4)	19 (73)	6 (23)
3000-0522	102	13 (13)	56 (55)	33 (32)	158	9 (6)	86 (54)	63 (40)	0	0	0	0	52	4 (8)	31 (60)	17 (33)
Total	154	20 (13)	88 (57)	46 (30)	214	17 (8)	111 (52)	86 (40)	382	61 (16)	207 (54)	114 (30)	151	9 (6)	91 (60)	51 (34)
Bronchoscopy																
3000-0409	0	0	0	0	11	0	1 (9)	10 (91)	29	7 (24)	17 (59)	5 (17)	15	3 (20)	7 (47)	5 (33)
3000-0524	102	19 (19)	51 (50)	32 (31)	150	27 (18)	81 (54)	42 (28)	0	0	0	0	0	0	0	0
Total	102	19 (19)	51 (50)	32 (31)	161	27 (17)	82 (51)	52 (32)	29	7 (24)	17 (59)	5 (17)	15	3 (20)	7 (47)	5 (33)
Minor procedures																
3000-0411	0	0	0	0	4	0	0	4 (100)	2	0	2 (100)	0	1	0	0	1 (100)
3000-0412	0	0	0	0	7	0	0	7 (100)	114	15 (13)	54 (47)	45 (39)	42	1 (2)	23 (55)	18 (43)
3000-0523	0	0	0	0	123	18 (15)	69 (56)	36 (29)	0	0	0	0	0	0	0	0
Total	0	0	0	0	134	18 (13)	69 (51)	47 (35)	116	15 (13)	56 (48)	45 (39)	43	1 (2)	23 (53)	19 (44)
Grand Total	256	39 (15)	139 (54)	78 (30)	509	62 (12)	262 (51)	185 (36)	527	83 (16)	280 (53)	164 (31)	209	13 (6)	121 (58)	75 (36)

Source data: Module 5.3.5.3, Table 88

Note: Patients in studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415 were randomized to receive a fixed dose (mg) of fospropofol, and patients in study 3000-0207 were randomized to receive weight-adjusted (mg/kg) (Part 1a) and fixed doses (mg) (Part 1b) of fospropofol.

¹Patients who were randomized to initial bolus doses of ≤5 mg/kg, >5-<8 mg/kg, and ≥8 mg/kg for 3000-0520, 3000-0522, 3000-0523 and 3000-0524 or patients who received these doses for 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415.

Table 7-A Special Population Distribution in Studies of Brief Therapeutic and/or Diagnostic Procedures by Initial Dose Randomized (3000-0520, 3000-0522, 3000-0523, and 3000-0524) or by Initial Dose Received (3000-0207, 3000--0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Population Study	Fospropofol ≤5 mg/kg ¹				Fospropofol >5-<8 mg/kg ¹				Fospropofol ≥8 mg/kg ¹				Midazolam			
	Total N	ASA P3/P4 n (%)	Hepatic ² n (%)	Renal ³ n (%)	Total N	ASA P3/P4 n (%)	Hepatic ² n (%)	Renal ³ n (%)	Total N	ASA P3/P4 n (%)	Hepatic ² n (%)	Renal ³ n (%)	Total N	ASA P3/P4 n (%)	Hepatic ² n (%)	Renal ³ n (%)
Colonoscopy																
3000-0207	1	N/C	0	0	23	N/C	0	0	140	N/C	0	5 (4)	0	N/C	0	0
3000-0410	0	0	0	0	7	2 (29)	0	0	203	3 (1)	0	1 (0)	68	1 (1)	0	0
3000-0415	0	0	0	0	0	0	0	0	15	1 (7)	0	2 (13)	5	0	0	0
3000-0520	51	1 (2)	0	2 (4)	26	0	0	0	24	0	0	2 (8)	26	2 (8)	0	0
3000-0522	102	4 (4)	0	0	158	5 (3)	0	2 (1)	0	0	0	0	52	3 (6)	0	1 (2)
Total	154	5 (3)	0	2 (1)	214	7 (3)	0	2 (1)	382	4 (1)	0	10 (3)	151	6 (4)	0	1 (1)
Bronchoscopy																
3000-0409	0	0	0	0	11	5 (45)	0	1 (9)	29	3 (10)	0	1 (3)	15	1 (7)	0	0
3000-0524	102	38 (37)	0	10 (10)	150	69 (46)	0	17 (11)	0	0	0	0	0	0	0	0
Total	102	38 (37)	0	10 (10)	161	74 (46)	0	18 (11)	29	3 (10)	0	1 (3)	15	1 (7)	0	0
Minor procedures																
3000-0411	0	0	0	0	4	0	0	0	2	1 (50)	0	0	1	1 (100)	0	0
3000-0412	0	0	0	0	7	1 (14)	0	0	114	1 (1)	0	1 (1)	42	2 (5)	0	0
3000-0523	0	0	0	0	123	23 (19)	1 (1)	13 (11)	0	0	0	0	0	0	0	0
Total	0	0	0	0	134	24 (18)	1 (1)	13 (10)	116	2 (2)	0	1 (1)	43	3 (7)	0	0
Grand Total	256	43 (17)	0	12 (5)	509	105 (21)	1 (0)	33 (6)	527	9 (2)	0	12 (2)	209	10 (5)	0	1 (0)

Source data: Module 5.3.5.3, Table 91

Note: Patients in studies 3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415 were randomized to receive a fixed dose (mg) of fospropofol, and patients in study 3000-0207 were randomized to receive weight-adjusted (mg/kg) (Part 1a) and fixed doses (mg) (Part 1b) of fospropofol.

N/C=not collected.

¹ Patients who were randomized to initial bolus doses of ≤5 mg/kg, >5-<8 mg/kg, and ≥8 mg/kg for 3000-0520, 3000-0522, 3000-0523 and 3000-0524 or patients who received these doses for 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415.

² Patients who had screening serum albumin levels <2.8 g/dL and screening total bilirubin levels >3 mg/dL.

³ Patients who had calculated screening creatinine clearance values ≤50 mL/min.

Table 8-A Worsening Clinically Significant Changes in Laboratory Test Results at any Time After Initiation of Study Drug in $\geq 2\%$ of Patients in the Double-Blind Studies (3000-0524, 3000-0522, and 3000-0520)

Laboratory Test	Pooled studies		3000-0522 (Colonoscopy)		3000-0524 (Bronchoscopy)	
	Initial Fospropofol dose (mg/kg)					
	2.0 (N=229) n/N (%)	6.5 (N=334) n/N (%)	2.0 (N=127) n/N (%)	6.5 (N=184) n/N (%)	2.0 (N=102) n/N (%)	6.5 (N=150) n/N (%)
Chemistry						
Albumin	7/218 (3.2)	10/330 (3.0)	1/124 (0.8)	3/183 (1.6)	6/94 (6.4)	7/147 (4.8)
Glucose	5/221 (2.3)	1/330 (0.3)	3/124 (2.4)	0/183 (0.0)	2/97 (2.1)	1/147 (0.7)
Phosphate	2/204 (1.0)	18/315 (5.7)	1/109 (0.9)	15/173 (8.7)	1/95 (1.1)	3/142 (2.1)
Total calcium	9/218 (4.1)	9/329 (2.7)	7/123 (5.7)	4/183 (2.2)	2/95 (2.1)	5/146 (3.4)
Hematology						
Hemoglobin	6/219 (2.7)	8/323 (2.5)	4/124 (3.2)	5/179 (2.8)	2/95 (2.1)	3/144 (2.1)
Hematocrit	2/218 (0.9)	8/322 (2.5)	1/124 (0.8)	1/178 (0.6)	1/94 (1.1)	7/144 (4.9)

Source data: Module 5.3.5.3, Table 195 of the NDA

Note: Clinically significant changes in laboratory test results experienced by $\geq 2\%$ of patients in the 2.0 mg/kg or 6.5 mg/kg groups for pooled data in double-blind studies are shown in this table.

Note: "n/N" is defined as follows: "n" is the number of patients who had a clinically significant change result for a parameter at any time after the start of study drug infusion, and N is the total number of patients with reliable data for the respective parameter at that time point. The percentages shown in this table are calculated using $n/N \times 100$.

Table 9-A Background Midazolam Information – From the Published Literature

<i>Article Title (Primary Author)</i>	<i>Procedures Conducted (N)</i>	<i>Dosing Details</i>	<i>Summary of Adverse Events</i>
Gastroenterologist-Administered Propofol Versus Meperidine and Midazolam for Advanced Upper Endoscopy: A Prospective, Randomized Trial (John J. Vargo, 2002)	The procedures performed were endoscopic unltrasonography (EUS) an endoscopic retrograde cholangiopancreatography (ERCP) In the study, there was a propofol arm (N=38) and a meperidine/midazolam arm (N=37) Data from the midazolam arm will be provided here	The average amount of midazolam received was 9.2 mg (.12 mg/kg) Initially, ≤50 mg of meperidine and ≤2 mg of midazolam were administered via IV Supplemental doses of meperidine (12.5-25 mg) and midazolam (0.5-1.0 mg) were administered if the patient showed signs of discomfort, restlessness, or agitation Both meperidine and midazolam were administered concomitantly	One patient required a reversal agent (naloxone and flumazenil) due to prolonged hypoxemia (SpO ₂ <85%) Supplemental O2 was required by 20 patients 27 patients experienced hypoxemia (O ₂ saturation <90%) – convert to percents 34 apneic episodes were recorded (RR <10 rpm) 7 patients experienced hypotension (≥25% drop in baseline systolic bp)
Frequent Hypoxemia and Apnea after Sedation with Midazolam and Fentanyl (Peter L. Bailey, 1990)	Investigated respiratory effects in healthy volunteers (N=12)	Patients evaluated in 3 separate sessions and received all 3 study drugs in random order: 1) 2 mcg/kg fentanyl IV 2) 0.05 mg/kg midazolam IV 3) 2 mcg/kg fentanyl + 0.05 mg/kg midazolam IV	no patient receiving midazolam alone became hypoxic hypoxemia occurred in 6 (50.0) of those receiving fentanyl hypoxemia occurred in 11 (91.7) of those receiving fentanyl + midazolam no apnea occurred in those receiving fentanyl alone or midazolam alone apnea occurred in 6 (50.0) of those receiving fentanyl + midazolam.

Table 9-A Background Midazolam Information – From the Published Literature

<i>Article Title (Primary Author)</i>	<i>Procedures Conducted (N)</i>	<i>Dosing Details</i>	<i>Summary of Adverse Events</i>
Moderate level of sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam (Lawrence B. Cohen, 2004)	Overall (N=100)	All patients were administered either meperidine or fentanyl with midazolam IV initially then were administered propofol.	In the EGD procedure arm, 4 patients experienced a deep sedation episode
	Colonoscopy (n=74)	30 patients received meperidine (mean dose 42 mg for colonoscopy and gastroscopy	In colonoscopy procedure arm, 9 patients experienced a deep sedation episode. No serious complication occurred
	Gastroscopy (EGD) (n=26)	68 patients received fentanyl (mean dose 69 mcg for colonoscopy, 63 mcg EGD) 2 patients received only midazolam (mean dose 0.9 mg for colonoscopy, 0.8 mg for EGD) and propofol (mean dose 98 mg for colonoscopy, 79 mg for EGD)	Hypoxemia (SaO2 <90%for >30 s) occurred in 2 patients (1 in colonoscopy and 1 in EGD) Hypotension (systolic/diastolic bp >20 mmHg) occurred in 41 patients Bradycardia (pulse <50 bpm) occurred in 5 patients No deaths, assisted ventilation or hospitalization occurred

Table 10-A Summary of Serious Adverse Events Considered by the Investigator to be Unrelated to Fospropofol Disodium – By Study and By Patient

Patient Number Procedure	Age, Sex, ASA Status	Serious Adverse Event (Verbatim Term)
0104-223-010 CABG	63-yr-old male ASA NA	Post procedural hemorrhage
0104-223-011 CABG ²	61-yr-old male ASA NA	Atrial fibrillation Pneumothorax (2 separate occurrences) Systemic Inflammatory Response Syndrome (SIRS)
0409-309-0007 Bronchoscopy	64-yr-old male ASA P2	Metastases to central nervous system (brain) Metastases to spine Nodule (3 occurrences: neck, temple, scalp)
0409-312-0008 Bronchoscopy	65-yr-old female ASA P3	Hepatic failure
0409-312-0009 Bronchoscopy ³	62-yr-old male ASA P2	Actinomycotic pulmonary infection
0409-312-0012 Bronchoscopy	61-yr-old male ASA P3	Pneumonia Hyperglycemia
0412-337-0009 Arthroplasty	40-yr-old female ASA P1	Appendicitis
0413-431-0002 ICU	77-yr-old male ASA P4	Acute respiratory failure ¹
0413-431-0042 ICU	72-yr-old male ASA P4	Septic shock ¹
0413-496-0021 ICU	61-yr-old male ASA P3	Rash Nausea Edema Dizziness
0413-497-0002 ICU	47-yr-old male ASA P3	Depression Pyrexia Nausea Vomiting Abdominal pain
0413-497-0007 ICU	65-yr-old male ASA P2	Post procedural bile leak Band neutrophil count increased Postoperative infection
0413-497-0012 ICU	45-yr-old female ASA P3	<i>Serratia</i> sepsis
0413-499-0004 ICU ²	76-yr-old male ASA P2	Gastrointestinal hemorrhage ¹ Respiratory distress
0413-506-0017 ICU ²	48-yr-old male ASA P2	Atrial fibrillation Fluid overload Hypoxia
0413-512-0039 ICU	65-yr-old male ASA P4	Wound infection

Table 10-A Summary of Serious Adverse Events Considered by the Investigator to be Unrelated to Fospropofol Disodium – By Study and By Patient

Patient Number Procedure	Age, Sex, ASA Status	Serious Adverse Event (Verbatim Term)
0413-516-0002 ICU ²	75-yr-old female ASA P4	International normalized ratio increased
0413-531-0016 ICU	77-yr-old male ASA P3	Respiratory failure ¹
0413-531-0080 ICU	71-yr-old male ASA P4	Cardio-respiratory arrest ¹
0522-267-0013 Colonoscopy	46-yr-old female ASA P1	Colon cancer
0522-518-0029 Colonoscopy ³	70-yr-old female ASA P2	Splenic hematoma Peritoneal hemorrhage
0523-447-0005 TEE	63-yr-old female ASA P3	Apnea Cardiac arrest
0523-547-0001 TEE	52-yr-old male ASA P2	Atrial septal defect
0523-547-0004 TEE	63-yr-old male ASA P3	Atrial septal defect
0523-565-0023 EGD	60-yr-old female ASA P3	Hepatic encephalopathy Ammonia increased
0524-309-0001 Bronchoscopy	43-yr-old male ASA P3	COPD (exacerbation) Acute respiratory failure Pneumonia pneumococcal Respiratory failure (hypoxemic hypercapnic)
0524-309-0004 Bronchoscopy	77-yr-old female ASA P2	Lung infection pseudomonal Bronchitis bacterial
0524-309-0006 Bronchoscopy ¹	70-yr-old female ASA P2	Lung neoplasm malignant Pneumonia COPD (exacerbation)
0524-309-0016 Bronchoscopy	55-yr-old female ASA P2	Pneumothorax
0524-312-0003 Bronchoscopy ¹	77-yr-old male ASA P3	Lung neoplasm malignant
0524-321-0025 Bronchoscopy	64-yr-old female ASA P2	Chest pain
0524-323-0007 Bronchoscopy	82-yr-old male ASA P3	Hypercalcemia
0524-430-0005 Bronchoscopy	67-yr-old male ASA P4	Cardiac failure congestive Cardiomyopathy Cerebrovascular accident
0524-430-0012 Bronchoscopy	55-yr-old male ASA P2	Muscle strain
0524-533-0004 Bronchoscopy	71-yr-old female ASA P3	Respiratory failure Laryngospasm
0524-533-0008 Bronchoscopy ¹	67-yr-old male ASA P2	Septic shock

Table 10-A Summary of Serious Adverse Events Considered by the Investigator to be Unrelated to Fospropofol Disodium – By Study and By Patient

Patient Number Procedure	Age, Sex, ASA Status	Serious Adverse Event (Verbatim Term)
0524-535-0004 Bronchoscopy	82-yr-old male ASA P1	Lung squamous cell carcinoma stage unspecified
0524-540-0002 Bronchoscopy	50-yr-old female ASA P3	Bronchitis acute (worsened)
0524-540-0004 Bronchoscopy	75-yr-old male ASA P2	COPD (exacerbation)
0524-540-0011 Bronchoscopy	47-yr-old female ASA P3	Respiratory failure
0524-540-0016 Bronchoscopy	71-yr-old female ASA P2	Pneumonia
0524-540-0018 Bronchoscopy	59-yr-old female ASA P3	COPD (exacerbation)
0524-540-0022 Bronchoscopy	83-yr-old male ASA P2	Bronchitis bacterial
0524-540-0023 Bronchoscopy	36-yr-old male ASA P3	COPD (exacerbation)
0524-540-0029 Bronchoscopy	52-yr-old male ASA P2	Non-small cell lung cancer
0524-540-0033 Bronchoscopy	79-yr-old male ASA P2	COPD (exacerbation)
0524-540-0037 Bronchoscopy	61-yr-old female ASA P3	Pneumonia Respiratory failure Abdominal abscess Large intestine perforation Intestinal perforation Abdominal sepsis
0524-540-0040 Bronchoscopy	57-yr-old female ASA P2	COPD (exacerbation)
0524-544-0003 Bronchoscopy ¹	61-yr-old male ASA P4	Respiratory arrest Pneumonia
0524-544-0009 Bronchoscopy ¹	46-yr-old male ASA P2	Respiratory failure Cardiac arrest Anoxic encephalopathy Sepsis Brain edema Brain herniation
0524-544-0017 Bronchoscopy	31-yr-old male ASA P4	Cystic fibrosis (exacerbation)
0524-544-0021 Bronchoscopy	64-yr-old male ASA P3	Ventricular tachycardia
0524-544-0022 Bronchoscopy	80-yr-old male ASA P2	Coronary artery disease (2 separate occurrences) Lung neoplasm malignant
0524-544-0024 Bronchoscopy	61-yr-old male ASA P2	Lung neoplasm malignant

Table 10-A Summary of Serious Adverse Events Considered by the Investigator to be Unrelated to Fospropofol Disodium – By Study and By Patient

Patient Number Procedure	Age, Sex, ASA Status	Serious Adverse Event (Verbatim Term)
0524-544-0025 Bronchoscopy	64-yr-old male ASA P2	Peritoneal hemorrhage
0524-544-0028 Bronchoscopy	56-yr-old female ASA P2	Lung neoplasm malignant
0524-566-0010 Bronchoscopy	75-yr-old male ASA P3	Hypotension (exacerbation) Hypovolemia
0524-566-0015 Bronchoscopy	51-yr-old female ASA P2	HIV test positive Enterococcal bacteremia

CABG = Coronary Artery Bypass Graft, COPD = Chronic Obstructive Pulmonary Disease,
 GD = Esophagogastroduodenoscopy, HIV = Human Immunodeficiency Virus, ICU = Intensive Care
 Unit, INR = International Normalized Ratio, TEE = Transesophageal Echocardiogram

¹ SAE resulted in death

² Patient received propofol only

³ Patient received midazolam only

Table 11-A Number (%) of Patients Whose MOAA/S Reached 0 or 1 at Any Time by Study (3000-0409, 3000-0410, 3000-0411, 3000-0412, and 3000-0415)

Study	MOAA/S	Fospropofol n/N (%)	Midazolam n/N (%)
3000-0409	1	14/40 (35.0%)	2/15 (13.3%)
	0	14/40 (35.0%)	1/15 (6.7%)
	0-1	21/40 (52.5%)	2/15 (13.3%)
3000-0410	1	79/210 (37.6%)	5/68 (7.4%)
	0	66/210 (31.4%)	4/68 (5.9%)
	0-1	108/210 (51.4%)	8/68 (11.8%)
3000-0411	1	4/6 (66.7%)	0
	0	1/6 (16.7%)	0
	0-1	4/6 (66.7%)	0
3000-0412	1	44/121 (36.4%)	6/42 (14.3%)
	0	71/121 (58.7%)	3/42 (7.1%)
	0-1	78/121 (64.5%)	7/42 (16.7%)
3000-0415	1	7/15 (46.7%)	0
	0	3/15 (20.0%)	0
	0-1	8/15 (53.3%)	0
Overall	1	148/392 (37.8%)	13/131 (9.9%)
	0	155/392 (39.5%)	8/131 (6.1%)
	0-1	219/392 (55.9%)	17/131 (13.0%)

Source: Final Tables and Listings ALSDAC, 30 Mar2008, Table 15

Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
3000-0523, 3000-0524)

STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	523	61	37	15	1	1	3	0.0639
524	548	73	37	15	1	1	3	0.0750
524	665	70	41	15.1	0	2	3	0.0548
524	601	61	44	19	1	1	3	0.0490
524	594	51	45	19.5	1	1	2	0.0493
524	618	46	45	14.7	0	2	2	0.0591
524	645	56	45	16.5	0	3	3	0.0785
523	448	73	47	18.4	1	2	2	0.0331
524	458	70	47	20.3	1	1	2	0.0699
522	283	59	48	18.7	1	1	1	0.0445
524	607	30	48	17.6	1	4	2	0.0537
524	606	60	49	19.6	1	1	3	0.0776
524	643	48	49	19.6	1	3	3	0.0693
524	469	56	50	17.7	0	2	3	0.0860
524	520	82	50	17.3	0	2	3	0.0336
524	660	64	50	23.1	1	1	4	0.1211
522	341	38	51	20.4	1	1	2	0.0303
522	332	51	52	20.1	1	1	2	0.0416
524	569	56	52	19.8	1	1	2	0.0479
522	374	55	53	22.1	1	1	2	0.0550
524	466	69	53	20.4	1	1	3	0.0570
524	604	57	53	19.9	1	1	2	0.0494
524	497	82	54	21.4	1	1	2	0.0535
523	676	71	54	25.7	1	2	3	0.0689
522	353	69	55	18.4	1	1	1	0.0291
523	427	66	55	22	0	1	2	0.0424
523	430	76	55	20.7	1	1	3	0.0461
524	510	80	55	19.5	1	1	2	0.0448
524	585	71	55	22.3	1	1	2	0.0537
524	671	73	55	20.7	1	1	2	0.0230
524	454	43	56	18.7	0	1	3	0.1700
523	431	82	57	23.7	1	1	3	0.0451
523	434	75	57	23.7	1	1	2	0.0335
523	438	75	57	20.9	1	1	3	0.0719
524	527	78	58	24.1	1	1	2	0.0391
524	638	51	58	23.5	1	1	1	0.0460
524	538	67	59	18.2	0	1	3	0.0492
524	573	70	60	20.8	1	1	2	0.0501
524	637	74	60	17.9	0	1	3	0.0210
522	286	79	61	22.4	1	1	2	0.0424
522	399	18	61	18.2	0	1	1	0.0210
524	593	58	61	26.4	1	1	2	0.0441
524	667	59	61	23	1	1	2	0.0343
522	331	72	62	22.8	1	1	1	0.0347

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Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
3000-0523, 3000-0524)

STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	489	61	62	22.8	0	1	2	0.0407
524	560	68	62	20.2	0	1	3	0.0762
524	570	69	62	23.1	1	1	2	0.0473
524	610	65	62	23.3	1	1	3	0.0678
522	408	73	63	24.6	1	1	2	0.0520
524	515	69	63	22.3	0	1	2	0.0464
524	519	37	63	21.8	0	1	2	0.0717
524	552	70	63	19.9	0	1	3	0.0682
524	553	73	63	20.3	0	1	4	0.0634
522	349	53	64	25.6	1	1	1	0.0396
524	475	70	64	25	1	1	4	0.0518
524	631	64	64	22.1	0	2	2	0.0375
522	323	49	65	27.1	0	1	2	0.0391
522	416	77	65	23.6	0	1	2	0.0434
523	447	56	65	22.5	1	1	2	0.0410
524	457	77	65	25.4	1	1	2	0.0592
524	627	63	65	20.5	0	1	3	0.0898
524	648	47	65	25.4	0	1	2	0.0434
522	318	55	66	26.8	1	1	2	0.0490
524	471	77	67	22.4	0	1	3	0.0503
524	572	58	67	22.4	0	3	2	0.0524
522	297	70	68	25	1	1	1	0.0380
522	335	47	68	22.7	1	1	2	0.0303
522	403	47	68	29	0	1	1	0.0308
524	657	72	68	26.6	1	1	3	0.0584
522	285	56	69	21.8	1	1	1	0.0394
522	315	51	69	23.9	1	1	1	0.0391
522	347	50	69	25.7	1	3	2	0.0389
524	621	62	69	21.3	0	2	3	0.0640
522	282	51	70	21.6	0	1	2	0.0472
522	386	53	70	25.7	1	1	2	0.0417
523	439	87	70	27.3	1	1	3	0.0358
524	512	83	70	27.7	1	1	3	0.0528
524	563	55	70	26.3	1	1	3	0.0441
524	599	66	70	20.9	0	1	3	0.0486
522	407	39	71	22.4	1	1	1	0.0532
524	498	82	71	22.4	0	1	2	0.0557
524	499	61	71	20.7	0	1	2	0.0550
524	530	76	71	23.7	0	1	3	0.0470
524	651	63	71	23.5	0	1	3	0.0478
524	460	82	72	23	0	1	2	0.0370
524	564	61	72	29.2	1	1	3	0.0668
524	673	62	72	19.7	0	1	2	0.0637
524	503	63	73	24.4	0	1	2	0.0329

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Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
3000-0523, 3000-0524)

STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	547	64	73	23.8	0	1	3	0.0435
524	559	57	73	22	0	1	3	0.0491
522	307	70	74	29.6	1	1	1	0.0339
522	346	38	74	29.3	1	1	1	0.0251
522	350	66	74	30.8	1	1	2	0.0512
522	378	59	74	28.9	1	1	2	0.0376
523	446	70	74	27.2	0	1	2	0.0345
523	451	69	74	23.4	0	1	3	0.0210
523	452	57	74	23.4	0	1	3	0.0368
524	505	48	74	24.7	0	1	2	0.0445
524	574	50	74	30	1	1	3	0.0619
524	577	60	74	28.9	1	1	3	0.0504
522	395	71	75	27.5	1	1	3	0.0420
522	418	26	75	26	0	1	2	0.0320
524	555	47	75	24.5	0	1	2	0.0386
524	625	45	75	26.6	0	1	4	0.0580
524	669	56	75	27.5	1	1	2	0.0522
522	289	47	76	24	0	1	1	0.0401
523	426	74	76	23.2	0	1	2	0.0461
523	442	80	76	28.6	1	1	2	0.0435
523	450	53	76	26.9	1	1	3	0.0314
524	481	67	76	24.8	0	1	1	0.0845
524	587	59	76	31.6	1	1	3	0.0523
524	655	50	76	24	0	2	1	0.0378
522	296	71	77	27.3	0	1	2	0.0313
522	338	39	77	34.2	1	3	2	0.0370
522	370	58	77	27.3	1	1	2	0.0380
522	373	66	77	28.3	0	3	2	0.0348
524	622	59	77	27.3	1	1	2	0.0364
522	306	57	78	29.4	1	1	2	0.0390
522	369	30	78	28.7	1	3	2	0.0447
523	440	69	78	27.6	1	1	3	0.0400
524	635	76	78	24.3	0	1	3	0.0410
524	644	60	78	28	1	1	2	0.0495
522	277	43	79	25.8	0	1	2	0.0267
522	364	51	79	29	1	1	2	0.0435
522	372	34	79	29.7	1	1	1	0.0366
523	425	67	79	24.9	0	1	2	0.0316
524	545	64	79	25.8	0	1	3	0.0545
524	649	69	79	31.6	1	2	3	0.0352
522	314	63	80	30.1	1	1	1	0.0605
522	336	43	80	28.3	0	3	3	0.0405
523	444	59	80	25.2	0	1	3	0.0403
524	473	67	80	26.7	0	1	3	0.0467

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Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
3000-0523, 3000-0524)

STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	611	58	80	25.2	0	1	3	0.0314
522	376	63	81	29.8	1	2	2	0.0371
522	391	85	81	28.7	0	1	2	0.0362
522	410	72	81	29.8	0	4	2	0.0436
524	540	68	81	28.7	0	1	2	0.0476
524	614	44	81	27.1	0	1	2	0.0441
524	670	66	81	22.9	0	1	2	0.0273
522	362	58	82	25.9	0	1	2	0.0325
524	477	73	82	27.4	0	1	2	0.0475
524	556	77	82	29.1	0	1	2	0.0393
524	620	36	82	30.1	1	2	2	0.0376
523	437	78	83	34.1	1	1	2	0.0421
524	479	69	83	25.9	0	1	1	0.0605
524	536	60	83	25.6	0	1	3	0.0400
524	663	72	83	24.3	0	1	2	0.0350
522	312	46	84	25.9	0	1	1	0.0420
522	380	57	84	30.9	1	1	1	0.0349
523	428	72	84	25.6	0	1	3	0.0343
523	432	76	84	26.5	0	1	3	0.0479
524	488	73	84	31.6	0	1	3	0.0375
524	509	73	84	28.1	1	1	3	0.0389
524	580	44	84	37.3	1	1	3	0.0616
522	419	45	85	24.8	0	1	2	0.0517
524	516	67	85	31.2	1	1	3	0.0537
524	617	75	85	34.5	1	1	4	0.0542
522	316	52	86	25.7	0	1	1	0.0291
522	392	68	86	24.3	0	1	2	0.0402
524	566	82	86	32.4	0	1	1	0.0667
524	567	52	86	33.6	1	1	2	0.0644
522	276	45	87	26	0	1	1	0.0399
522	302	54	87	30.8	1	1	2	0.0333
524	465	55	87	25.4	0	1	2	0.0401
524	463	60	88	23.6	0	1	2	0.0535
524	494	55	88	28.1	0	1	2	0.0248
522	274	54	89	26.6	0	1	2	0.0210
522	326	33	89	27.5	0	1	1	0.0288
522	384	66	89	26.6	0	1	2	0.0332
522	389	61	89	28.1	0	1	1	0.0336
524	629	80	89	26	0	1	2	0.0449
524	658	66	89	29.1	0	1	2	0.0466
523	675	64	89	29.1	0	2	4	0.0173
522	385	57	90	27.8	0	1	2	0.0372
522	422	75	90	28.4	0	1	2	0.0295
522	424	58	90	28.4	1	1	1	0.0431

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Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
3000-0523, 3000-0524)

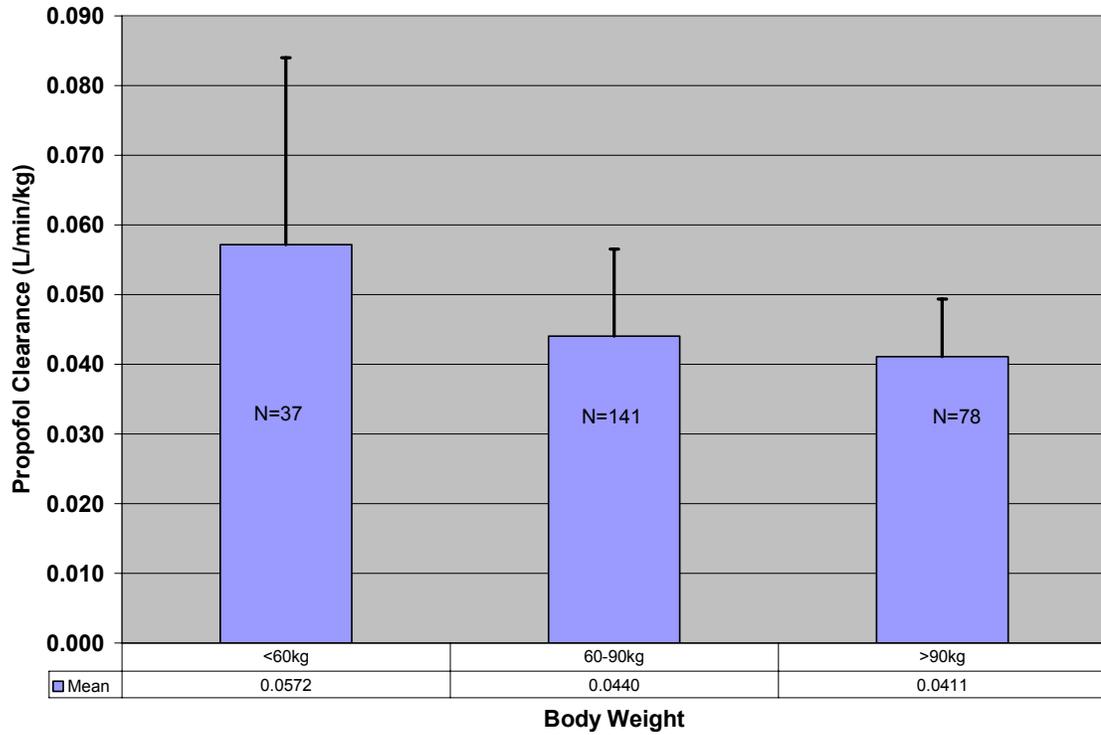
STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	539	74	90	30.1	0	1	3	0.0605
524	628	64	90	33.9	0	1	3	0.0627
522	321	57	91	31.5	1	1	2	0.0363
524	542	48	91	29.7	0	1	4	0.0408
524	605	55	91	29.7	0	2	3	0.0445
522	287	52	92	27.5	0	1	1	0.0403
522	288	60	92	30.7	0	1	1	0.0626
522	365	26	92	33.8	1	1	1	0.0424
523	435	84	92	30.7	0	1	2	0.0473
524	472	68	92	29	0	1	3	0.0407
524	532	78	92	28.4	0	1	3	0.0352
524	615	72	92	30	0	1	3	0.0327
524	652	69	92	38.3	1	1	4	0.0570
522	272	67	93	25	0	1	1	0.0415
523	429	68	93	32.2	0	1	2	0.0327
524	529	67	93	28.7	0	1	4	0.0370
524	576	79	93	36.3	1	1	3	0.0485
524	596	64	93	28.1	0	2	3	0.0356
524	526	78	94	26.6	0	1	2	0.0475
524	581	68	94	29.7	0	1	2	0.0517
522	299	52	95	34.9	1	1	2	0.0439
524	551	57	95	29.3	0	1	3	0.0475
524	595	52	95	32.1	0	1	2	0.0347
522	414	59	96	38.5	1	1	2	0.0440
524	544	56	96	30.6	0	1	3	0.0429
523	441	63	97	29	0	1	3	0.0401
522	381	67	98	30.9	0	1	3	0.0486
522	328	51	99	31.2	0	2	1	0.0291
522	394	60	99	40.2	1	1	2	0.0320
524	484	65	99	38.7	1	1	2	0.0403
524	602	68	99	29.6	0	1	3	0.0428
522	284	61	100	35.4	1	1	3	0.0615
522	361	51	100	27.7	0	2	2	0.0571
522	404	41	100	30.9	1	1	1	0.0357
524	495	57	100	34.6	0	2	2	0.0315
524	630	61	100	31.6	0	1	2	0.0369
522	280	31	101	25.8	0	1	1	0.0331
522	343	61	101	38.5	1	3	2	0.0283
524	487	61	102	44.1	1	1	2	0.0551
524	557	40	102	30.5	0	1	2	0.0300
524	588	64	102	35.3	1	1	3	0.0437
522	305	41	104	40.6	1	1	2	0.0369
522	320	59	104	40.6	1	1	2	0.0384
522	330	71	105	31.4	0	1	2	0.0359

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Table 12-A Total Body Clearance and Body Weight by Patient (3000-0522,
 3000-0523, 3000-0524)

STUDY	ID	AGE (yrs)	WT (kg)	BMI	SEX	RACE	ASA	CLp (L/min/kg)
524	506	70	105	34.3	0	1	2	0.0349
524	591	63	105	45.4	1	1	3	0.0498
522	298	67	106	32.7	0	1	1	0.0292
522	301	62	106	39.9	1	1	2	0.0484
522	388	46	106	35.4	1	1	2	0.0574
522	291	59	107	30.3	0	1	2	0.0303
522	294	46	107	33.4	0	1	2	0.0309
522	423	57	107	34.9	0	1	2	0.0393
523	436	77	108	32.6	0	1	2	0.0425
523	449	72	108	32.2	0	1	3	0.0512
523	433	67	109	29.9	0	1	4	0.0469
524	579	49	109	44.2	1	1	3	0.0329
524	464	39	110	40.4	1	1	2	0.0435
522	396	59	111	43.9	1	1	2	0.0326
522	327	32	113	31	0	1	2	0.0368
523	445	46	114	35.2	0	1	3	0.0497
522	359	59	115	38.4	1	2	2	0.0361
522	397	57	115	39.8	1	1	1	0.0362
524	483	48	115	42.2	1	1	2	0.0483
523	443	72	119	36.7	0	1	2	0.0412
522	358	58	120	37.9	0	1	2	0.0298
524	491	71	120	35.8	0	1	3	0.0424
524	525	60	122	34.5	0	1	2	0.0494
522	303	51	123	48	1	1	2	0.0310
522	400	55	123	40.2	0	1	1	0.0387
524	534	26	124	34.7	0	1	3	0.0326
522	342	31	127	35.2	0	1	2	0.0236
524	586	73	127	41.9	1	1	2	0.0445
524	642	59	128	50	1	1	2	0.0471
522	405	47	135	54.8	1	1	1	0.0361
524	662	46	136	40.6	0	1	2	0.0534
522	356	30	137	50.3	1	1	2	0.0447
522	411	43	147	52.1	1	1	3	0.0441
524	521	25	148	35.9	0	1	2	0.0425
524	478	39	154	48.6	0	1	1	0.0369
524	633	45	154	58	1	1	3	0.0457

Figure 1-A Propofol Total Body Clearance vs Body Weight Plot in Patients Receiving 6.5 mg/kg and Supplemental Doses (Studies 3000-0522, 3000-0523, and 3000-0524)



Appendix B Clinical Study Summaries

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
Pivotal, adequate, well-controlled, double-blind studies							
3000-0520 (started Aug 2005, completed Oct. 2005) Location: United States	Randomized, double-blind, dose-response, parallel group study of fospropofol injection in patients undergoing colonoscopy. Patients received an initial bolus dose of fospropofol followed by supplemental doses at 25% of the bolus to reach minimal-to-moderate sedation. Two supplemental doses were provided for administration during the sedation initiation phase. After the start of the procedure, supplemental doses at 25% of the initial bolus were permitted to maintain sedation. All patients were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Sixteen study sites ≥18 years of age, ASA status of P1 - P4	Dose response Efficacy and safety	Initial 5.0-mg/kg bolus + 1.25-mg/kg supplements, IV (N=26), or Initial 6.5-mg/kg bolus + 1.625-mg/kg supplements, IV, (N=26), or Initial 8.0-mg/kg bolus + 2.0-mg/kg supplements, IV (N=24). Fospropofol control group: Initial 2.0-mg/kg bolus + 0.5-mg/kg supplements, IV (N=25)	Fentanyl 50 µg 5 min predose; supplemental doses of 25 µg as needed for analgesia.	Midazolam: Initial 0.02-mg/kg bolus + 0.01-mg/kg supplements, IV (N=26)	Fifty-eight male and 69 female patients, 18 to 80 years of age. Two patients had an ASA P3 status and 1 patient was ASA P4.	-Sedation-related adverse events (SRAEs) -Airway Assistance -Treatment-emergent AEs (TEAEs) -Laboratory, pulse oximetry, vital signs, physical examination, and electrocardiogram (ECG) results -Purposeful movement -Concomitant medications

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0522 (started Mar 2006, completed Aug 2006) Location: United States	<p>Randomized, double-blind, parallel group, dose-controlled study of fospropofol injection in patients undergoing colonoscopy. Patients received an initial bolus dose of fospropofol followed by supplemental doses at 25% of the bolus to reach minimal-to-moderate sedation. Three supplemental doses were provided for administration during the sedation initiation phase. After the start of the procedure, supplemental doses at 25% of the initial bolus were permitted to maintain sedation.</p> <p>All patients were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure.</p> <p>Eighteen study sites.</p> <p>≥18 years of age, ASA status of P1 - P4.</p>	Efficacy and safety	<p>Initial 6.5-mg/kg bolus + 1.625-mg/kg supplements, IV (N=160)</p> <p>Fospropofol control group: initial 2.0-mg/kg bolus + 0.5-mg/kg supplements, IV (N=102)</p>	Fentanyl 50 µg 5 min predose; 1 supplemental dose of 25 µg permitted for analgesia.	Midazolam: Initial 0.02-mg/kg bolus + 0.01-mg/kg supplements, IV (N=52)	<p>A total of 156 male and 156 female patients, ages 18 to 85 years.</p> <p>Twelve patients had an ASA P3 status and no patient was ASA P4.</p>	<p>-SRAEs</p> <p>-Airway Assistance</p> <p>-TEAEs</p> <p>-Laboratory, pulse oximetry, vital signs, physical examination, and ECG results</p> <p>-Purposeful movement</p>

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0524 (started April 2006, completed Feb 2007) Location: United States	<p>Randomized, double-blind, parallel group, dose-controlled study of fospropofol injection in patients undergoing bronchoscopy. Patients received an initial bolus dose of fospropofol followed by supplemental doses at 25% of the bolus to reach minimal-to-moderate sedation. Three supplemental doses were provided for administration during the sedation initiation phase. After the start of the procedure, supplemental doses at 25% of the initial bolus were permitted to maintain sedation.</p> <p>All patients were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. In addition, lidocaine was administered as a topical anesthetic for suppression of cough upon the introduction of the flexible bronchoscope (dose was ≤300 mg, or ≤4.5 mg/kg whichever was less).</p> <p>Twenty-four study sites.</p> <p>≥18 years of age, ASA status of P1 to P4.</p>	Efficacy and safety	<p>Initial 6.5-mg/kg bolus + 1.625-mg/kg supplements, IV (N=150)</p> <p>Fospropofol control group: initial 2.0-mg/kg bolus + 0.5-mg/kg supplements, IV (N=100)</p>	Fentanyl 50 µg 5 min predose; 1 supplemental dose of 25 µg permitted for analgesia	None	<p>A total of 140 male and 112 female patients, ages 22 to 84 years</p> <p>Ninety-two patients had an ASA P3 status and 15 patients were ASA P4.</p>	<p>-SRAEs</p> <p>-Airway Assistance</p> <p>-TEAEs</p> <p>-Laboratory, pulse oximetry, vital signs, physical examination, and ECG results</p> <p>-Purposeful movement</p>

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
Open-label, supportive studies							
3000-0207 (started Jan 2003, completed Feb 2004) Location: United States	Phase 2, randomized, open-label, multicenter, 2-part, adaptive dose-ranging study of fospropofol injection in patients undergoing colonoscopy. Part 1 initially investigated the use of premedication with fentanyl, celecoxib 400 mg, and a fospropofol priming dose (N=12 patients). Part 1 was subdivided into 2 sub-parts (1A and 1B). Part 2 of the study was never initiated. Part 1A used a matrix-adaptive randomization scheme to evaluate 3 fentanyl pretreatment doses followed by bolus doses of fospropofol. Part 1B of this study was designed to evaluate a weight-based, fixed-dose regimen of fospropofol in conjunction with fentanyl. In Part 1A, supplemental oxygen was administered only if the saturation of hemoglobin with oxygen in peripheral blood (SpO ₂ , as determined by pulse oximetry) fell below 90%, or if medical intervention was required. In Part 1B, all patients were to be placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Eight study sites. ≥18 years of age with ASA status of P1 or P2.	Dose response Efficacy and safety	Part 1A: Initial fospropofol bolus of 7.5, 10.0, or 12.5 mg/kg IV; up to 4 supplemental doses (range, 1.5 to 5.0 mg/kg per dose) (N=100) Part 1B: Initial fospropofol bolus of 630/700 mg, 805 mg, 910 mg, or 980 mg IV (N=64)	Part 1A: fentanyl 0.5, 1.0, or 1.5 µg/kg, IV Supplemental doses as needed. Part 1B: fentanyl 30/50/60 µg; 70/80 µg; 80 µg; or 100 µg IV Supplemental doses up to 200 µg total.	None	Part 1A: Forty-six male and 54 female patients, 20 to 80 years of age. Part 1B: Twenty-six male and 38 female patients, 23 to 85 years of age.	-SRAEs -Airway Assistance -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Concomitant medications -Plasma concentrations of formate

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0523 (started May 2006, database lock in Mar 2007; enrollment is currently ongoing for recruitment of patients with hepatic impairment) Location: United States	<p>Open-label, multicenter, single-arm study of fospropofol injection in patients undergoing minor surgical procedures.</p> <p>Patients received an initial bolus dose of fospropofol followed by supplemental doses at 25% of the bolus to reach minimal-to-moderate sedation and to complete the procedure. Patients were to receive 5 supplemental doses before rescue with an alternative sedative medication.</p> <p>All patients were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure.</p> <p>Twelve study sites.</p> <p>≥18 years of age, ASA status of P1 - P4.</p>	Safety	Initial 6.5-mg/kg bolus + 1.625-mg/kg supplements, IV (N=123)	Fentanyl 50 µg 5 min pre-dose; 1 supplemental dose of 25 µg permitted for analgesia.	NA	<p>Fifty-six male and 67 female patients, 18 to 87 years of age.</p> <p>Twenty-two patients had an ASA P3 status and 1 patient was ASA P4.</p>	<p>-SRAEs</p> <p>-Airway Assistance</p> <p>-TEAEs</p> <p>-Laboratory, pulse oximetry, vital signs, physical examination, and ECG results</p> <p>-Purposeful movement</p> <p>-Concomitant medications</p>

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
Open-label, fixed-dose, supportive studies							
3000-0409 (started Sep 2004, completed Mar 2005) Location: United States Terminated prior to completion	Phase 3, randomized, open-label study of fospropofol injection versus midazolam HCl for sedation in patients undergoing flexible bronchoscopy procedures. Initial bolus dose and up to 4 supplemental doses of fospropofol or midazolam. Fentanyl pretreatment 5 min prior to dosing. All patients were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Twelve study sites. ≥18 years of age, ASA status of P1 – P3.	Comparative efficacy and safety (closed prior to study completion)	Original initial fospropofol bolus dose of 700 mg to 980 mg IV based on weight; supplemental doses of 140 mg IV (N=20). After Amendment 2, initial fospropofol bolus dose of 385 mg to 735 mg IV; supplemental doses of 70 mg to 105 mg, based on age and weight (N=40).	Originally fentanyl 1 µg/kg IV; after Amendment 2, fentanyl 0.5 µg/kg. Supplemental doses ≤50% of original dose.	Midazolam HCl initial bolus doses of 0.5 mg to 2.0 mg; supplemental doses of 0.25 mg to 1.0 mg, based on age and weight (N=15)	Twenty-eight male and 27 female patients, 24 to 68 years of age. Three patients had an ASA status of P3 and no patient was ASA P4.	-SRAEs -Airway Assistance -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Concomitant medications

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0410 (started Sep 2004, completed Jan 2005) Location: United States	Phase 3, randomized, open-label study of fospropofol versus midazolam HCl following pretreatment with fentanyl citrate injection in patients undergoing colonoscopy. Initial bolus dose and up to 4 supplemental doses of fospropofol or midazolam. Fentanyl pretreatment 5 min prior to dosing. All patients were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Sixteen study sites. ≥18 to 65 years of age; ASA status of P1 – P3.	Comparative efficacy and safety	Initial fospropofol bolus dose of 700 mg to 980 mg IV based on weight; supplemental doses of 140 mg IV (N=191).	Fentanyl 0.5 µg/kg IV; supplemental doses ≤50% of original dose.	Midazolam HCl initial bolus doses of 1.0 mg to 2.0 mg; supplemental doses of 0.5 mg to 1.0 mg, based on age and weight (N=62)	A total of 102 patients were male and 151 were female, 19 to 65 years of age. Two patients had an ASA status of P3 and no patient was ASA P4.	-SRAEs -Airway Assistance -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Concomitant medications

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0411 (started Feb 2005, completed Mar 2005) Location: United States Terminated prior to completion	Phase 3, randomized, open-label, multicenter study of fospropofol Injection versus midazolam HCl following pretreatment with fentanyl citrate injection in patients undergoing percutaneous coronary procedures Initial bolus dose and up to 4 supplemental doses of fospropofol or midazolam. Fentanyl pretreatment 5 min prior to dosing. All patients were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Four study sites. ≥18 years of age, ASA status of P1 – P3.	Comparative efficacy and safety (closed prior to study completion)	Initial fospropofol bolus doses were to range from 385 mg to 735 mg IV. Possible supplemental doses of 70 mg to 105 mg, based on age and weight (N=6)	Fentanyl 0.5 µg/kg IV; supplemental doses ≤50% of original dose.	Midazolam HCl initial bolus doses were to range from 0.5 mg to 2.0 mg IV; possible supplemental doses of 0.25 mg to 1.0 mg, based on age and weight (N=1).	Three male and 4 female patients, 55 to 64 years of age. Two patients were ASA P3 and no patient had an ASA status of P4.	-SRAEs -Airway Assistance -TEAEs -Concomitant medications -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0412 (started Oct 2004, completed Mar 2005) Location: United States Terminated prior to completion	Phase 3, randomized, open-label study of fospropofol injection versus midazolam HCl following pretreatment with fentanyl citrate injection in patients undergoing minor surgical and/or therapeutic procedures. Initial bolus dose and up to 4 supplemental doses of fospropofol or midazolam. Fentanyl pretreatment 5 min prior to dosing. All patients were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Eighteen study sites. ≥18 years of age, ASA status of P1 – P3.	Comparative efficacy and safety (closed prior to study completion)	Initial fospropofol bolus doses of 525 to 980 mg IV; supplemental doses of 105 mg to 140 mg, based on age and weight (N=121).	Fentanyl 1.0 µg/kg IV After first amendment, 0.5 µg/kg for patients >65 years of age.	Midazolam HCl initial bolus doses of 0.5 mg to 2 mg IV; supplemental doses of 0.25 mg to 1 mg, based on age and weight (N=42).	Fifty-five male and 108 female patients, 19 to 65 years of age. Four patients had an ASA status of P3 and no patient was ASA P4.	-SRAEs -Airway Assistance -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Concomitant medications -Alternative sedation/hypnotic medications

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0415 (started Feb 2005, completed Mar 2005) Location: United States Terminated prior to completion	Phase 2, randomized, open-label study of fospropofol injection versus midazolam HCl following pretreatment with fentanyl citrate injection in elderly patients undergoing colonoscopy Initial bolus dose and up to 4 supplemental doses of fospropofol or midazolam. Fentanyl pretreatment 5 min prior to dosing. All patients were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to fentanyl dosing and continuing until the patient recovered from the procedure. Sixteen study sites. >65 years of age, ASA status of P1--P3.	Comparative safety and efficacy (closed prior to study completion)	Initial fospropofol bolus doses of 525, 595, or 735 mg IV based on weight; supplemental doses of 105 mg (N=15).	Fentanyl 0.5 µg/kg IV	Midazolam HCl initial IV bolus doses of 0.5, 0.75, or 1 mg; supplemental doses of 0.25, 0.35, or 0.5 mg, based on weight (N=5).	Eight male patients and 12 female patients, 65 to 76 years of age. One patient had an ASA status of P3 and no patient was ASA P4.	-SRAEs -Airway Assistance -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Concomitant medications -Alternative sedation/hypnotic medications

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
Prolonged treatment duration studies in intubated and mechanically ventilated patients							
3000-0104 (started Jun 2002, completed Jul 2003) Location: Germany	Phase 2, randomized, open-label study of fospropofol injection versus propofol injectable emulsion in patients undergoing elective coronary artery bypass graft (CABG) surgery. After pretreatment with lignocaine, preoperative sedation began using a target-controlled (TCI) infusion system to attain the desired plasma concentrations of fospropofol or propofol injectable emulsion. One study site. ≥21 to 70 years of age; cardiac ejection fraction ≥50%; first time elective cardiac surgery; 1 to 4 grafts planned.	Comparative safety and efficacy; pharmacokinetic (PK)	Using a TCI system, the target plasma concentrations of propofol following fospropofol injection were 0.7 µg/mL (sedation) and 2.5 µg/mL (to maintain anesthesia). Maximum infusion rate was 250 mg/min. (N=8)	Clorazepate 20 mg and multivitamin night before. Midazolam 3.75 to 15 mg 60 min before study drug Lignocaine 0.5 mg/kg pre-operatively and pre-induction	Propofol injectable emulsion at target plasma concentration of 1.0 µg/mL (sedation) and 3.0 µg/mL (to maintain anesthesia). Maximum infusion rate was 50 mg/min. (N=8)	Fourteen male and 2 female subjects, 56 to 70 years of age.	-TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, ECG, electroencephalogram (EEG), and bispectral (BIS) index results

Table 1-B Tabular Summary of All Clinical Studies in Patients in the Fospropofol Disodium Program

Protocol number	Study design Treatment regimen Number of sites Main inclusion criteria	Study objectives	Fospropofol treatment group(s)	Pre-treatment (all groups)	Reference group	Gender Age (range) ASA P3, P4	Safety endpoints
3000-0413 (started Sep 2005, completed Nov 2006) Location: United States	Phase 2, randomized, open-label study of fospropofol injection versus propofol injectable emulsion in patients requiring intubation and mechanical ventilation in the intensive care unit (ICU) setting. Fospropofol or propofol injectable emulsion at sedative doses administered over periods of 2 to 12 hours. Ten study sites. ≥18 to 80 years of age; ASA status of P1 – P4.	Comparative safety and efficacy	1. Fospropofol as a bolus of 100 mg plus infusion (N=18) 2. Fospropofol as an infusion only (N=20) A 25-µg/kg/min infusion rate was used for induction; the dose was increased or decreased by 25 µg/kg/min at 5-min intervals to maintain sedation.	Morphine sulfate, fentanyl citrate, or hydromorphone as needed for analgesia	Propofol injectable emulsion at 5 µg/kg/min (N=22). The infusion rate was increased by 5 to 10 µg/kg/min every 5 min until the desired level of sedation was achieved.	Forty-five male and 15 female patients, 20 to 79 years of age. Twenty-nine patients had an ASA status of P3 and 20 patients were ASA P4.	-SRAEs -TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Plasma concentrations of formate

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0001 (non-IND study; started Jan 2001, completed Jan 2001) Location: Germany	<p>Single-center, open-label, 2-part, dose-escalation, crossover study in healthy subjects.</p> <p>Part 1 was a dose-escalation, safety, and PK study. In Part 2, 9 subjects received propofol injectable emulsion followed by a 2-week wash-out period. Then, subjects were crossed over to receive fospropofol.</p> <p>One study site.</p> <p>Eighteen to 45 years of age.</p>	<p>Safety and tolerability of fospropofol; comparative PK/PD analysis of propofol between subjects treated with fospropofol and subjects with propofol injectable emulsion</p>	<p>In Part 1 (dose escalation), 3 subjects per dose group received 290 mg, 580 mg, or 1160 mg of fospropofol by IV infusion over 10 minutes.</p> <p>In Part 2 (crossover), subjects received propofol injectable emulsion by continuous IV infusion over 60 minutes. Infusions were controlled to achieve plasma propofol concentrations of 5 µg/mL by 20 minutes and 1.5 µg/mL by end of infusion.</p> <p>The mean actual dose of propofol injectable emulsion was 505.0 mg over 60 minutes.</p> <p>After a washout period of approximately 2 weeks, subjects received fospropofol infusions. Using propofol PK data from Part 1, PK modeling was performed to guide targeted infusion to achieve the same plasma propofol concentrations as described above.</p> <p>The mean actual dose of fospropofol was 2387.9 mg/60 min.</p>	<p>A total of 12 male subjects, 19 to 35 years of age, participated in the study. Nine subjects participated in Part 1. Nine subjects participated in Part 2, including 6 subjects who also participated in Part 1 and 3 new subjects</p>	<p>-TEAEs</p> <p>-Laboratory, vital signs, physical and neurological examination, pulse oximetry, and ECG results.</p>

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0102 (started Jul 2001, completed Aug 2001) Location: Germany	Open-label, nonrandomized study of fospropofol in healthy subjects. One study site. Eighteen to 55 years of age.	Safety and tolerability of fospropofol; evaluate dosing paradigm for clinical sedation; determine PK/PD of propofol derived from fospropofol.	Subjects received fospropofol by targeted IV infusion to achieve a plasma propofol concentration 1.8 µg/mL as rapidly as possible and to maintain this plasma concentration for 1 hour. The infusion rate was adjusted if necessary during the second hour of infusion to achieve a Modified OAA/S score of 2 or 3. Three subjects required no dose adjustments, 7 subjects required adjustments to a targeted plasma concentration of 2.4 µg/mL, and 2 subjects required adjustments to 3.0 µg/mL. The mean total amounts of fospropofol administered for these 3 treatment groups were 2232.7 mg (no adjustment group), 2564.9 mg (2.4-µg/mL group), and 2878.5 mg (3.0-µg/mL group).	Six male and 6 female subjects, 24 to 40 years of age.	-TEAEs -Laboratory, vital signs, physical and neurological examination, pulse oximetry, and ECG results.

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0103 (started Dec 2001, completed Apr 2002) Location: Belgium	Open-label, nonrandomized, crossover study of fospropofol in healthy subjects. All subjects were placed on supplemental oxygen for at least 3 minutes prior to study drug administration. One study site. Eighteen to 45 years of age; body mass index of 20 to 28 kg/m ² .	Safety and tolerability of fospropofol up to a dose producing maximal hypnotic effect as defined by EEG assessment; comparative PK/PD analysis of propofol between subjects treated with fospropofol and subjects treated with propofol injectable emulsion.	In the first treatment period, 3 groups of subjects (3 males and 3 females per group) received single bolus doses of fospropofol according to a dose-escalation scheme that was dependent on reaching the maximal effect criterion, a burst suppression rate >10 as shown on the BIS monitor. The 3 dosing groups received 5 mg/kg, 10 mg/kg, or 20 mg/kg of fospropofol). An additional 3 groups received 15 mg/kg, 25 mg/kg, or 30 mg/kg such that doses up to the maximum planned dose (30 mg/kg) were tested. After a 7-day washout period, subjects received propofol injectable emulsion doses in the second treatment period that were targeted to achieve the same EEG effect, as measured by minimal BIS index, as the peak EEG effect produced by fospropofol in the previous treatment period.	Eighteen female and 18 male subjects, 19 to 43 years of age	-TEAEs -Laboratory, vital signs, physical and neurological examination, pulse oximetry, end-tidal CO ₂ , ECG, EEG, and BIS index results
3000-0205 (started Jul 2002, completed Oct 2002) Location: United States	Open-label, single-dose, PK, mass balance study of fospropofol in healthy subjects. One study site. Eighteen to 45 years of age, body mass index of 20 to 28 kg/m ² .	Pharmacokinetic profile of the radioactivity of ¹⁴ C-fospropofol after a single intravenous administration; determine the routes of elimination and mass balance following an administration of ¹⁴ C-fospropofol; assess the safety and tolerability of a single-dose administration of ¹⁴ C-fospropofol.	Subjects received a single IV infusion of 400 mg of ¹⁴ C-fospropofol (100 µCi) over 10 minutes.	Eight males, 21 to 37 years of age.	-TEAEs -Laboratory, pulse oximetry, vital signs, physical and neurological examination, ECG, EEG, and BIS index results -Concomitant medications

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0206 (started May 2002 and completed Aug 2002) Location: United States	Randomized, open-label, safety, tolerability, and PK/PD study of fospropofol in healthy subjects. One study site. Eighteen to 45 years of age, body mass index of 20 to 28 kg/m ² .	Safety of a 400-mg dose of fospropofol by bolus infusion, by varying rates of infusion, and with fentanyl or meperidine premedication. Pharmacokinetic and PD profile of fospropofol and propofol at each dosing condition.	Subjects (6 per group) were randomized to 1 of the following 9 dosing groups: 400-mg bolus injection 200-mg/min infusion over 2 minutes 40-mg/min infusion over 10 minutes 30-mg/min infusion over 5 minutes, followed by a 250-mg bolus injection 50-mg bolus injection, wait 5 minutes, followed by a 350-mg bolus injection 0.10 mg of fentanyl, wait 5 minutes, followed by 400-mg bolus injection 0.10 mg of fentanyl, wait 5 minutes, followed by 200-mg/min infusion over 2 minutes 0.10 mg of fentanyl, wait 5 minutes, followed by 40-mg/min infusion over 10 minutes 75 mg meperidine, wait 5 minutes, followed by 400-mg bolus injection	54 male subjects, 18 to 43 years of age.	-TEAEs -Laboratory, pulse oximetry, vital signs, physical and neurological examination, and ECG results -Concomitant medications

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0308 (started Aug 2003 and completed Sep 2003) Location: United States	Open-label, de-escalation, safety, and tolerability study of fospropofol in healthy subjects premedicated with lidocaine HCl injection. One study site. Eighteen to 50 years of age.	Determine whether systemic pretreatment with lidocaine reduces or eliminates paresthesias associated with fospropofol administration. Determine safety of pretreatment with systemic lidocaine followed by bolus infusion of fospropofol.	The first cohort of 5 subjects received 50 mg of lidocaine IV over 1 minute. Approximately 60 seconds following lidocaine treatment, subjects received 12.5 mg/kg of fospropofol by bolus IV infusion. If paresthesias were mitigated at the 50-mg dose of lidocaine, subsequent cohorts were to receive decreasing lidocaine doses (40 mg, 30 mg, and 20 mg) before fospropofol bolus. If paresthesias were still observed in the first cohort, a second cohort of 5 subjects was to receive 50 mg of lidocaine followed by 12.5 mg/kg of fospropofol. Paresthesias were observed in the first and second cohorts of subjects. No further cohorts were enrolled in the study.	Ten subjects (8 males and 2 females), 21 to 48 years of age.	-TEAEs -Laboratory, pulse oximetry, vital signs, physical examination, and ECG results -Changes in formate levels

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0414 (started May 2005, completed Jul 2005) Location: United States	Randomized, double-blind, placebo-controlled, parallel-design, drug interaction study of fospropofol and premedications in healthy, adult subjects. All subjects were placed on supplemental oxygen via nasal cannula (2 L/min) beginning prior to premedication and continuing until the patient recovered from sedation. One study site. Eighteen to 45 years; body mass index of 18 to 30 kg/m ² .	Drug interaction: dose response, safety, tolerability, PD, and PK.	Subjects received 1 of 5 blinded pretreatments (12 subjects per group): fentanyl (1 µg/kg), meperidine (0.75 mg/kg), midazolam (0.01 mg/kg), morphine (0.1 mg/kg), or placebo (saline). Subjects received an initial bolus dose of 8 mg/kg IV and up to 4 supplemental doses (2.0 mg/kg) of fospropofol until a Modified OAA/S score of ≤3 was reached.	Twenty female and 40 male subjects, 18 to 45 years of age.	-SRAEs -TEAEs -Laboratory, pulse oximetry, vital signs, physical and neurological examination, ECG, and end-tidal CO ₂ results
3000-0521 (started Sep 2005, completed Dec 2006) Location: United States	Randomized, 4-sequence, 4-treatment crossover study of fospropofol versus placebo or positive control in healthy subjects. (N=70) All subjects were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to dosing and continuing until the patient recovered from sedation. One study site. Eighteen to 45 years of age; body mass index of 18 to 30 kg/m ² .	Maximal time-based change in corrected QT (QTc) interval; quantify the dose, concentration, and time relationships of fospropofol on QTc interval at therapeutic and supratherapeutic doses; PK of fospropofol and fospropofol-derived propofol in venous plasma.	Subjects received each of the following 4 treatments: A) Placebo (normal saline) IV B) Moxifloxacin 400 mg per oral (p.o.) C) Fospropofol 6 mg/kg IV (not less than 360 mg and not greater than 540 mg) D) Fospropofol 18 mg/kg IV (not less than 1080 mg and not greater than 1620 mg) Subjects were randomly assigned at a 1:1:1:1 ratio to receive treatments in the following sequences: ADCB, BACD, CBDA, and DCAB.	Thirty-eight male and 32 female subjects, 18 to 45 years of age.	-QTc-prolongation-related AEs -TEAEs -Laboratory, pulse oximetry, vital signs, physical and neurological examination, and ECG results

Table 2-B Tabular Summary of Clinical Safety Studies in Healthy Subjects in the Fospropofol Disodium Program

Protocol number	Study design Number of sites Main inclusion criteria	Study objectives	Treatments	Number of subjects Age (range)	Safety endpoints
3000-0625 (started Sep 2006, completed Sep 2006) Location: United States	<p>Randomized, 2-treatment, crossover pharmacokinetic/pharmacodynamic (PK/PD) study of fospropofol versus propofol injectable emulsion in healthy subjects.</p> <p>All subjects were placed on supplemental oxygen via nasal cannula (4 L/min) beginning prior to dosing and continuing until the patient recovered from sedation.</p> <p>One study site.</p> <p>Eighteen to 45 years of age; body mass index of 18 to 30 kg/m².</p>	Comparative PK/PD profile of propofol derived from fospropofol and propofol derived from propofol injectable emulsion	Subjects received fospropofol 10 mg/kg IV in the first treatment period. After a 7-day washout period, subjects received propofol injectable emulsion 50 mg/min IV in the second treatment period. Propofol injectable emulsion infusions continued until the peak EEG effect, as measured by minimal BIS index, was the same as the peak EEG effect produced by fospropofol in the previous treatment period.	Six male and 6 female subjects, 20 to 40 years of age.	<p>-SRAEs</p> <p>-Airway Assistance</p> <p>-TEAEs</p> <p>-Laboratory, pulse oximetry, vital signs, physical and neurological examination, and ECG results</p> <p>-Purposeful movement</p>

**Appendix C Patient Narratives for Deaths and Serious Adverse Events
Considered at Least Possibly Related to Study Drug**

Patient Narratives for Deaths

Study 3000-0524 (Bronchoscopy)

Patient 0524-309-0006 (fospropofol disodium 6.5 mg/kg; reduced by 25%), a 70-year-old white female, who weighed 47 kg, and had an ASA status of P2, experienced serious adverse events (SAEs) of pneumonia, chronic obstructive pulmonary disease (COPD), and lung carcinoma that were considered unrelated to study drug. Her medical history included COPD, right upper lung lobe mass, cough, left lower leg claudication, left iliofemoral bypass graft, fracture left patella, left knee arthroscopy, left knee repair tuberosity fracture and repair with fixation, right carpal fracture, closed manipulation right carpal fracture, osteoporosis, generalized arthralgia, hypertension, chest tightness, hyperlipidemia, urinary tract infection, depression, anxiety, sinusitis, fatigue, intermittent headache, recent 15-pound weight loss, postmenopausal, tonsillectomy/adenoidectomy, and tobacco abuse. Concomitant medications included benzonatate, diazepam, alendronate, losartan/hydrochlorothiazide, clopidogrel, [redacted] the patient received fentanyl 50 mcg intravenously (IV) once at 1634 hours followed by an initial dose of fospropofol disodium 6.0 mg/kg (280mg) IV at 1639. She received 1 supplemental dose of fospropofol disodium 1.5 mg/kg (70 mg) IV at 1652 during a flexible bronchoscopy. Total study drugs administered were fospropofol disodium 350.0 mg and fentanyl 50 mcg.

On [redacted] 18 days after receiving study therapy, the patient was hospitalized for post obstruction pneumonia (severe), COPD (severe), and right upper lung carcinoma (diagnosed [redacted]). She had reported progressive dyspnea over several months and cough productive of purulent phlegm. A previously performed chest x-ray and subsequent computerized tomography (CT) scan had revealed a right-sided lung mass with right-sided atelectasis. She underwent bronchoscopy on [redacted] which demonstrated cells consistent with poorly differentiated carcinoma; the right upper lobe was effaced. Her white blood cell (WBC) was 25,000. She underwent a CT of the abdomen, magnetic resonance imaging (MRI) of the brain, and a bone scan; all were negative for metastases. During a visit with her physician on 27 September 2006, it was noted that she had lost an additional 5 pounds and was using oxygen 24 hours a day. Upon presentation to the emergency department on [redacted] she had profound weakness and was in respiratory failure. Laboratory results from [redacted] included pH 7.14, CO₂ 84 mmHg, O₂ 83 mmHg, and WBC 50.2 with a left differential shift. Her right lung had a progressive infiltrate. Physical exam on admission was remarkable for decreased breath sounds and crackles throughout the right chest, a few crackles on the left chest, and a prolonged expiratory phase. The patient underwent [redacted] bation, was started on cefepime, levofloxacin, and levalbuterol. On [redacted] the patient died. The death certificate listed pneumonia and lung cancer as causes of death. No action was taken regarding study therapy. The Investigator

considered the severe COPD, which was ongoing until the patient's death and the post obstruction pneumonia and right upper lung carcinoma, which were fatal, related to underlying disease, and unrelated to study therapy.

Patient 0524-312-0003 (fospropofol disodium 6.5-mg/kg; reduced by 25%), a 77-year-old white male, who weighed 67 kg, and had an ASA status of PS3, experienced an SAE of lung carcinoma that was considered unrelated to study drug. His medical history included COPD, lung mass, pneumonia, thrombocytopenia, pulmonary embolism, placement of Greenfield filter, gastroesophageal reflux disease (GERD), benign prostatic hypertrophy, cholecystectomy, trace bilateral edema, laminectomy, anxiety, constipation, hyperglycemia, anemia, sinus tachycardia, back pain, allergy to intravenous pyelogram (IVP) dye, and 65 pack-year smoker. Concomitant medications included oxycodone/acetaminophen, pantoprazole, sucralfate, levalbuterol, tiotropium, albuterol, fluticasone propionate/salmeterol, oxygen, docusate sodium, ceftriaxone, azithromycin, methylprednisolone, clonazepam, folic acid, and terazosin. On [REDACTED] the patient received fentanyl 50 mcg IV once at 1054 hours followed by an initial dose of fospropofol disodium 5.0 mg/kg (332.5 mg) IV at 1059. He received 1 supplemental dose of fospropofol disodium 1.3 mg/kg (87.5 mg) IV at 1103 during a flexible bronchoscopy. Total study drugs administered were fospropofol disodium 420.0 mg and fentanyl 50 mcg.

On [REDACTED] after receiving study therapy, the patient was diagnosed with lung cancer (severe). He had been hospitalized 2 days prior to the diagnosis due to worsening shortness of breath. He reported coughing and wheezing with chest tightness initially, as well as worsened lower extremity edema over the previous couple of days. Physical examination upon admission was remarkable for trace edema at his ankles, bilateral inspiratory and expiratory wheezes throughout his lungs, and decreased breath sounds. Laboratory values included hemoglobin 11.1 g/dL (which had decreased from 13.8 g/dL) and platelets 28,000 (which had decreased from 40,000 the previous day). He received a platelet transfusion on the day of the bronchoscopy. A portable chest x-ray done on [REDACTED] showed worsening of a right hilar mass which was worrisome for neoplasm with post obstructive pneumonia. A post bronchoscopy chest x-ray on [REDACTED] demonstrated stable thoracic appearance since the previous x-ray and revealed no evidence of acute complications. A right upper lobe brushing cytology smear from [REDACTED] contained atypical cells suspicious for malignancy and a transbronchial biopsy of the right upper lobe showed poorly preserved carcinoma with features suggestive of neuroendocrine carcinoma. A fine needle aspiration of the right lung was performed on [REDACTED] which found cytomorphology most consistent with neuroendocrine carcinoma; immunohistochemistry results were pending. The patient remained short of breath despite treatment with steroids, inhalers, and piperacillin/tazobactam. On [REDACTED] the patient's status worsened; another portable chest x-ray was obtained [REDACTED] with previous x-rays. The diffuse area of parenchymal consolidation in the right mid lung remained unchanged. There were new mixed interstitial and alveolar opacities in the lung bases (left greater than right), the central vasculature appeared slightly more prominent, and there was possible development of right pleural fluid. The findings were suggestive of early edema

superimposed on severe chronic lung disease. The possibility of a new inflammatory infiltrate in the left base could not be completely excluded. The patient requested 'do not resuscitate' status and the [REDACTED] to proceed with comfort care and hospice. He subsequently died on [REDACTED] due to lung cancer. No action was taken regarding study therapy. The Investigator considered the event related to underlying disease and unrelated to study therapy.

Patient 0524-533-0008 (fospropofol disodium 2.0 mg/kg; reduced by 25%), a 67-year-old black male, who weighed 61 kg, and had an ASA status of P2, experienced an SAE of septic shock that was considered unrelated to study drug. His medical history included metastatic lung cancer, malignant right middle lobe lung mass, smoker's cough, hypertension, prostate cancer, left renal lesions, left adrenal gland lesion, generalized aches and pains, and inguinal hernias with repairs. Concomitant medication included paracetamol and irbesartan/hydrochlorothiazide. On [REDACTED] the patient received fentanyl 50 mcg IV at 1139 hours followed by an initial dose of fospropofol disodium 1.4 mg/kg (87.5 mg) IV at 1144. He received 3 supplemental doses of fospropofol disodium 0.3 mg/kg (17.5 mg each) IV at 1148, 1152, and 1156 during a flexible bronchoscopy. The patient was declared a sedation failure and received midazolam 2 mg IV at 1157. He received 2 additional doses of fentanyl (50 mcg each) at 1157 and 1204. Total study drugs administered were fospropofol disodium 140.0 mg, fentanyl 150 mcg, and midazolam 2 mg.

On [REDACTED], 17 days after receiving study therapy, the patient was hospitalized due to septic shock (severe). The patient had been treated with chemotherapy for metastatic lung cancer, which caused him to develop neutropenia followed by septic shock. Antibiotic, antifungal, and corticosteroid treatment included cefepime, vancomycin, meropenem, fluconazole, caspofungin, methylprednisolone, and hydrocortisone. On [REDACTED] the patient died due to septic shock. No autopsy was performed. No action was taken regarding study therapy. The Investigator considered the event unrelated to study therapy.

Patient 0524-544-0003 (fospropofol disodium 2.0 mg/kg; reduced by 25%), a 61-year-old white male, who weighed 74 kg, and had an ASA status of P4, experienced SAEs of pneumonia and respiratory arrest that were considered unrelated to study drug. His medical history included non-small cell lung cancer, COPD, depression, cough, insomnia, hypokalemia, acute bronchitis (bacterial infection), anemia, chronic hyponatremia, malnutrition with mild hypoalbuminemia, metastases to liver, diet-controlled diabetes mellitus type 2, endobronchial stent, cancer-related pain of the chest, liver enzyme elevation, and sulfa allergy. Concomitant medications included albuterol, ipratropium, temazepam, paroxetine, and amoxicillin. On [REDACTED] the patient received fentanyl 50 mcg IV once at 1205 hours followed by an initial dose of fospropofol disodium 1.4 mg/kg (105 mg) IV at 1210. He received 5 supplemental doses of fospropofol disodium 0.5 mg/kg (35 mg each) at 1214, 1220, 1224, 1228, and 1232 during a flexible bronchoscopy. Total study drugs administered were fospropofol disodium 280.0 mg and fentanyl 50 mcg.

On [REDACTED] 9 days after receiving study therapy, the patient was hospitalized for acute pneumonia (severe) and on [REDACTED] he experienced fatal respiratory arrest (severe). He presented with shortness of breath, nonproductive cough, and a history of poor oral intake and confusion. His vital signs included heart rate 105 bpm, blood pressure (BP) 118/40 mmHg, and oxygen saturation 96% on face mask. On examination, the patient was noted to have rhonchi and coarse breath sounds bilaterally. Laboratory results included WBC 26.1, hemoglobin 11.8 g/dL, platelets 516,000, bicarbonate 26 mEq/L, blood urea nitrogen (BUN) 9 mg/dL, creatinine 1.2 mg/dL, brain natriuretic peptide (BNP) 375, D-dimer 1.09, creatine phosphokinase (CK) 56, CK-MB 3.3, and troponin 0.7. A urinalysis showed protein 100. He was placed on palliative care. The patient's family was informed of the increased troponin and stated that no further work-up was desired. The patient died on [REDACTED] due to respiratory arrest caused by hypoxemic respiratory failure from terminal lung cancer. Acute pneumonia was ongoing at the time of death. No action was taken regarding study therapy. The Investigator considered the event related to underlying disease and unrelated to study therapy.

Patient 0524-544-0009 (fospropofol disodium 6.5 mg/kg), a 46-year-old black male, who weighed 45 kg, and had an ASA status of P2, experienced SAEs of respiratory failure, cardiac arrest, sepsis, cerebral edema, and brain herniation that were considered unrelated to study drug. His medical history included weight loss, migraine headaches, and seasonal allergies. Concomitant medications included amphotericin B, flucytosine, nystatin, hydrocodone/acetaminophen, metoclopramide, acetaminophen, diphenhydramine, potassium chloride, and sulfamethoxazole/trimethoprim. The patient was hospitalized on [REDACTED] and was diagnosed with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), cryptococcal meningitis, lung nodules suspicious for tuberculosis, thrush, nausea, and hypokalemia. On [REDACTED] [REDACTED], the patient received fentanyl 50 mcg IV once at 1119 hours and an initial dose of fospropofol disodium 8.6 mg/kg (385 mg) IV at 1124 for sedation during a flexible bronchoscopy. Total study drugs administered were fospropofol disodium 385.0 mg and fentanyl 50 mcg.

On [REDACTED] 3 days after receiving study therapy, the patient experienced life-threatening respiratory failure (severe), cardiac arrest (severe), sepsis (severe), cerebral edema (severe), and brain herniation (severe). At 1715, the patient was found to be unresponsive and had irregular respirations. He was subsequently intubated for respiratory failure. At approximately 1800, the patient experienced cardiac arrest and required cardiopulmonary resuscitation (chest compressions and epinephrine). Cardiac arrest resolved with sequelae on [REDACTED]. The patient remained on ventilator support and required norepinephrine at 60 mcg/kg/min to maintain BP. Laboratory values included pH 7.28, PaCO₂ 28 mmHg, PaO₂ 200 mmHg, sodium 165 mmol/L, chloride 154 mmol/L, potassium 3.1 mmol/L, bicarbonate 16 mEq/L, BUN 7 mg/dL, creatinine 0.7 mg/dL, and magnesium 3.7 mEq/L. An electrocardiogram (ECG) showed normal sinus rhythm with T-wave inversion. A CT scan of the brain showed cerebral edema with impending herniation. On [REDACTED] 4 days after receiving study therapy, the patient died due to anoxic brain injury (severe). Respiratory failure, sepsis,

cerebral edema, and brain herniation were considered ongoing at the time of death. No action was taken regarding study therapy. The Investigator considered the events to be related to underlying disease and unrelated to study therapy.

Study 3000-0413 (Prolonged Exposure in Mechanically Intubated and Ventilated Patients in the ICU Setting)

Patient 0413-431-0002 (fospropofol disodium infusion only), a 76-year-old white male, who weighed 82 kg, and had an ASA status of P4, experienced an SAE of acute respiratory failure that was considered unrelated to study drug. His medical history included COPD, pneumonia, hypertension, coronary artery disease, paroxysmal atrial fibrillation, atrial flutter, pulmonary hypertension, mitral regurgitation, cerebrovascular accident, hyperlipidemia, benign prostatic hypertrophy, GERD, depression, diverticulitis, and seasonal allergy. Concomitant included ceftriaxone, azithromycin, prednisolone, enoxaparin, digoxin, amiodarone, metoprolol, furosemide, lansoprazole, nystatin, insulin, and morphine. The patient received fospropofol disodium 25 mcg/kg/min IV infusion from 1600 hours on [redacted] to 0400 on [redacted] for sedation in the intensive care unit (ICU). He required intubation and ICU care for shortness of breath related to pneumonia and underlying advanced COPD. Total study drug administered was fospropofol disodium 1472 mg.

On [redacted] 16 days after receiving study drug, the patient was hospitalized due to acute respiratory failure (severe). Upon admission, he was nonverbal with a respiratory rate of 26 breaths/minute. Examination of his lungs revealed bilateral coarse breath sounds, occasional scattered rhonchi, and labored respiration with accessory muscle use. On [redacted], arterial blood gases on 50% face mask included PaO₂ 69 mmHg, PaCO₂ 59 mmHg, and pH 7.34. A chest x-ray from [redacted] showed no definite infiltrate, but recurring aspiration was suspected. The patient received frequent suctioning for comfort care, nebulizer treatments, oxygen therapy, morphine sulfate, haloperidol, and lorazepam. On [redacted] 17 days after receiving study drug, the patient experienced rapid deterioration and died due to acute respiratory failure. No action was taken regarding study drug. The Investigator considered the event, which was fatal, related to underlying disease and unrelated to study drug.

Patient 0413-431-0042 (fospropofol disodium infusion only), a 72-year-old white male, who weighed 53 kg, and had an ASA status of P4, experienced an SAE of septic shock that was considered unrelated to study drug. His medical history included multiple myeloma, myocardial infarction, coronary artery disease, hypertension, renal failure, aspiration pneumonia, stable aneurysm, hyperlipidemia, anemia, coagulopathy, epistaxis, diffuse lytic bone lesion, glaucoma, cataract surgery, appendectomy, and orchiectomy. Concomitant medications included magnesium oxide, albuterol/ipratropium, and sodium chloride IV as needed to keep the vein open. He received fospropofol disodium 25 mcg/kg/min IV from 1450 hours on [redacted] to 0250 on [redacted] for sedation in the ICU. He required intubation and ICU care for

respiratory failure secondary to aspiration pneumonia. Total study drug administered was fospropofol disodium 951 mg.

On [REDACTED] 1 day following the administration of study drug, the patient developed septic shock (severe) and died. The patient had been hospitalized on [REDACTED] with complaints of epistaxis secondary to a high international (INR). He had initially received fresh frozen plasma to correct his INR. On [REDACTED] the patient developed desaturation, shortness of breath, and unstable vital signs. He was placed on oxygen per nasal cannula, aspiration precautions, and antibiotics for possible aspiration pneumonia. A chest x-ray revealed new left upper lobe lingular infiltrate. The patient's condition deteriorated significantly and the patient was placed in the ICU. That same day/night in ICU, the patient had a grand mal episode with hypotension and desaturation, and underwent emergency intubation. A bronchoscopy was performed to obtain specimens for possible opportunistic infections. An echocardiogram showed a thoracic aortic aneurysm with a clot and no active bleeding. Treatment included antiepileptic medications, broad-spectrum antibiotics, vasopressors, and mechanical ventilation. Cultures and pathology report did not show any opportunistic infections. After a week of supportive care, [REDACTED] lation, and BP support, his condition continued to deteriorate. On [REDACTED] the patient was placed on a comfort care protocol and subsequently died at 1520 that same day. The cause of death was septic shock secondary to respiratory failure and aspiration pneumonia. No action was taken regarding study drug. The Investigator considered the event related to septic shock and unrelated to study drug.

Patient 0413-531-0016 (fospropofol disodium infusion only), a 77-year-old white male, who weighed 91 kg, and had an ASA status of P3, experienced an SAE of respiratory failure that was considered unrelated to study drug. His medical history included COPD, *Staphylococcus aureus* bacteremia ([REDACTED]), *Staphylococcus aureus* pneumonia ([REDACTED]), coronary artery disease, hypertension, high cholesterol, hyperlipidemia, obesity, emphysema, non-insulin dependent diabetes mellitus, urethral stenosis, Alzheimer's disease, dementia, depression, L4 and L5 lower disc bulge, back pain, and allergy to iodine. Concomitant medications included acetylsalicylic acid, famotidine, human insulin, nafcillin, sertraline, and midazolam. On [REDACTED], the patient received fospropofol disodium IV infusion (25 mcg/kg/min from 1525 hours to 1537, 50 mcg/kg/min from 1538 to 1550, 75 mcg/kg/min from 1551 to 1557, 100 mcg/kg/min from 1558 to 1630, and 75 mcg/kg/min from 1631 to 2243) for sedation in the ICU after being hospitalized for atrial fibrillation. Total study drug administered was fospropofol disodium 2953 mg.

On [REDACTED] 9 days after receiving study drug, the patient experienced fatal respiratory failure (se [REDACTED] had been hospitalized since [REDACTED] Blood cultures on [REDACTED] and [REDACTED] revealed *Staphylococcus aureus*. On [REDACTED], the patient's condition worsened and he was transferred to the critical care unit where he was intubated and placed on a ventilator. A sputum culture obtained on [REDACTED] showed rare *Staphylococcus aureus*, rare yeast (isolated as *Candida albicans*), and rare normal respiratory flora. On [REDACTED] the patient went into respiratory distress with

an SpO₂ of 85% to 90% on 3 liters of oxygen. At 1055 on [REDACTED] the patient died due to acute respiratory failure secondary to *Staphylococcus aureus* pneumonia and bacteremia. No action was taken regarding study drug. The Investigator considered the events related to underlying disease and unrelated to study drug.

Patient 0413-531-0080 (fospropofol disodium bolus/infusion), a 71-year-old black male, who weighed 107 kg, and had an ASA status of P4, experienced an SAE of cardio-respiratory arrest that was considered unrelated to study drug. His medical history included intercerebral hemorrhage ([REDACTED]), ventilator dependent respiratory failure ([REDACTED]), hypertension, peripheral vascular disease, abnormal ECG-sinus rhythm with premature atrial complexes ([REDACTED]), syncope, insulin-dependent diabetes, asthma, pneumonia, anemia, thrombocytopenia, hematuria, proteinuria, high cholesterol, increased liver function tests, glaucoma, and right eye surgery. Concomitant medications included morphine, metoprolol, paracetamol, and sodium chloride. The patient received fospropofol disodium (25 to 100 mcg/kg/min IV infusions starting at 1619 hours on [REDACTED] until 0251 on [REDACTED] for sedation in the ICU after being hospitalized for a cerebrovascular accident. Total study drug administered was fospropofol disodium 5008 mg.

The patient was hospitalized on [REDACTED]. A CT scan of the head on [REDACTED] [REDACTED] showed an acute intraparenchymal hemorrhage at the level of the left basal ganglia/internal capsule (approximately 4.1 cm by 1.6 cm). The CT scan also revealed a small amount of intraventricular hemorrhage within the occipital horns, signs of chronic small vessel white matter changes, mild cerebral atrophy, and some evidence of a small deformed hyperdense left globe consistent with phthisis bulbi. The patient was placed on comfort care measures. On [REDACTED] 3 days after receiving study drug, the patient experienced fatal cardiopulmonary arrest (severe). He was extubated at 1821 hours and subsequently died at 1824. No action was taken regarding study drug. The Investigator considered the events related to underlying disease and unrelated to study drug.

Patient 0413-499-0004 (propofol injectable emulsion), a 76-year-old white male, who weighed 82 kg, and had an ASA status of P2, experienced SAEs of gastrointestinal hemorrhage and respiratory distress that were considered unrelated to study drug. His medical history included merkel cell carcinoma, hypertension, benign prostate hypertrophy, rectal bleeding, right parotidectomy, radiation following parotidectomy, left parotid surgery, surgery for bladder detachment, right knee surgery, septal infarct, left axis deviation, and Q axis/left axis deviation. There were no concomitant medications reported. The patient received propofol 2.5 to 5.0 mcg/kg/min IV infusions from [REDACTED] at 1730 hours to [REDACTED] at 0130 for sedation in the ICU after radial neck dissection. Total study drug administered was propofol injectable emulsion 115 mg.

On [REDACTED], 26 days after receiving study drug, the patient was hospitalized due to a gastrointestinal bleed (severe). He presented with weakness, rectal bleeding (continuing since the previous year), hypertension, anemia, and a hematocrit (HCT) of 22. He was hemodynamically stable upon admission. Laboratory results from [REDACTED] revealed

hemoglobin 7.2 g/dL, HCT 22.4%, red blood cell (RBC) $2.36 \times 10^6/\mu\text{L}$, platelets $82 \times 10^3/\mu\text{L}$, protime (PT) 14.2 sec, INR 1.2, and activated partial thromboplastin time (aPTT) 23.8 sec. The patient underwent an upper endoscopy that revealed 2 small duodenal erosions and gastropathy. Abdominal imaging studies showed advanced alcoholic cirrhosis. A fecal occult blood test from [REDACTED] was positive. The patient was provided with supportive care and blood transfusions including packed red blood cells, platelets, and fresh frozen plasma. On [REDACTED] 30 days after receiving study drug, the patient developed respiratory distress and was intubated. Despite aggressive efforts, the patient died on [REDACTED], due to complications of advanced alcoholic cirrhosis. No action was taken regarding study drug. The Investigator considered the events related to underlying disease and unrelated to study drug.

Serious Adverse Events Considered at Least Possibly Related to Study Drug

Study 3000-0207 (Colonoscopy)

Patient 0207-265-0004 (fospropofol disodium bolus), a 57-year-old white female, who weighed 77 kg, and had an ASA status of P2, experienced an SAE of apnea that was considered related to study drug. Her medical history included hernia surgery, bladder repair, hysterectomy with bilateral salpingo-oophorectomy, cesarean section, and allergies to codeine and penicillin. No concomitant medications were reported. The patient received celebrex 400 mg orally once followed by fospropofol disodium 10 mg/kg (759 mg) IV. The patient received 1 supplemental dose of fospropofol disodium 5 mg/kg (379.5 mg) IV along with 1 dose of fentanyl 100 mcg IV for burning sensation during a colonoscopy. Total study drugs administered were fospropofol disodium 1138.5 mg; fentanyl 100 mcg; celebrex 400 mg.

During the procedure, the patient experienced apnea that was documented to have lasted about 3 minutes, from 1357 hours to 1400. The Bispectral Index Score at onset of the event was recorded as 66, and ETCO₂ was recorded as 19 mm Hg at 1357. Respiratory rate had dropped to 8 breaths per minute at 1357, but then increased to 12 breathes per minute by 1359. Positive pressure via manual ventilation was provided to maintain the airway. No further intervention was required. No sequelae were noted upon resolution of the event. During the apneic episode, the blood pressure and heart rate were within normal limits. Patient was discharged later that day. The event was assessed as serious and probably related to study drug by the Sponsor.

Study 3000-0409 (Bronchoscopy)

Patient 0409-316-0001 (fospropofol disodium; original dose), a 62-year-old white male, who weighed 66 kg, and had an ASA status of P2 experienced SAEs of apnea and hypotension that were considered probably related to study drug. His medical history included Waldenstrom's macroglobulinemia, round cell lymphatic lymphoma, pulmonary infiltrates, and cough. Concomitant medications included gamma globulin, aspirin, levofloxacin, guaifenesin/codeine, atropine, and fentanyl. The patient received fentanyl 66 mcg IV once and fospropofol disodium 12.2 mg/kg (805 mg) IV on [REDACTED] during a bronchoscopy. Total study drugs administered were fospropofol disodium 805 mg; fentanyl 66 mcg.

On [REDACTED] during the bronchoscopy and within minutes of receiving fospropofol disodium and fentanyl, the patient experienced apnea and hypotension. The patient received an increased rate of O₂ and manual ventilation with a bag-valve mask. His feet were elevated and 1900 mL of IV fluids were administered. The patient returned to spontaneous breathing and became fully 29 minutes after the initial bolus of fospropofol disodium. The event was

considered resolved, and the patient was discharged. The Investigator considered both events to be probably related to study drug.

Study 3000-0411 (Minor Surgical Cardiac Procedures)

Patient 0411-412-0001 (fospropofol disodium bolus), a 55-year-old black female, who weighed 63 kg, and had an ASA status of P3, experienced an SAE of apnea that was considered definitely related to study drug. Her medical history included cerebral vascular accident, emphysema, hypertension, hypercholesterolemia, coronary artery bypass graft, coronary stent, percutaneous transluminal coronary angioplasty x2, diabetes, peripheral stent, arthritis, carpal tunnel repair, tubal ligation, and seasonal allergies. Concomitant medications included metolazone, insulin, gabapentin, digoxin, diltiazem, atorvastatin, cetirizine, hydrochloride, ramipril, carvedilol, aspirin, ibuprofen, clopidogrel bisulfate, nitroglycerine, furosemide, and stool softener. On [REDACTED] the patient received 32 mcg of fentanyl IV once at 1121 hours followed by fospropofol disodium 9.4 mg/kg (595 mg) IV at 1126 during a percutaneous coronary artery intervention. Total study drugs administered were fospropofol disodium 595 mg; fentanyl 32 mcg.

On [REDACTED] during the procedure, the patient experienced apnea (severe). The patient was unresponsive to painful stimuli and required manual assisted ventilation with 100% oxygen for 29 minutes from 1132 hours to 1201. She was administered dopamine 2.5 mcg starting at 1140, and increased to 5 mcg at 1145. Baseline vitals included blood pressure 133/79 mm Hg, heart rate 68, respirations 16, and SpO₂ 99%. At 1131, the patient's vitals dropped to 88/48 mm Hg, heart rate 61, respirations 8, and SpO₂ 81%; at which time manual ventilation was started. Her Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale at 1132 dropped to 0 and remained 0 until 1202. During this time, she was also unable to demonstrate purposeful response. The patient's vitals slowly began to increase and by 1201 her vitals included blood pressure 116/64 mm Hg, heart rate 64, respirations 16, and SpO₂ 100%. By 1204, she was able to demonstrate purposeful response and her MOAA/S increased to 2. It gradually increased and was 5 by 1216. The patient was fully alert by 1240 and was discharged at 1436. The Investigator considered the event to be definitely related to study drug.

Study 3000-0413 (Prolonged Exposure in Mechanically Intubated and Ventilated Patients in the ICU Setting)

Patient 0413-497-0020 (fospropofol disodium bolus/infusion), a 69-year-old white female, who weighed 96 kg, and had an ASA status of P2, experienced an SAE of nonsustained ventricular tachycardia that was considered possibly related to study drug. Her medical history included 2 prior Achilles wound repairs, hypertension, hypothyroidism, thyroidectomy, s/p nephrectomy for renal cell cancer, urinary incontinence, hysterectomy, osteoarthritis, and allergy to

azithromycin. Concomitant medications included levothyroxine. Medications administered during anesthesia/surgery included midazolam, fentanyl, propofol, vecuronium, lidocaine, cefazolin, hydromorphone, hydralazine, labetalol, heparin, isoflurane, nitrous oxide, hetastarch, lactated ringers, dextrose, oxygen, and multivitamin. The patient received fospropofol disodium IV infusion 25 mcg/kg/min titrated up to 200 mcg/kg/min in combination with seven 100 mg IV boluses from [REDACTED] at 2040 hours to [REDACTED] at 0535 for sedation in the ICU where she remained for 24 hours following an uncomplicated left forearm fasciocutaneous free tissue transfer to the right Achilles region. Total study drug administered was fospropofol disodium 6369 mg.

On [REDACTED] at 2130, 50 minutes after the start of study drug infusion (estimated dose administered [REDACTED] g), the patient experienced ventricular tachycardia (mild). The Investigator witnessed a short (5 to 10 seconds), self-limited, and hemodynamically stable run of ventricular tachycardia on the ECG monitor, with an estimated ventricular rate of 160 beats/min (an ECG strip was not printed and could not be retrieved retrospectively). The Investigator confirmed that the event was not Torsade de Pointes. Magnesium and potassium were administered via IV infusion, because magnesium and potassium levels had been in the lower normal range prior to the event. Laboratory results at 2037 were within normal ranges. The event resolved on [REDACTED] at 2130. The study drug was continued with increasing doses for another 8 hours and 5 minutes without further episodes of ventricular tachycardia or other type of cardiac arrhythmia noted. Both a previous 12-lead ECG from [REDACTED] and a second ECG from [REDACTED] were unremarkable. The patient was discharged home in stable condition on [REDACTED]. The Investigator considered the event possibly related to study drug, as he could not exclude that study drug could have caused the event.

Study 3000-0414 (Healthy Volunteer; Drug Interaction Study)

Patient 0414-493-1050 (fospropofol disodium 8.0 mg/kg), a 20-year-old Hispanic female, who weighed 76 kg, experienced an SAE of psychogenic paralysis that was considered possibly related to study drug. She had no prior medical history, and she had no concomitant medications. On [REDACTED] the patient received an initial dose of fospropofol disodium 8.0 mg/kg (608 mg) IV and 1 supplemental dose of fospropofol disodium 2.0 mg/kg (152 mg) IV for sedation. The patient's sedation was unremarkable with good oxygen saturations, blood pressure, heart rate, and respiratory rate. Total study drug administered was fospropofol disodium 760 mg.

On [REDACTED] approximately 45 minutes after the administration of fospropofol disodium and the patient awoke, she was unable to speak or move with the exception of her eyes and mouth; however, she was able to answer questions nodding her head. Sensory and spine reflexes were reported to be intact. A neurological exam was performed and findings were inconsistent with a

true paralysis/weakness. The patient was diagnosed with paralysis and muscular weakness of psychogenic origin. The patient was transferred to the emergency room for observation and subsequently admitted to the hospital for further neurological evaluation.

The neurologist's exam found that after approximately 45 minutes of receiving fospropofol disodium, the patient awoke but was unable to move her arms and legs. She remained able to breathe continuously without hypoxemia. There was no difficulty with her eye movements and she was able to respond by shaking her head yes or no. No seizure activity was noted. The patient denied any numbness and had not had any similar symptoms in the past. She denied any headaches. The patient was conscious, alert and awake. She was able to answer questions by shaking her head yes or no. Peripheral visual fields were normal. Eye fundi showed clear disc margins without any pallor, exudates or signs of hemorrhage. Eye movements were full. No nystagmus was observed. Facial sensations were normal. No facial weakness was noted, and the facial folds were symmetrical and react normally. Hearing was symmetrical with normal speech discrimination. Uvula and tongue were midline and their movement was normal. No atrophy or fasciculations were observed. The patient stated that she was unable to move her arms and legs, but yet she prevented her arm from striking her face when it was released from above. She was also able to hold her arm up against gravity when not realizing it. She was also able to display adequate strength of her triceps, biceps and quadriceps muscles when she had not realized they were being tested. Despite this obvious ability to move her extremities, when voluntarily asked, she was unable to move her limbs. Deep tendon reflexes were 2+ symmetrical and equal. There was no Babinski reflex. Fine touch, pin prick, vibration and position senses were normal. The patient's generalized weakness appeared to be of psychogenic origin. No additional neurological testing was recommended. A psychiatric consultation was thought to be of benefit.

The patient was admitted to the hospital at 1800 on [REDACTED] and by 1900 claimed full recovery of her paralytic symptoms. She complained of headache, weakness, and dizziness until [REDACTED], at which time all symptoms resolved and the patient was discharged home. On [REDACTED], the patient had an end-of-study physical. Her physical and neurological exams were normal; lab work and ECG results did not reveal any clinically significant results.

Initially, the Investigator assessed the event as unrelated to study drug. After further review of the case, the Investigator felt that he could not completely rule out a causal relationship of psychogenic paralysis to fospropofol disodium, so changed the relationship to possibly related to study drug.

Study 3000-0524 (Bronchoscopy)

Patient 0524-430-0006 (fospropofol disodium 6.5 mg/kg; reduced by 25%), was a 78-year-old white male, who weighed 92 kg, and had an ASA status of P3, who experienced and SAE of

hypoxemia that was considered probably related to study drug. His medical history included severe hypoxemia with ambulatory oxygen, COPD, recurrent pneumonia, GERD, arteriosclerosis, coronary artery disease, hypertension, diabetes mellitus, chronic lymphocytic leukemia, congestive heart failure, edema, anemia, recurrent chest pain, and hypothyroidism. Concomitant medications included oxygen 4 L/min (for prior 2 years), tiotropium, salbutamol, insulin, digoxin, furosemide, lisinopril, amlodipine, atenolol, clopidogrel, simvastatin, acetylsalicylic acid, levothyroxine, doxazosin, omeprazole, naproxen sodium, vitamin B complex, and multivitamin. His physical examination was significant for decreased breath sounds in the right base. His ECG showed a left bundle branch block. He was scheduled for fiberoptic bronchoscopy. However, the procedure was canceled as the patient was felt to be too unstable at that time. Three weeks later, he was again scheduled for a fiberoptic bronchoscopy and he was randomized to the fospropofol disodium 6.5 mg/kg group to receive a 25% reduced dose. His admission vital signs included BP of 151/70 mm Hg, heart rate 65 bpm, respirations 13, and SpO₂ 92% in the sitting position with further desaturation noted in the recumbent position. Medications associated with the bronchoscopy procedure included atropine intramuscularly to prevent hypersecretions, cetacaine topically for cough suppression, lidocaine topically per protocol, acetylcysteine 4 mL topically for copious secretion, and oxygen 4 to 15 L/min nasally. On [REDACTED], the patient received fentanyl 50 mcg IV once at 0700 and fospropofol disodium 4.8 mg/kg (437.5 mg) IV once at 0705 during a bronchoscopy. Total study drugs administered were fospropofol disodium 437.5 mg and fentanyl 50 mcg.

Approximately 5 minutes after receiving fospropofol disodium (07:10:13 hours), the patient experienced hypoxemia (severe) requiring intervention. At both 1 minute before receiving fentanyl (0659 hours) and immediately before receiving fospropofol disodium (0705), the patient's SpO₂ was 90% and his respirations 16. He received fospropofol disodium at 0705 and the bronchoscope was inserted at 0707. At 0709 (4 minutes after the fospropofol disodium dose), his MOAA/S had decreased to 3, he had purposeful movement, his BP was 137/56 mm Hg, heart rate 69 bpm, respirations 28, and SpO₂ had decreased to 83%. Oxygen flow was increased. His SpO₂ dropped to 79% and manual ventilation (bag-valve mask) was administered from 0710:13 to 0711:52. He required manual ventilation again from 0713:10 (SpO₂ 86%) to 0715:42 (SpO₂ 91%) and from 0717:04 (SpO₂ 90%) to 0719:05 (SpO₂ 89%). At the time of the second manual ventilation, his MOAA/S was 0-1 and he did not have purposeful movement. At the time of the third manual ventilation, his MOAA/S was 3-4 and he was able to demonstrate purposeful movement. The bronchoscope was withdrawn at 0720. The lowest recorded SpO₂ was 72% at 0737. Beginning about 5 minutes following the fospropofol disodium administration and for an additional 9 minutes, the patient required 3 separate occasions of manual ventilation, the longest lasting about 2 minutes and 30 seconds. Treatment included oxygen via nasal cannula (4 to 15 L/min), albuterol, levalbuterol, and EzPAP (positive airway pressure) with levalbuterol. The bronchoscopy procedure lasted 13 minutes. The patient was awake and alert within 1 minute of the conclusion of the procedure. Post procedure, he was treated with oxygen and salbutamol. His systolic BP was generally 150 to 160 mm Hg, with 1 episode of systolic BP

at 91 mm Hg occurring about 5 minutes post procedure that did not require treatment. His diastolic BP ranged from 56 to 77 mm Hg, his heart rate ranged from about 62 to 84 bpm, and his SpO₂ was 72% to 94% with a respiratory rate of 18 to 24. He was discharged on oxygen 5 L/min with an SpO₂ of 92% and a respiratory rate of 22. The patient did not experience apnea during the study. The event resolved with sequelae at 09:10:00 (SpO₂ 94%) on . The Investigator considered the event probably related to study drug.