AQUAVAN®
(Fospropofol Disodium)
Injection

Anesthetic and Life Support Drugs Advisory Committee

Gaithersburg, Maryland

May 7, 2008

Introduction

Jacqueline M. Kline, Ph.D.
Director Regulatory Affairs

MGI PHARMA, INC.
(a wholly owned subsidiary of Eisai)

Agenda

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Medical Need	**Lawrence B. Cohen, MD** Associate Clinical Professor Mount Sinai Hospital, New York, NY
Clinical Pharmacology	**Stephen J. Waters, PhD** VP Science & Technology, MGI PHARMA, INC.
Clinical Efficacy	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.
Clinical Safety	**Michael T. Cullen, MD** Chief Medical Officer, MGI PHARMA, INC.
Risk/Benefit Summary	**John B. Leslie, MD** Consulting Professor of Anesthesiology Mayo Clinic, Scottsdale, AZ
Conclusion	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.

AQUAVAN® (fospropofol disodium) Injection Proposed Indication

AQUAVAN is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures.

Dosage and Administration

- Standard dosing regimen
  - 6.5 mg/kg initial IV bolus dose
  - 1.6 mg/kg supplements as needed
- Supplemental doses administered only
  - When patients can demonstrate purposeful movement
  - No more frequently than every 4 min
- Modified dosing regimen
  - 75% of the standard dosing regimen
  - Patients ≥ 65 yr and/or ASA P3 or P4
- Weight bounds
  - Adults > 90 kg dosed equivalent to a 90 kg dose
  - Adults < 60 kg dosed equivalent to a 60 kg dose

Dosage and Administration
Adults 18 to < 65 yr of Age, ASA P1 or P2

	Initial Dose		Supplemental Dose No more frequently than every 4 min	
Weight (kg)	**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	[illegible]
66 to [illegible]	437.5	[illegible]	[illegible]05.0	[illegible]

Patient Evaluation and Monitoring

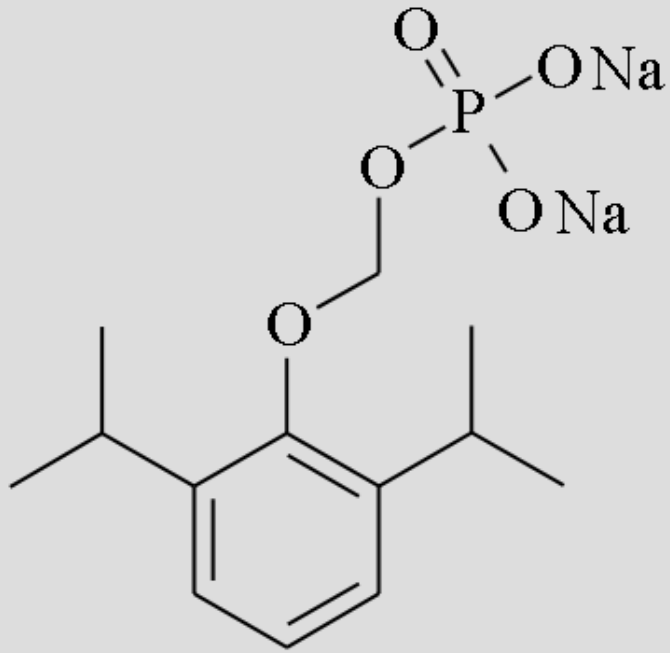
- Pre-procedure Patient Evaluation
  - History
  - Physical exam including vital signs and evaluation of the airway
- Monitoring performed by a designated individual, other than the practitioner performing the procedure
  - Pulse oximetry
  - Adequacy of spontaneous respirations
  - Blood pressure
  - Electrocardiograph
  - Purposeful response
  - Assess for early detection of sedation related events

Education and Training

- Clear directions for use in the package insert
- Support use aligned with ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists
- Medical education initiatives
  - Support sedation education and training programs sponsored by established societies
  - Provide comprehensive information on fospropofol pharmacology to organizations that provide sedation training

Fospropofol Disodium
2,6-diisopropylphenoxymethyl phosphate, disodium salt

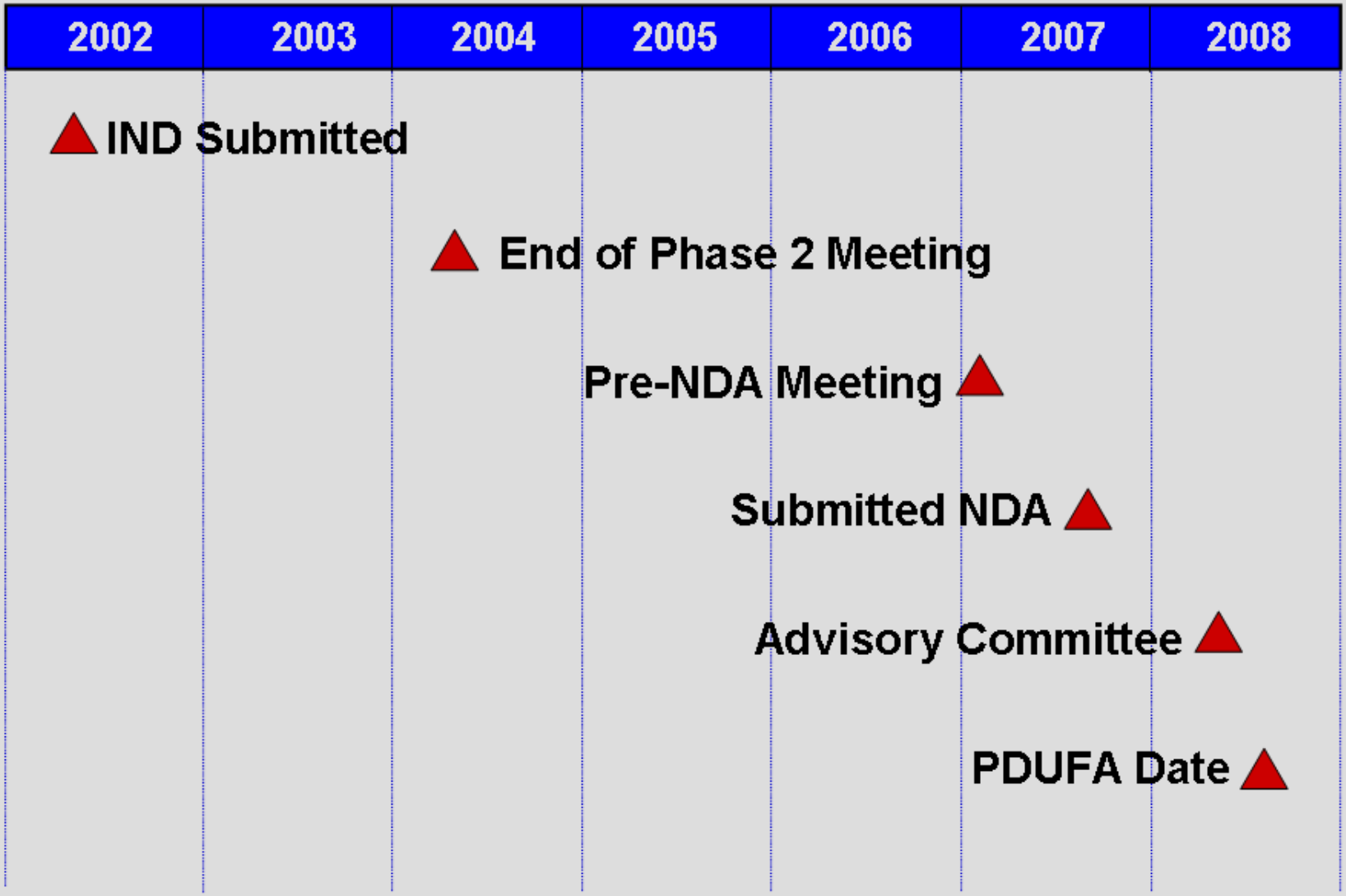
- Prodrug of propofol
- Aqueous formulation
- Clear colorless solution
- 35 mg/mL in single-use 30 mL glass vial, ready for IV injection



Fospropofol Development Hypothesis

- Fospropofol is rapidly and completely metabolized to propofol
- An aqueous-based propofol prodrug would
  - provide a smooth pharmacodynamic profile conducive for use by non-anesthesiologists
  - allow IV bolus injection
  - provide the propofol experience

Development Milestones



Sedation for Diagnostic & Therapeutic Procedures Clinical Development Program

Proof of concept	High initial bolus dose, fixed weight ranges	Dose response	6.5 mg/kg initial bolus; dose titration
Study 0207 Colonoscopy N = 164	Study 0409 Bronchoscopy N = 40	Study 0520 Colonoscopy N = 101	Study 0522 Colonoscopy N = 260
	Study 0410 Colonoscopy N = 210		Study 0524 Bronchoscopy N = 252
	Study 0411 Percutaneous Cardiac Interventions N = 6		Study 0523 Minor Procedures N = 123
	Study 0412 Minor Procedures N = 121		
	Study 0415 Colonoscopy Patients ≥ 65 yrs N = 15		

Extrapolation to Clinical Practice

- Clinical trials consistent with intended use in clinical practice
  - Clinical trial protocols did not require the presence of an anesthesia professional
  - MGI did not provide training in sedation or patient monitoring to the clinical sites
- Clinical trial sites included ambulatory surgi-centers, hospitals, and office based practices

Efficacy Summary

- Clearly demonstrated in phase 3 studies
- Demonstrated in subpopulations based on age, weight, gender, race, ASA status, and patients with renal insufficiency
- Excursions to deep sedation occurred infrequently

Safety Summary

- Safety profile consistent with current sedation practice as reported in the literature
- Adverse events
  - Most common are associated with phosphate prodrugs
  - Sedation-related adverse events occurred at a relatively low incidence

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Procedural Sedation: Challenges and Opportunities

Lawrence B. Cohen, M.D., AGAF, FACG, FASGE

Department of Medicine (Gastroenterology)
The Mount Sinai School of Medicine
New York, NY

Procedural Sedation

- Over 40 M procedures are performed each year with moderate sedation
- Approximately 23 M endoscopic procedures are performed annually
- For approximately two-thirds of the endoscopic procedures, sedation is performed by nonanesthesia professionals

Thomson Healthcare, Inc. *MarketScan® Hospital drug Database & MarketScan® Outpatient View*. 2006.

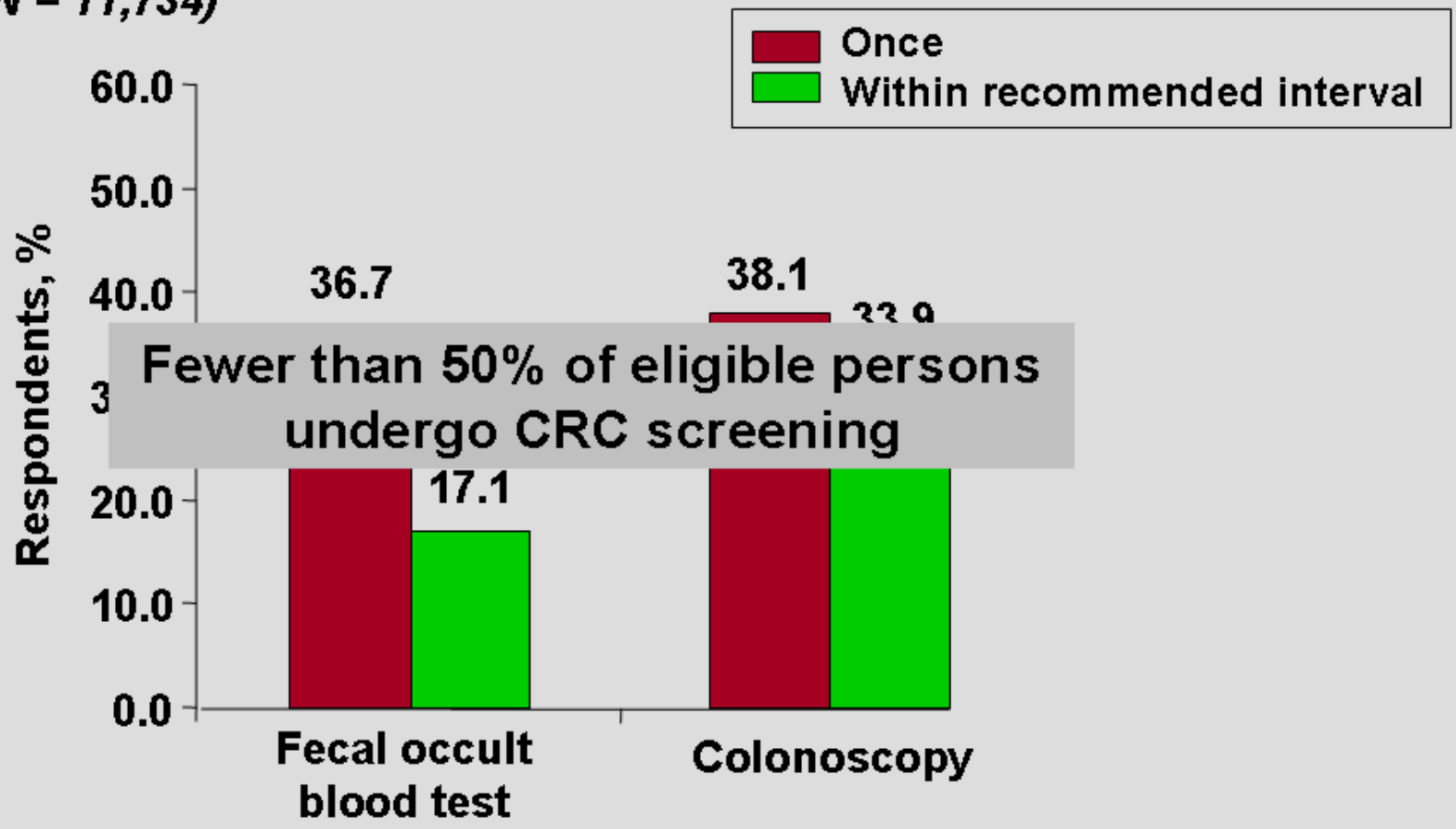
Growth in Endoscopic Procedures

- Over 5% annual growth rate in GI endoscopic procedures with moderate sedation
- Colonoscopy and polypectomy capable of reducing number of colorectal CA by up to 90%
- Heightened public awareness of the benefits of CRC screening has increased patient compliance
- Many insurance plans, including Medicare, pay for CRC screening

Thomson Healthcare, Inc. *MarketScan® Hospital drug Database & MarketScan® Outpatient View*. 2006.

Fewer Than 50% of Eligible Persons Undergo Any Type of CRC Screening

(NCHS N = 11,734)



NCHS = National Center for Health Statistics.

Seeff et al. *Cancer.* 2004;100:2093-2103.

Sedation is a Key Component of Endoscopy

- Relief of anxiety and fear associated with the procedure
- Relief of discomfort associated with the procedure
- Improves patient compliance with screening/surveillance guidelines
- Enhances quality of examination
- Minimize risk of physical injury to patient

Benzodiazepine and Opioid: The Sedation Standard

- 99% of colonoscopies are performed with sedation
  - 75% with benzodiazepine and opioid
  - 25% with propofol
    - 93% of sedation with propofol is performed with the presence of anesthesia professionals

Cohen, et al. *Am J Gastroenterol.* 2006;101:967-74.

Benzodiazepine and Opioid: The Sedation Standard

- Benefits
  - Effective for 85% patients[1]
  - Reversal agents are available
- Challenges
  - Significant pharmacodynamic variability
  - Drug interactions
  - Potential for respiratory depression

1. Cohen L Gastroenterology 2007; 133:675-701.

Benzodiazepine and Opioid: The Sedation Standard

- Challenges
  - Delayed recovery, not "clear headed", and patients unable to recall postprocedure discussion
  - Potential for nausea and vomiting
  - Duration of effect may persist > 24 hr[1]

1. Jonas DE Am J Gastroenterol 2007; 102:2401-2410.

Benzodiazepine + Opioid: The Sedation Standard

Benzodiazepine + opioid

- **Retrospective analysis of 324,737 endoscopic procedures including: colonoscopy, EGD, ERCP & EUS**
- **Incidence of cardiopulmonary events**
  range overall: 0.6 - 2.1%
  colonoscopy: 1.1%
  - **Bradycardia, hypotension, hypoxemia, tachycardia, pulmonary edema, respiratory depression, death**

Sharma VK Gastrointest Endosc 2007;66:27-34.

EUS: endoscopic ultrasound; EGD: esophagogastroduodenoscopy; ERCP: endoscopic retrograde cholangiopancreatography.

Propofol: The De Facto Standard of Care

- Benefits
  - Rapid onset and offset
  - Clear headed recovery
  - Preferred by patients and physicians
    - 38% of endoscopy is performed with propofol
    - Use has grown steadily for the last 5 yr
- Procedural challenges
  - Painful burning on injection
  - Risks associated with lipid emulsion
  - Monitored anesthesia care (MAC) requirement

Propofol: Sedation Related Adverse Events

- Propofol
  - Retrospective analysis of 11,683 colonoscopies
  - Incidence of cardiopulmonary events range: 0.86 - 1.66%
  - Bradycardia, hypotension, hypoxemia, tachycardia, pulmonary edema, vasovagal reaction

Vargo, et al. Aliment Pharmacol Ther. 2006. 24:955.

New Options are Needed

- Midazolam and opioid are not suitable for all patients
- Propofol use requires MAC sedation

Summary

- Alternative sedation choices for the nonanesthesia professional are needed to accommodate the growing demand for procedural sedation and the needs and wishes of patients.
- This need would be fulfilled by a sedation agent that provides the benefits of propofol in a formulation safe and effective when administered by nonanesthesia professionals.

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Fospropofol Disodium Clinical Pharmacology

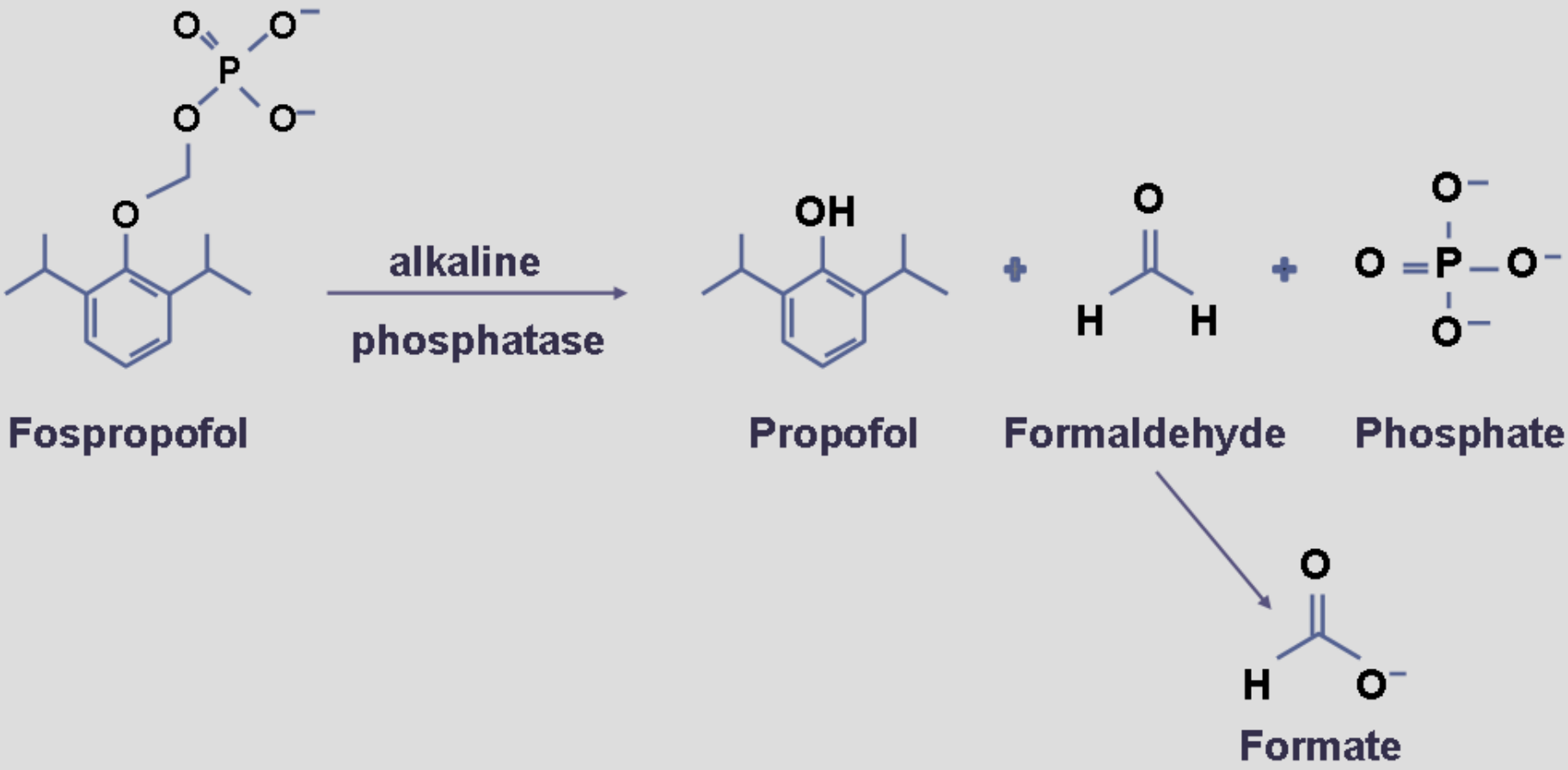
Stephen J. Waters, PhD

Vice President, Science and Technology
MGI PHARMA, INC.

Key Attributes of Fospropofol

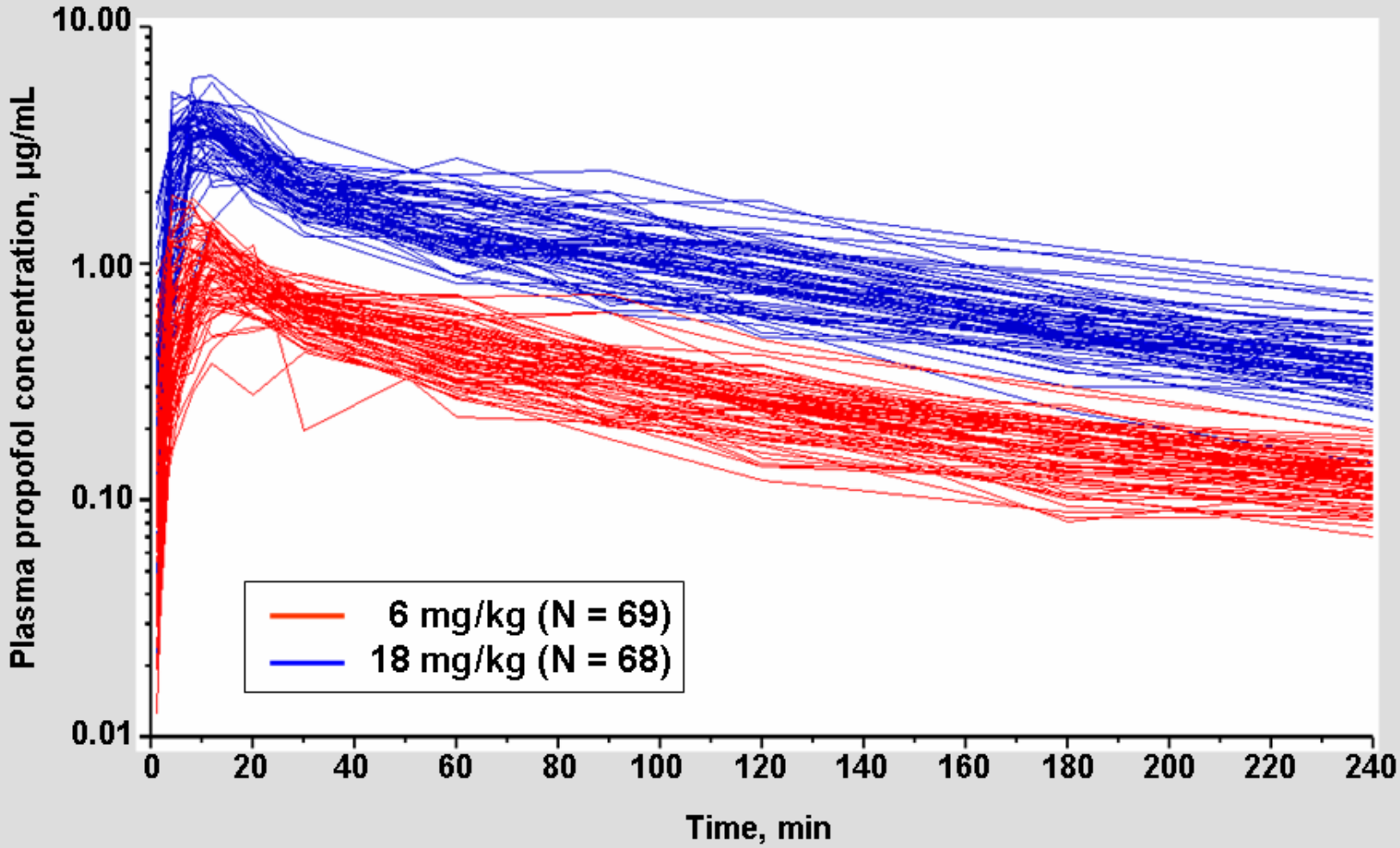
- Rapid and complete metabolism of the prodrug (fospropofol) liberating the active moiety (propofol)
- Dose proportional PK in healthy subjects and patient populations
- Gradual onset and dose-related depth of sedation with a predictable PK-PD relationship achieved using the proposed dosing regimen

Propofol is Liberated From Fospropofol



Propofol Concentrations (Liberated From Fospropofol) Are Dose Proportional

Study 0521



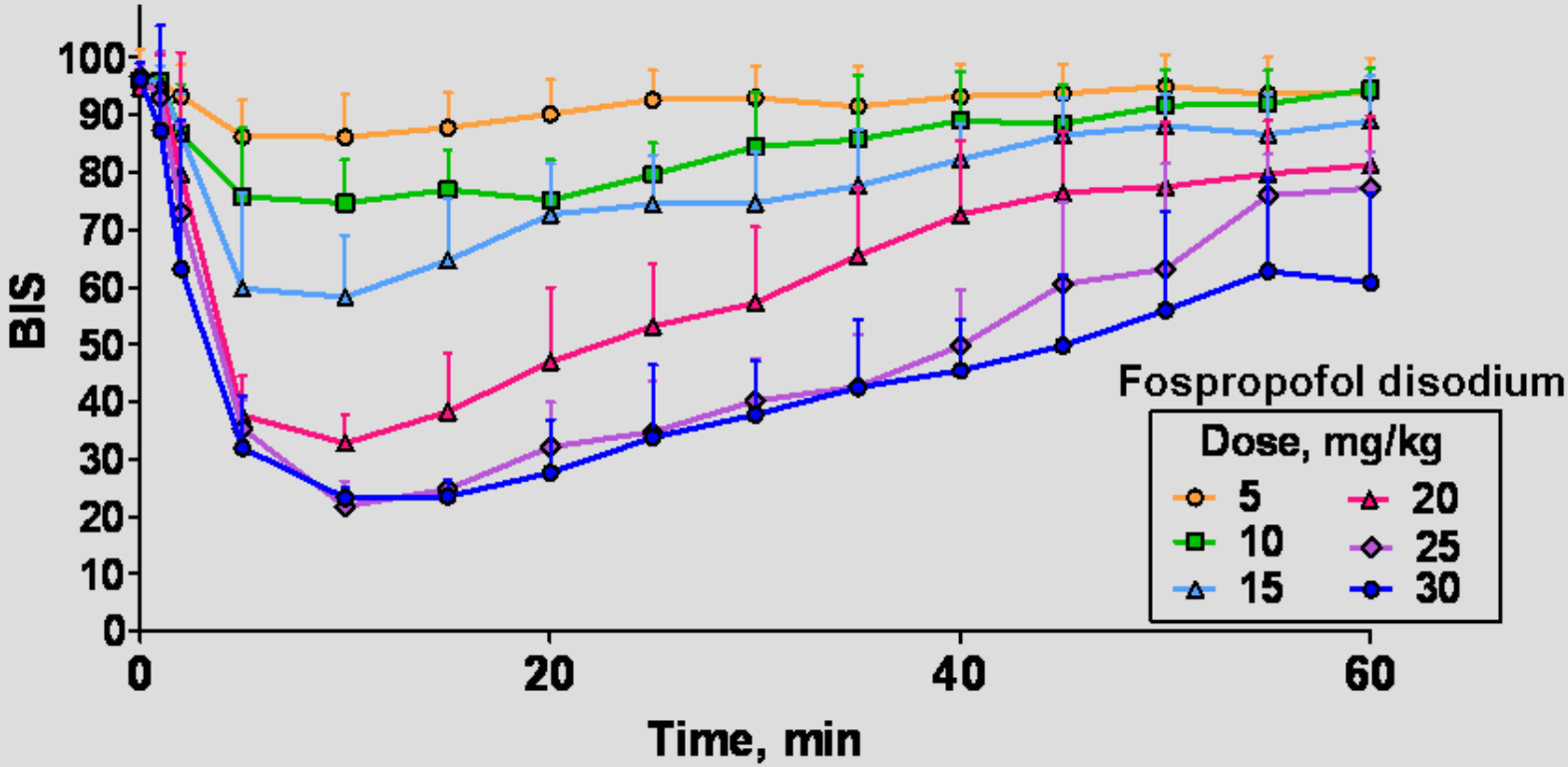
Propofol (Liberated From Fospropofol) Pharmacokinetics Are Dose Proportional

Study 0521

Fospropofol (mg/kg)	Propofol			
	Cmax† (µg/mL)	Tmax‡ (min)	t1/2† (h)	CL_p† (L/h/kg)
6 (N = 69)	1.08 ± 0.330	12	2.06 ± 0.770	1.95 ± 0.345
18 (N = 68)	3.90 ± 0.822	8	1.76 ± 0.540	1.79 ± 0.390

† Mean ± SD.
‡ Tmax data are median.

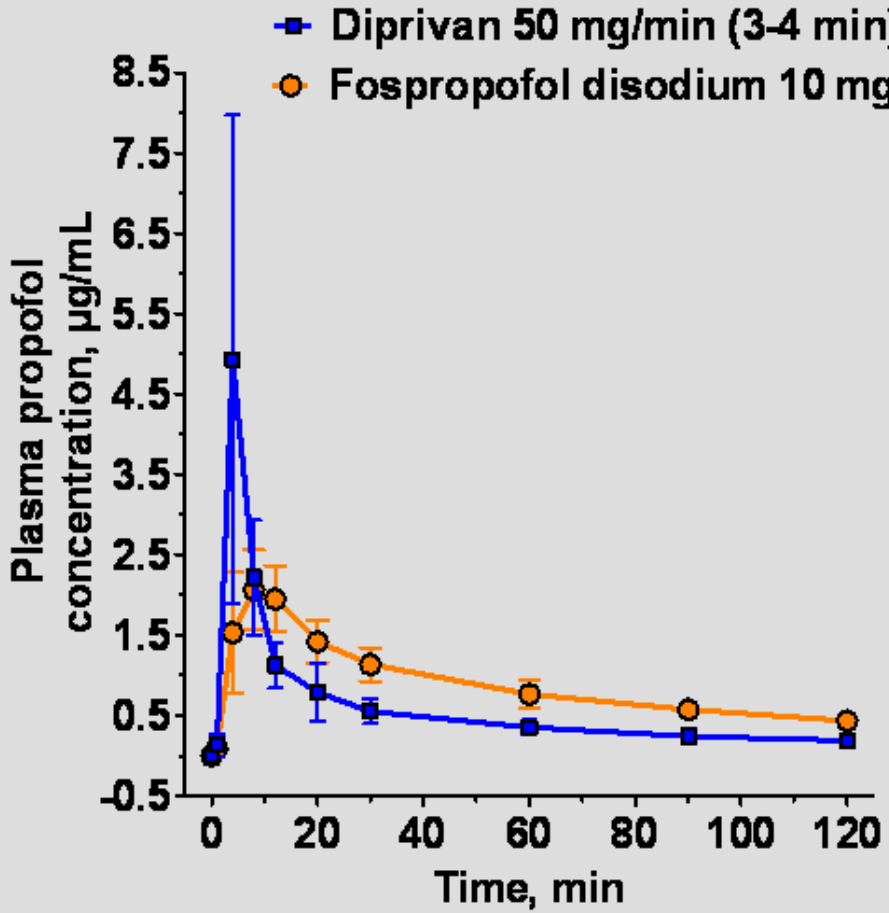
Depth of Sedation is Dose-Related
Study 0103

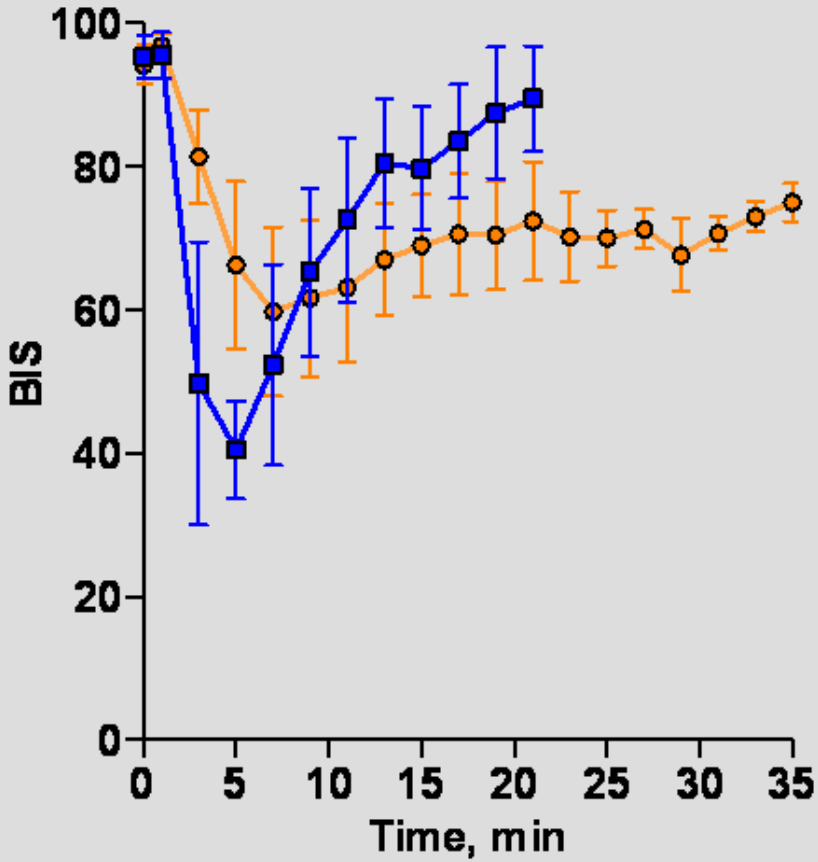


- Time to maximal sedation is consistent across doses

Mean ± SD (N = 6 subjects per dose).

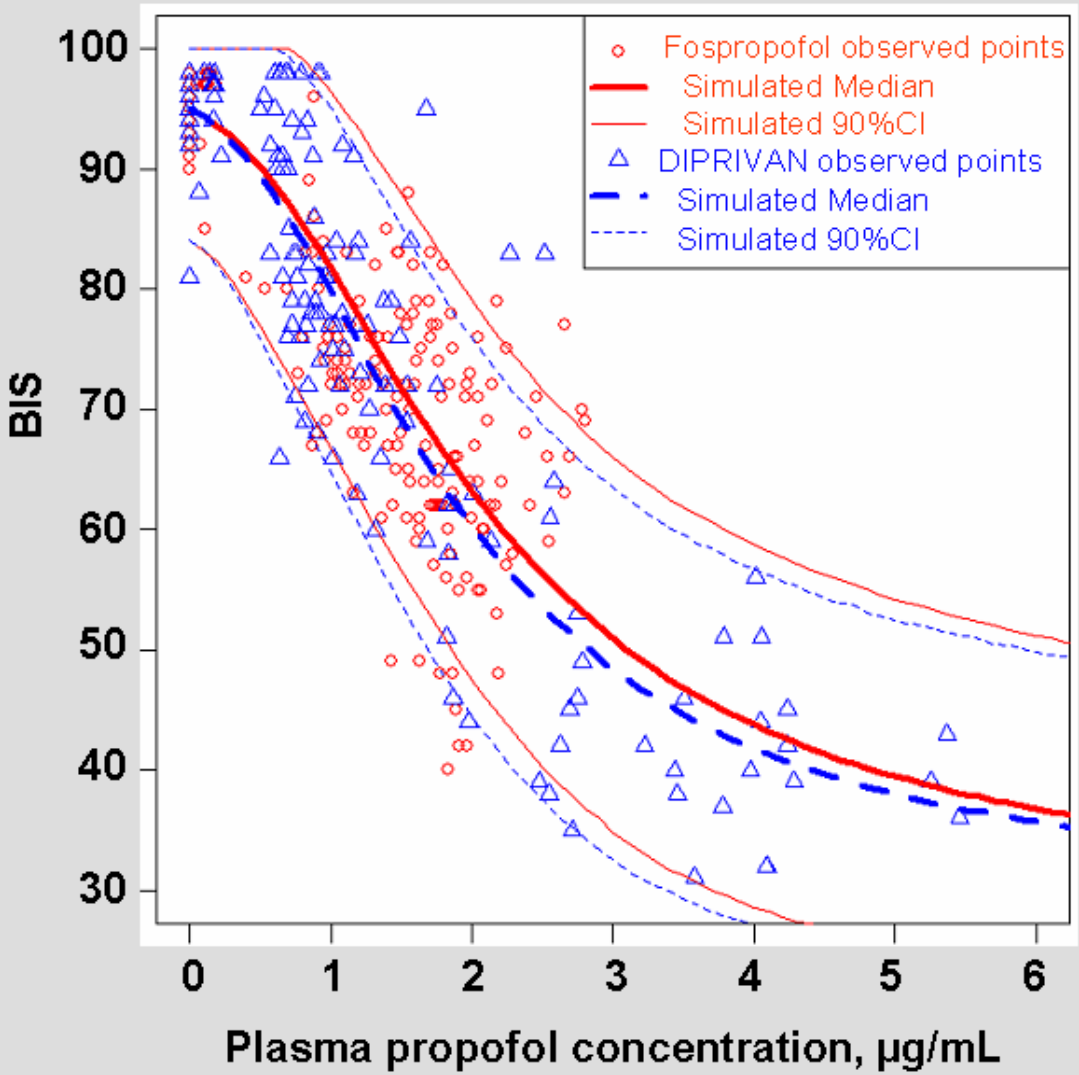
Propofol PD is Consistent with PK Profile
Study 0625





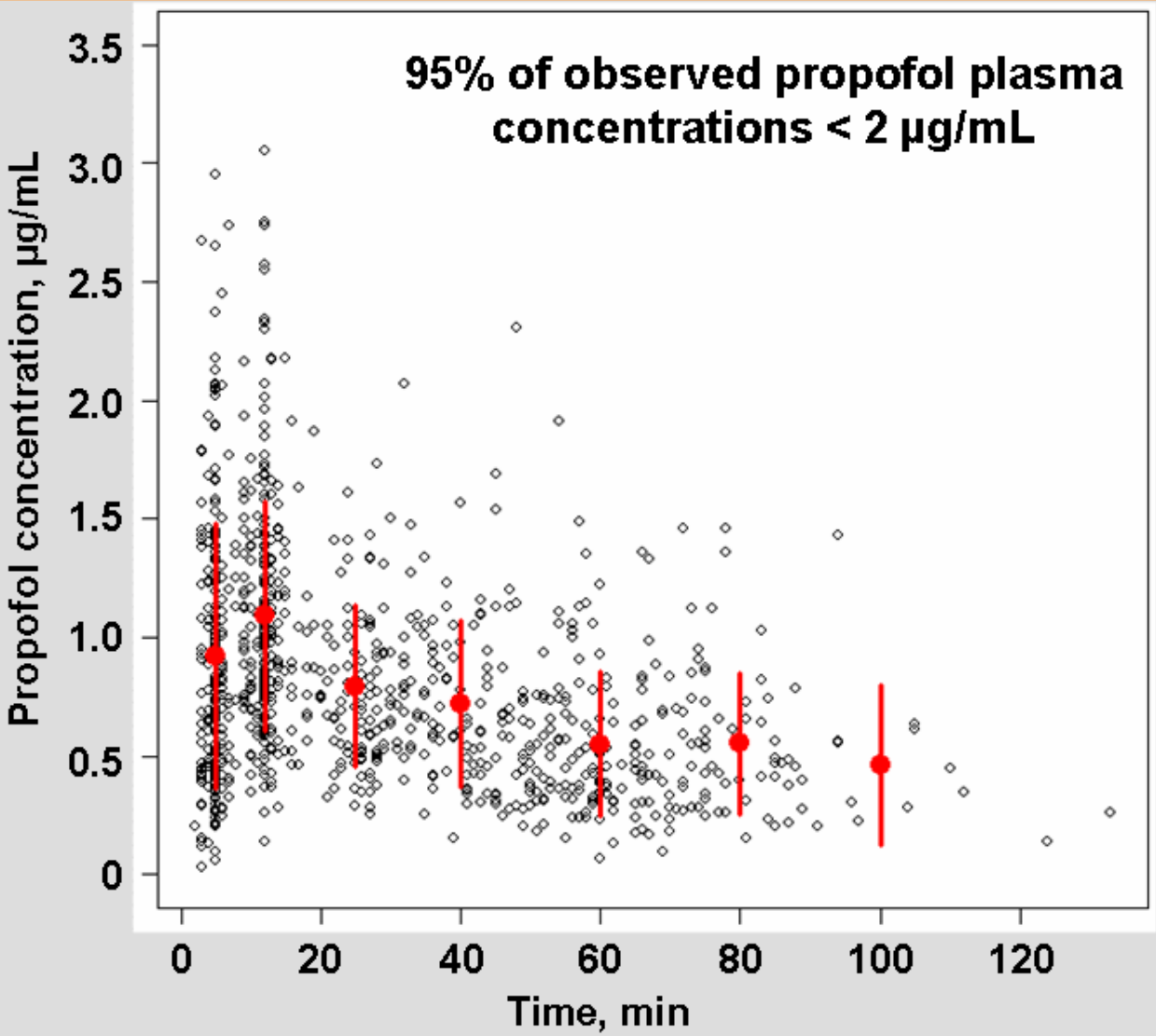
Mean ± SD (N = 12 subjects).

PK-PD Profile for Propofol Activity is Independent of Source (Either Liberated From Fospropofol or From DIPRIVAN)



Propofol Plasma Concentrations with the Proposed Dose Titration Regimen

Population PK (0522, 0523, 0524)



Clinical Pharmacology Conclusions

- IV bolus dosing produces a gradual increase in plasma propofol concentration
- Dosing over a wide range results in dose-proportional propofol pharmacokinetics
- Proposed dosing regimen produces propofol plasma concentrations consistent with minimal to moderate sedation

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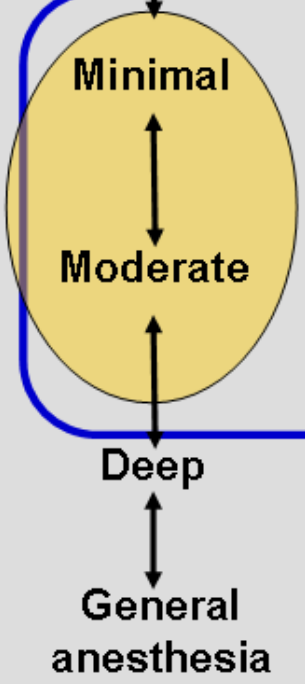
Fospropofol Disodium Injection Efficacy

Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Agenda

- Modified Observer's Assessment of Alertness/Sedation Scale
- Clinical Program Overview
- Primary Endpoint
- Dose Response Study Highlights
- Phase 3 Randomized, Double-blind, Dose-controlled Studies

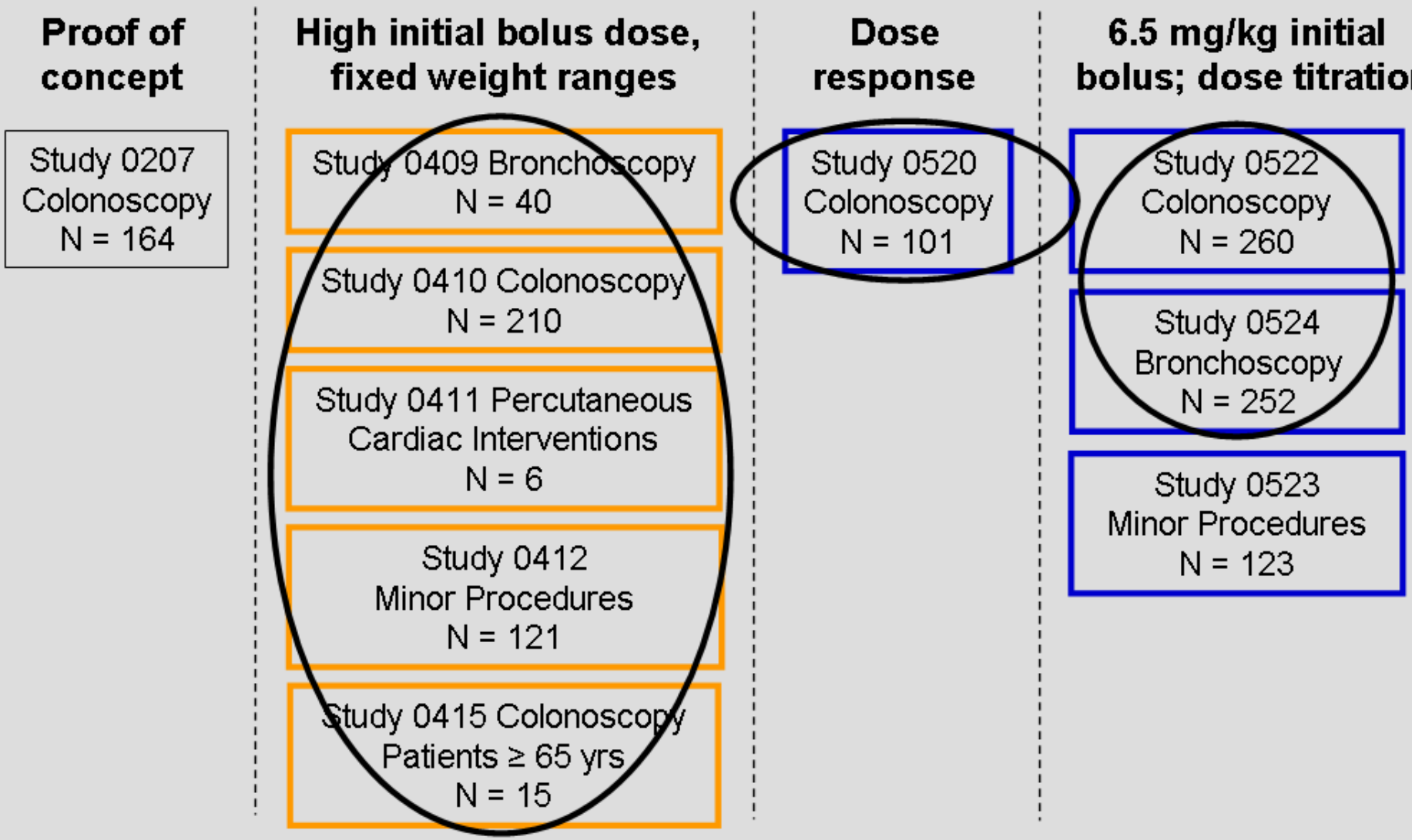
Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)



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

Chernik DA, et al. *J Clin Psychopharmacol.* 1990;10:244-251.
ASA Practice Guidelines. *Anesthesiology.* 2002;96:1004-1017.

Sedation for Diagnostic & Therapeutic Procedures Clinical Development Program



Primary Endpoint—Sedation Success

Composite endpoint

1. 3 consecutive† MOAA/S scores of ≤ 4 (lethargic response to name spoken in normal tone) after administration of sedative medication
2. Completing the procedure
3. Without use of alternative sedative medication
4. Without requiring manual (bag-valve-mask) or mechanical ventilation (intubation)

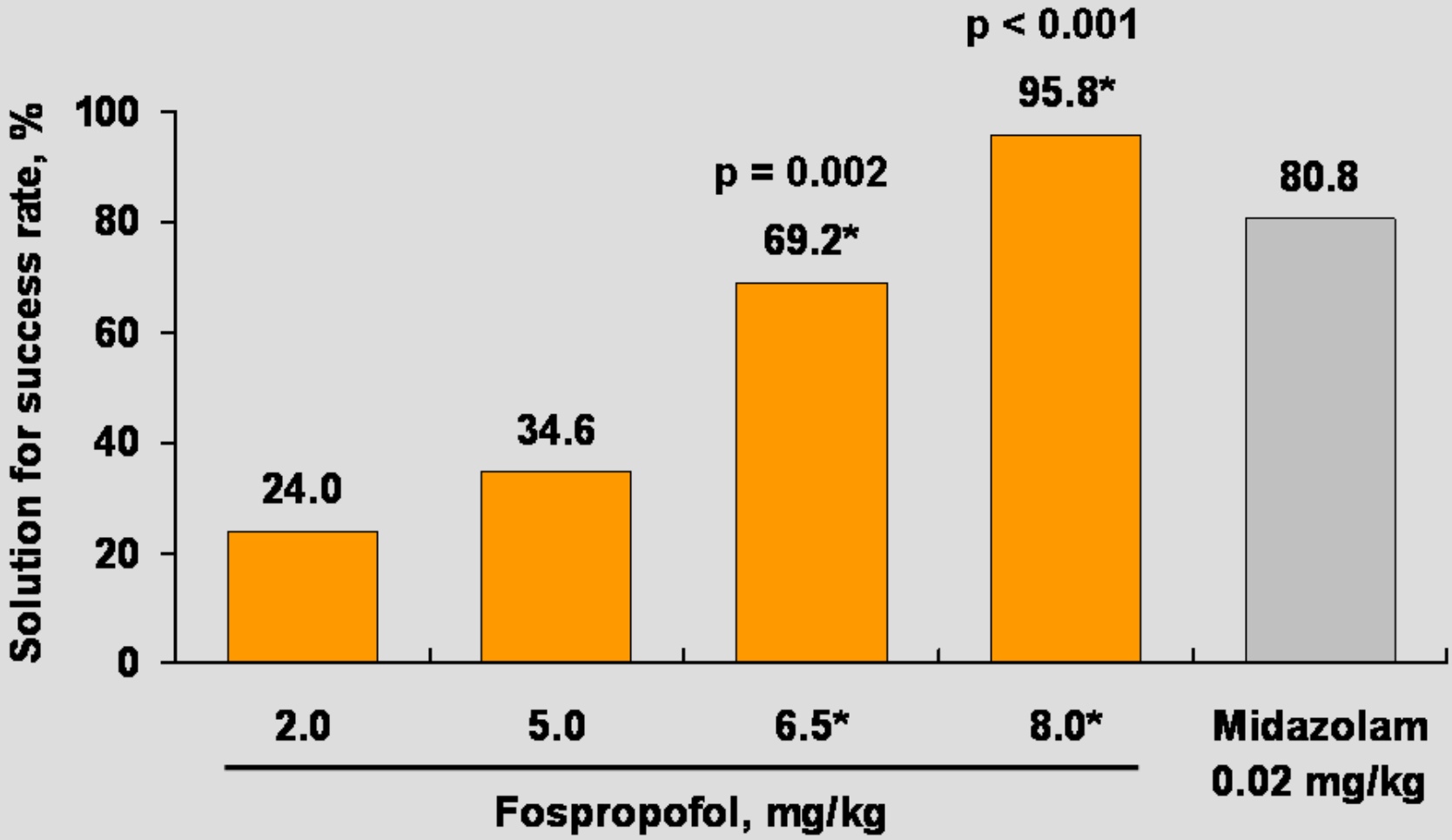
† MOAA/S assessed every 2 min.

Dose Response in Patients Undergoing Colonoscopy in Study 3000-0520

Dose Response
Study 0520 Colonoscopy

Design	Randomized, double-blind, dose-controlled
Patients	Patients undergoing colonoscopy Ages ≥ 18 yr, ASA P1 to P4 Excluded patients with difficult airways N = 125
Duration	1 procedure
Sites	16 sites (US)
Treatments	5 arms, equal randomization (2.0, 5.0, 6.5, and 8.0 mg/kg fospropofol; 0.02 mg/kg midazolam)
1º Endpoint	Sedation success

Sedation Success
Study 0520 Colonoscopy



*Statistically different from 2.0 mg/kg (Fisher's exact test).

Dose Selection for Clinical Trials
Study 0520 Colonoscopy

- Sedation success
  - 6.5 mg/kg group: 69.2%
  - 8 mg/kg group: 95.8%
- Patients who reached MOAA/S of 0 or 1
  - 6.5 mg/kg group: 1/26 (4%)
  - 8 mg/kg group: 6/24 (25%)
- 6.5 mg/kg dose selected for further study

Phase 3 Randomized, Double-Blind Dose Controlled Studies

Study 0522 Sedation in Patients Undergoing Colonoscopy

Study 0524 Sedation in Patients Undergoing Flexible Bronchoscopy

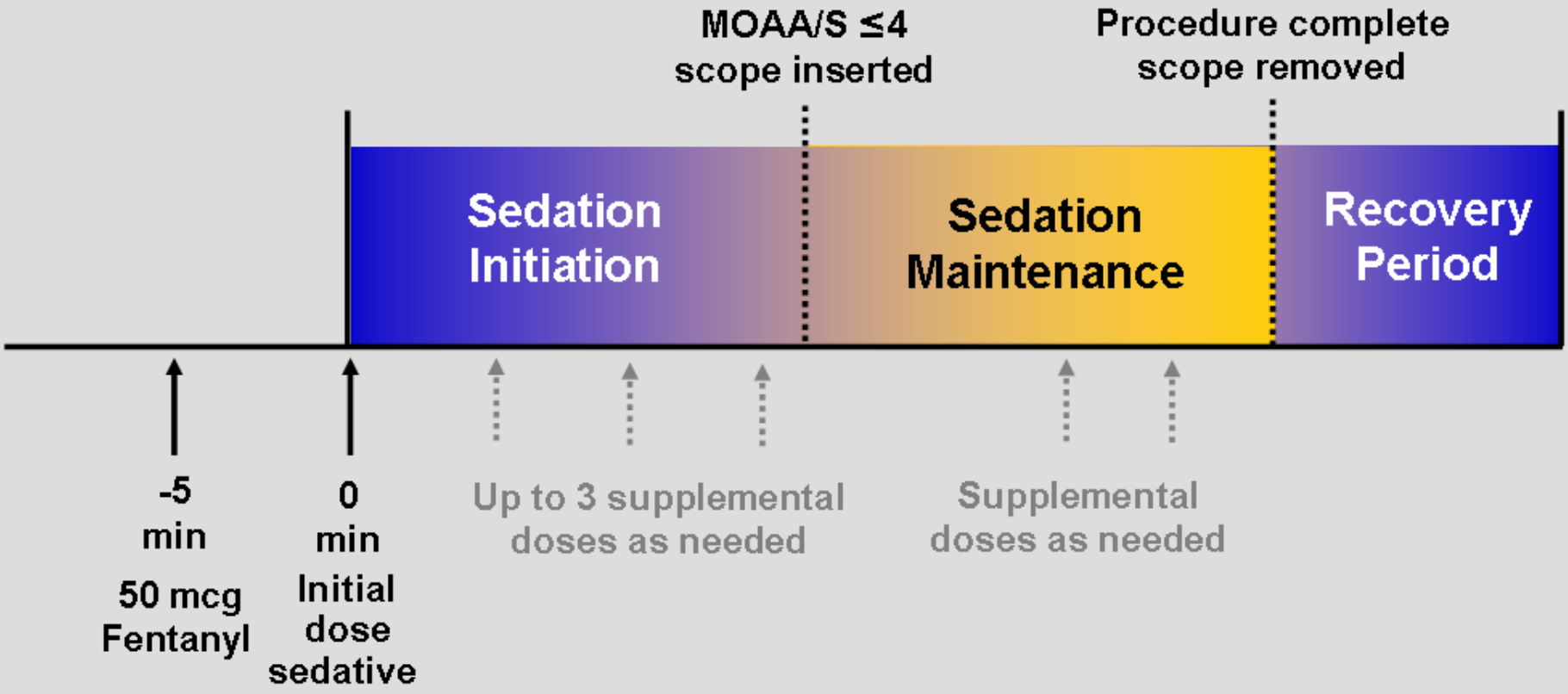
Pivotal Program
Study 0522 Colonoscopy, 0524 Bronchoscopy

Study	3000-0522	3000-0524
Design	Randomized, double-blind, dose-controlled superiority study	
Patients	Colonoscopy, N = 300	Flexible bronchoscopy, N = 250
	Ages ≥ 18 yr, ASA P1 to P4 Excluded patients with difficult airways	
Duration	1 procedure	
Sites (US)	18 sites	24 sites
Treatments	3 arms, 3:2:1 randomization 6.5 mg/kg fospropofol 2.0 mg/kg fospropofol 0.02 mg/kg midazolam	2 arms, 3:2 randomization 6.5 mg/kg fospropofol 2.0 mg/kg fospropofol
1° Endpoint	Sedation Success	
2° Endpoints	Treatment Success Patients receiving supplemental analgesics (3° in 0524) Patients who do not recall being awake during the procedure Patients willing to be treated with study sedative again	

Statistical Hypothesis
Study 0522 Colonoscopy, 0524 Bronchoscopy

- Primary hypothesis: Sedation success rate for fospropofol 6.5 mg/kg dose greater than for 2.0 mg/kg dose group
- Low dose control
  - Maintain the blind given the occurrence of paresthesias and/or pruritus in patients receiving fospropofol is not dose related
  - Used in agreement with FDA
- Midazolam was included in the colonoscopy study for general information and was not planned or intended for efficacy comparisons

Study Design
Study 0522 Colonoscopy, 0524 Bronchoscopy



- Purposeful response and MOAA/S score measured every 2 min
- Supplemental doses administered as needed (no closer than 4 min apart) to initiate and maintain sedation

Study Populations

	Fospropofol mg/kg		Midazolam mg/kg	All patients
	2.0	6.5	0.02	
0522 Colonoscopy				
Patients randomized	102	160	52	314
mITT	102	158	52	312
0524 Bronchoscopy				
Patients randomized	103	153	—	256
mITT	102	150	—	252

All 6 subjects not included in the mITT did not receive any study sedative drug.

Demographics
Study 0522 Colonoscopy

	Fospropofol mg/kg 2.0 N = 102	Fospropofol mg/kg 6.5 N = 158	Midazolam mg/kg 0.02 N = 52
Mean age, yr	52.4	52.9	54.0
Age group, %			
18 - 64 yr	86.3	86.7	80.8
≥ 65 yr	13.7	13.3	19.2
Female, %	54.9	51.9	34.6
Weight group, %			
< 60 kg	12.7	5.7	7.7
60 - < 90 kg	54.9	54.4	59.6
≥ 90 kg	32.4	39.9	32.7
ASA status, %			
P1 and P2	96.1	96.9	94.2
P3	3.9	3.2	5.8
P4	0	0	0

Demographics
Study 0524 Bronchoscopy

	Fospropofol mg/kg 2.0 N = 102	Fospropofol mg/kg 6.5 N = 150
Mean age, yr	60.1	60.8
Age group, %		
18 - 64 yr	58.8	59.3
≥ 65 yr	41.2	40.7
Gender, %		
Female	47.1	42.7
Weight group, %		
< 60 kg	18.6	18.0
60 - < 90 kg	50.0	54.0
≥ 90 kg	31.4	28.0
ASA status, %		
P1 and P2	62.8	54.0
P3	30.4	40.7
P4	6.9	5.3

Comparison of Trial Populations
Study 0522 Colonoscopy, 0524 Bronchoscopy

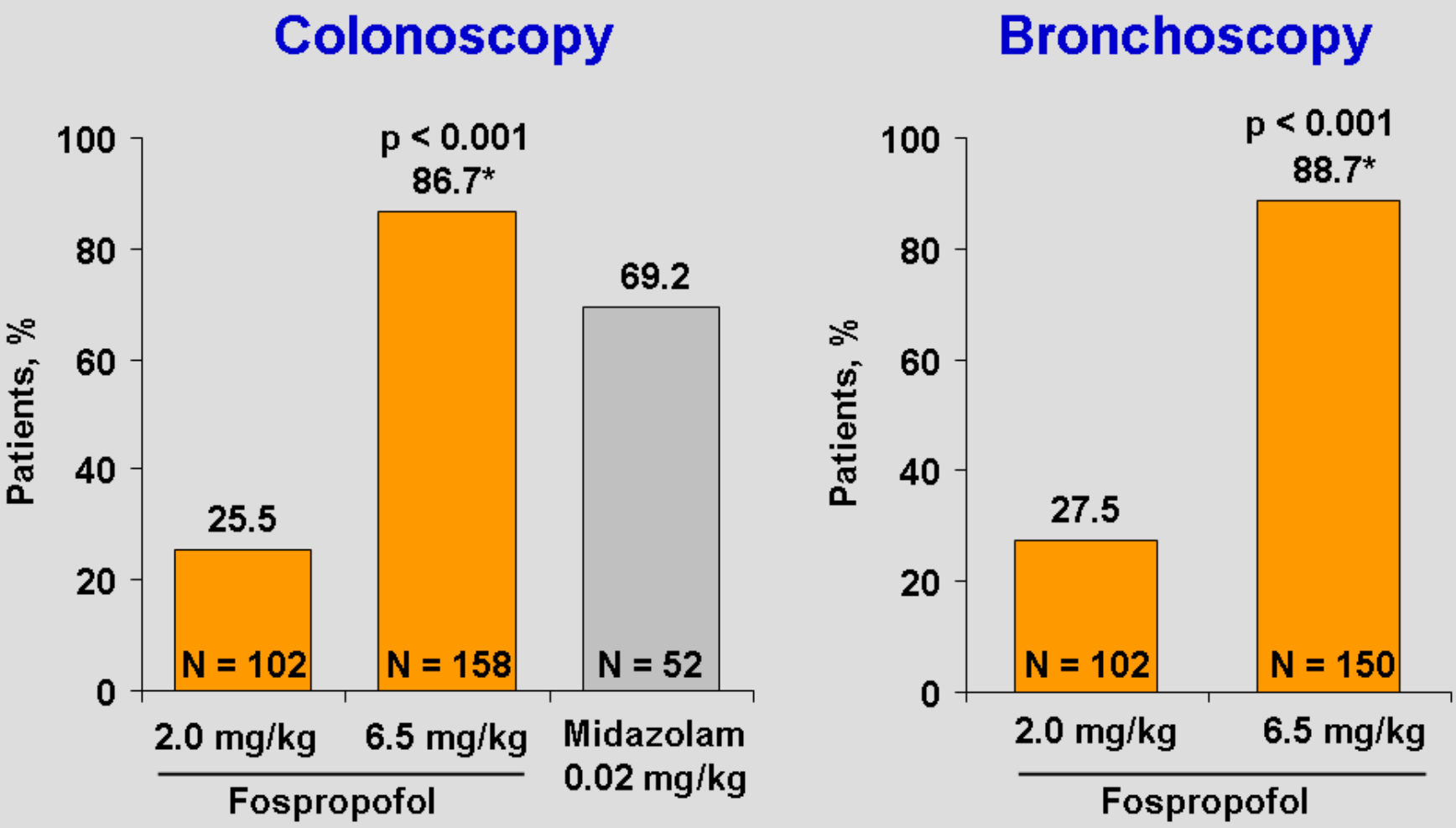
ASA classification	Patient description	Colonoscopy	Bronchoscopy
ASA P1	No known systemic disease	31%	5%
ASA P2	Mild systemic disease	65%	52%
ASA P3	Severe systemic disease	4%	37%
ASA P4	Systemic disease that is a constant threat to life	None	6%
Age	Mean age, yr	52.9	60.5

Primary Endpoint—Sedation Success

- Composite endpoint
  1. 3 consecutive† MOAA/S scores of ≤ 4 (lethargic response to name spoken in normal tone) after administration of sedative medication
  2. Completing the procedure
  3. Without use of alternative sedative medication
  4. Without requiring manual (bag-valve-mask) or mechanical ventilation

† MOAA/S assessed every 2 min.

Sedation Success
Study 0522 Colonoscopy, 0524 Bronchoscopy



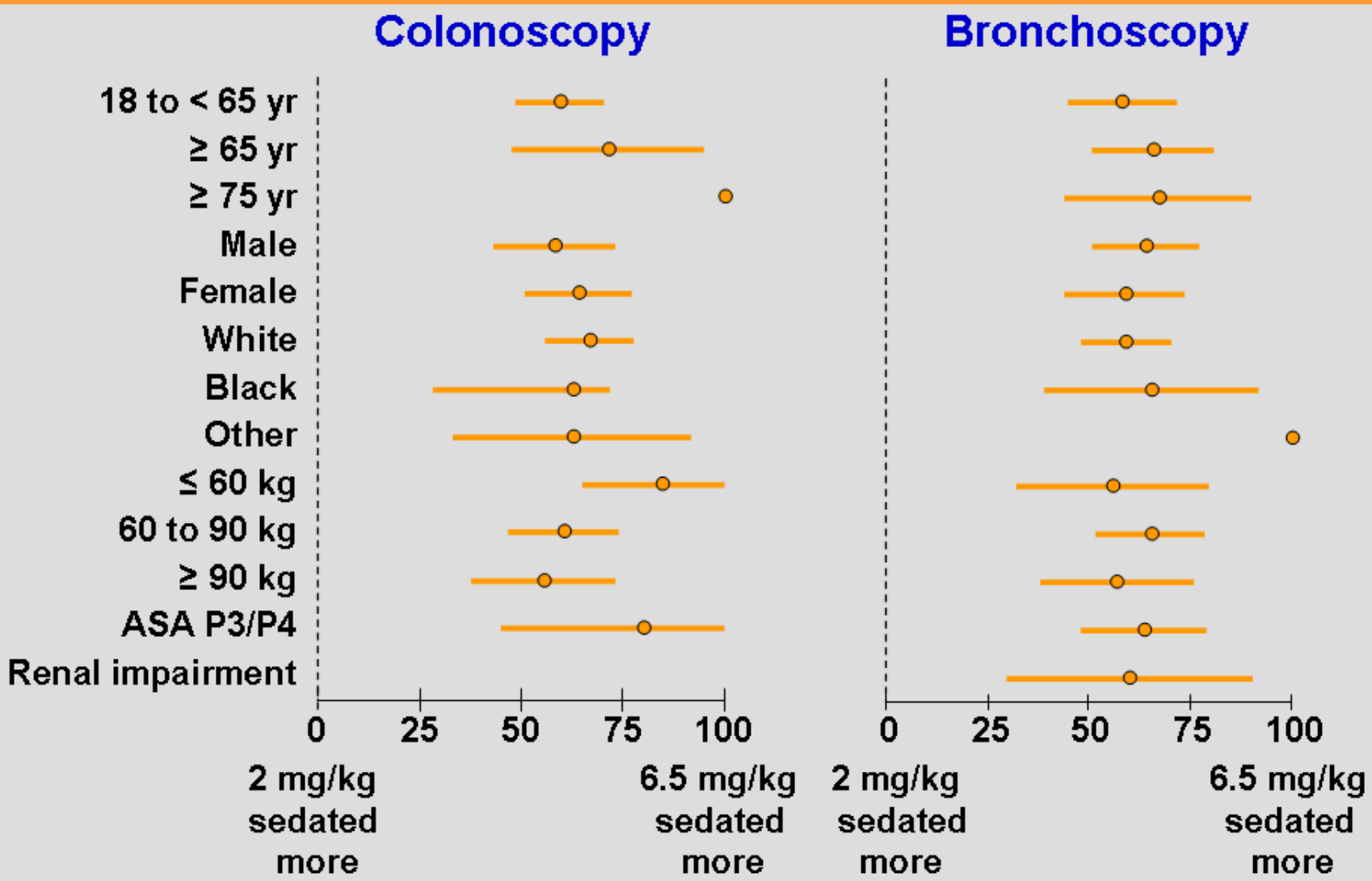
*Statistically different from 2.0 mg/kg (Fisher's exact test).

Efficacy in Subgroups
Studies 0522 Colonoscopy and 0524 Bronchoscopy

- Primary endpoint analyzed by 5 demographic factors
  - Age group (18 to < 65, ≥ 65, and ≥ 75 yr)
  - Sex
  - Race (white, black, or other)
  - Weight group (< 60, 60 to < 90, and ≥ 90 kg)
  - Special disease population (ASA P3/P4, creatinine clearance ≤ 50 mL/min)
- Sedation success for fospropofol 6.5 mg/kg group was statistically significantly higher than the 2.0 mg/kg group for all subgroups

95% CI for the Difference (Fospropofol 6.5 mg/kg to 2.0 mg/kg) in % Patients Having Sedation Success

Studies 0522 Colonoscopy and 0524 Bronchoscopy



Secondary Endpoints
Studies 0522 Colonoscopy and 0524 Bronchoscopy

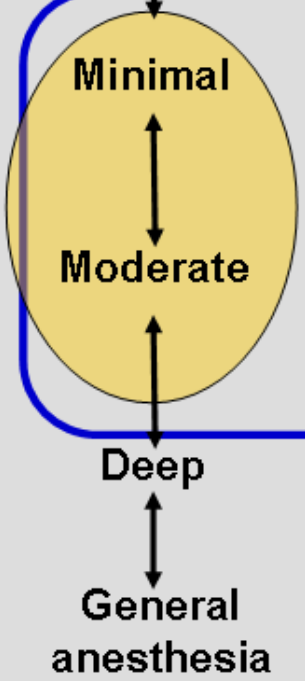
	Patients, %			
	Colonoscopy		Bronchoscopy	
	Fospropofol mg/kg		Fospropofol mg/kg	
	2.0 n = 102	6.5 n = 158	2.0 n = 102	6.5 n = 150
Treatment success (%)	28.4	88.0*	41.2	91.3*
Patients receiving supplemental analgesics	76.5	55.1*	37.3	16.7*
Patients who do not recall being awake during the procedure	44.1	52.5	55.4	83.3*
Patients willing to be treated with study sedative again	91.2	95.6	78.2	94.6*

*Statistically different from 2.0 mg/kg (Fisher's exact test).

Supplemental Doses of Study Sedative
Studies 0522 Colonoscopy and 0524 Bronchoscopy

	Colonoscopy		Bronchoscopy	
	Fospropofol mg/kg		Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	2.0 N = 102	6.5 N = 150
Initiation period				
mean ± SD	2.8 ± 0.7	1.6 ± 1.1	2.4 ± 0.9	0.9 ± 1.0
Total supplemental doses				
mean ± SD	3.2 ± 1.0	2.3 ± 1.4	2.9 ± 0.9	1.7 ± 1.6

Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

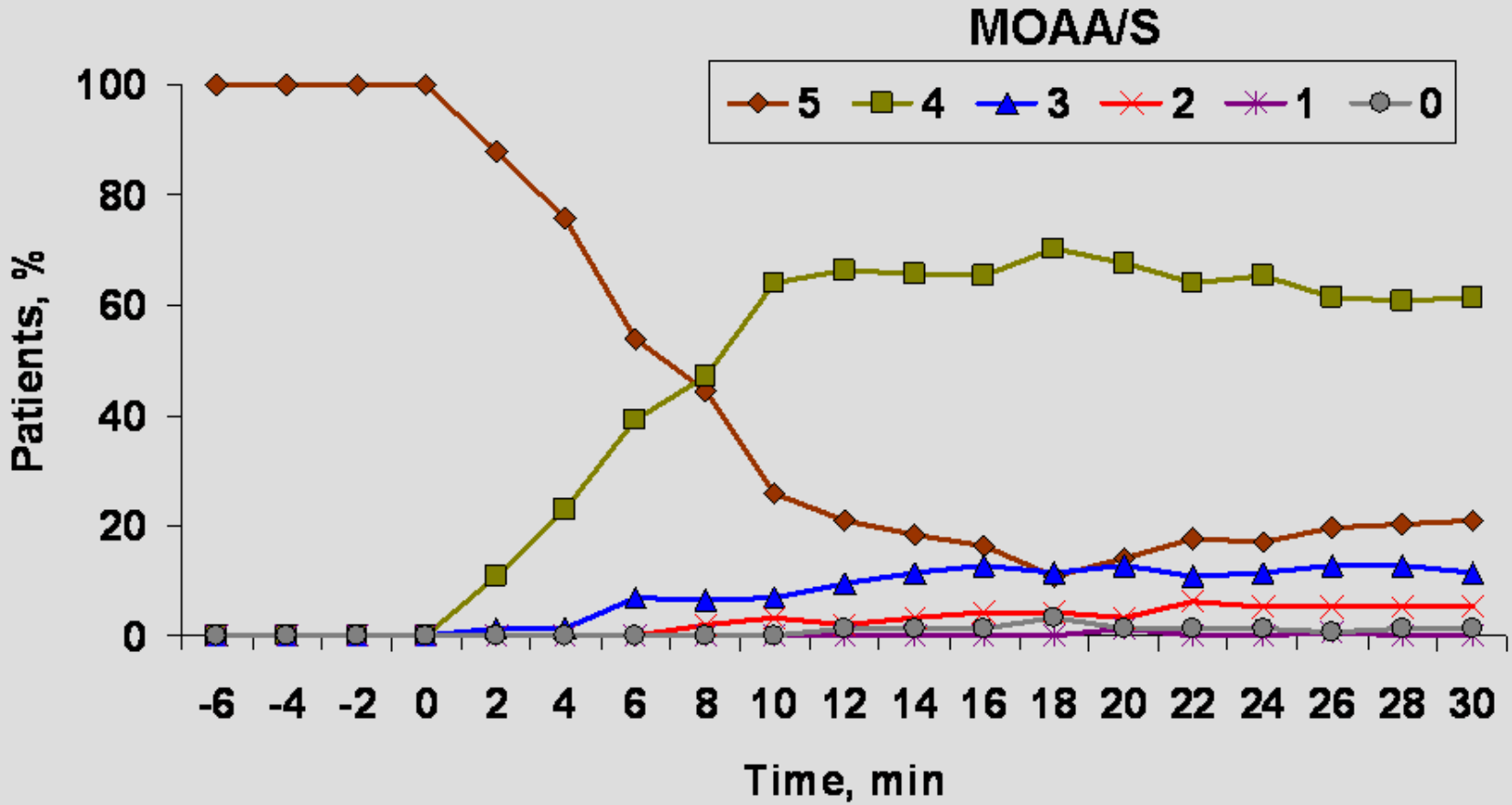


Responsiveness	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond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

Chernik DA, et al. *J Clin Psychopharmacol.* 1990;10:244-251.
ASA Practice Guidelines. *Anesthesiology.* 2002;96:1004-1017.

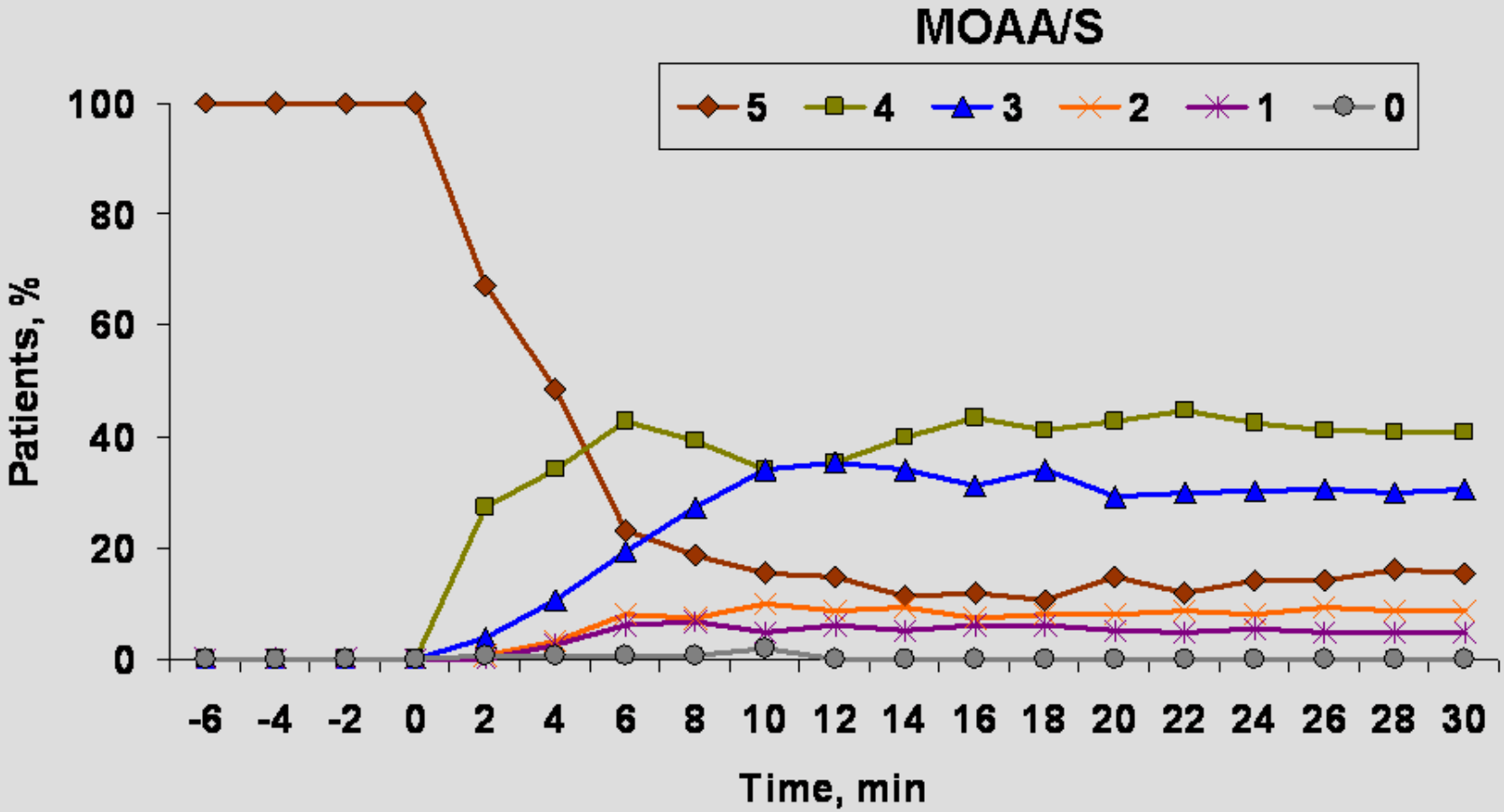
Percentage of Patients at Each MOAA/S Score Over Time, 6.5 mg/kg Dose Group

Study 0522 Colonoscopy



Percentage of Patients at Each MOAA/S Score Over Time, 6.5 mg/kg Dose Group

Study 0524 Bronchoscopy



Sedation Continuum (ASA, Oct. 2004)

	Minimal sedation (anxiolysis)	Moderate sedation/ analgesia ("conscious sedation")	Deep sedation/ analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

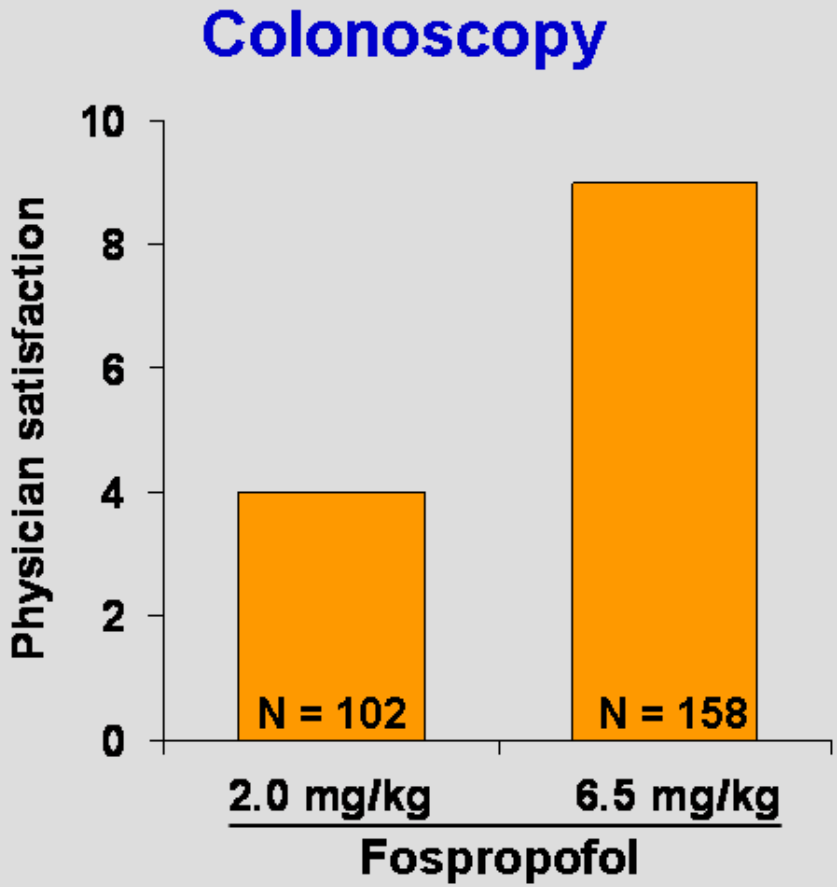
** Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

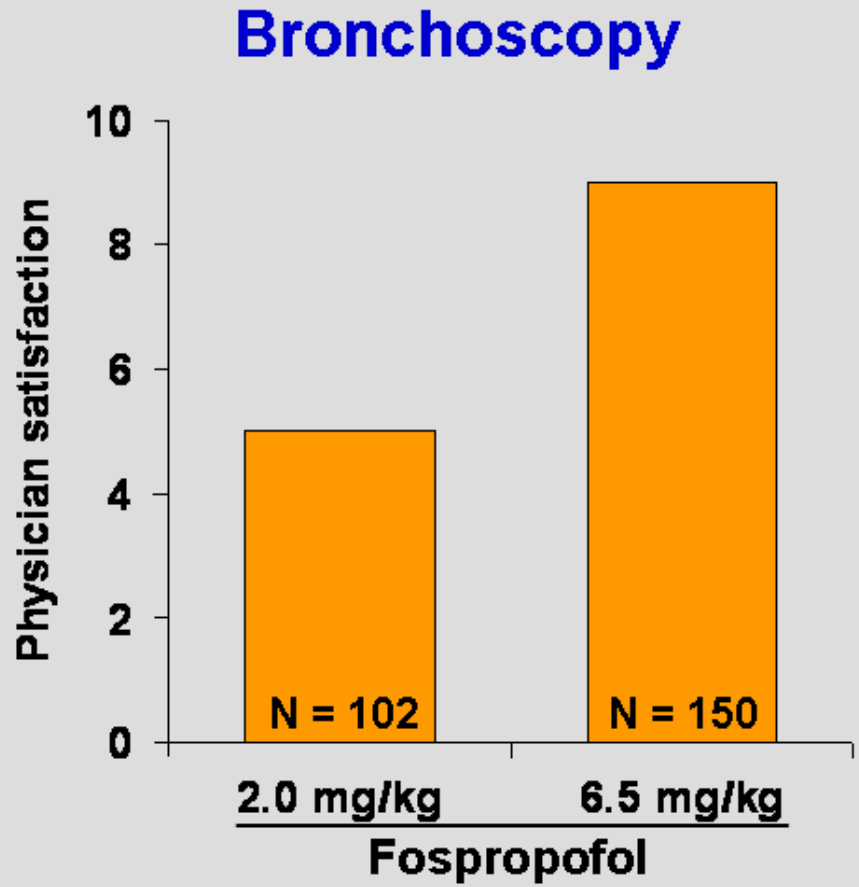
Correlation of Purposeful Response with MOAA/S Score within the Range of Moderate Sedation

Studies 0520 and 0522 Colonoscopy and 0524 Bronchoscopy

Yes Response (%) N = 14,967	MOAA/S Score
99.97	2 to 5
0.03	1
0	0

Physician Satisfaction
Studies 0522 Colonoscopy and 0524 Bronchoscopy





At the end of the procedure, physicians asked to rate level of satisfaction with the study sedative medication administered on a scale of 1 to 10.

Efficacy Conclusions

- Proposed dose regimen provides predictable and titratable sedation
  - 88% of patients undergoing colonoscopy and 91 % undergoing bronchoscopy completed procedure without requiring alternative sedative
  - Excursions to deep sedation occurred infrequently

Agenda

Introduction	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.
Medical Need	**Lawrence B. Cohen, MD** Associate Clinical Professor Mount Sinai Hospital, New York, NY
Clinical Pharmacology	**Stephen J. Waters, PhD** VP Science & Technology, MGI PHARMA, INC.
Clinical Efficacy	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.
Clinical Safety	**Michael T. Cullen, MD** Chief Medical Officer, MGI PHARMA, INC.
Risk/Benefit Summary	**John B. Leslie, MD** Consulting Professor of Anesthesiology Mayo Clinic, Scottsdale, AZ
Conclusion	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.

Fospropofol disodium Clinical Safety

Michael T. Cullen, MD

Chief Medical Officer
MGI PHARMA, INC.

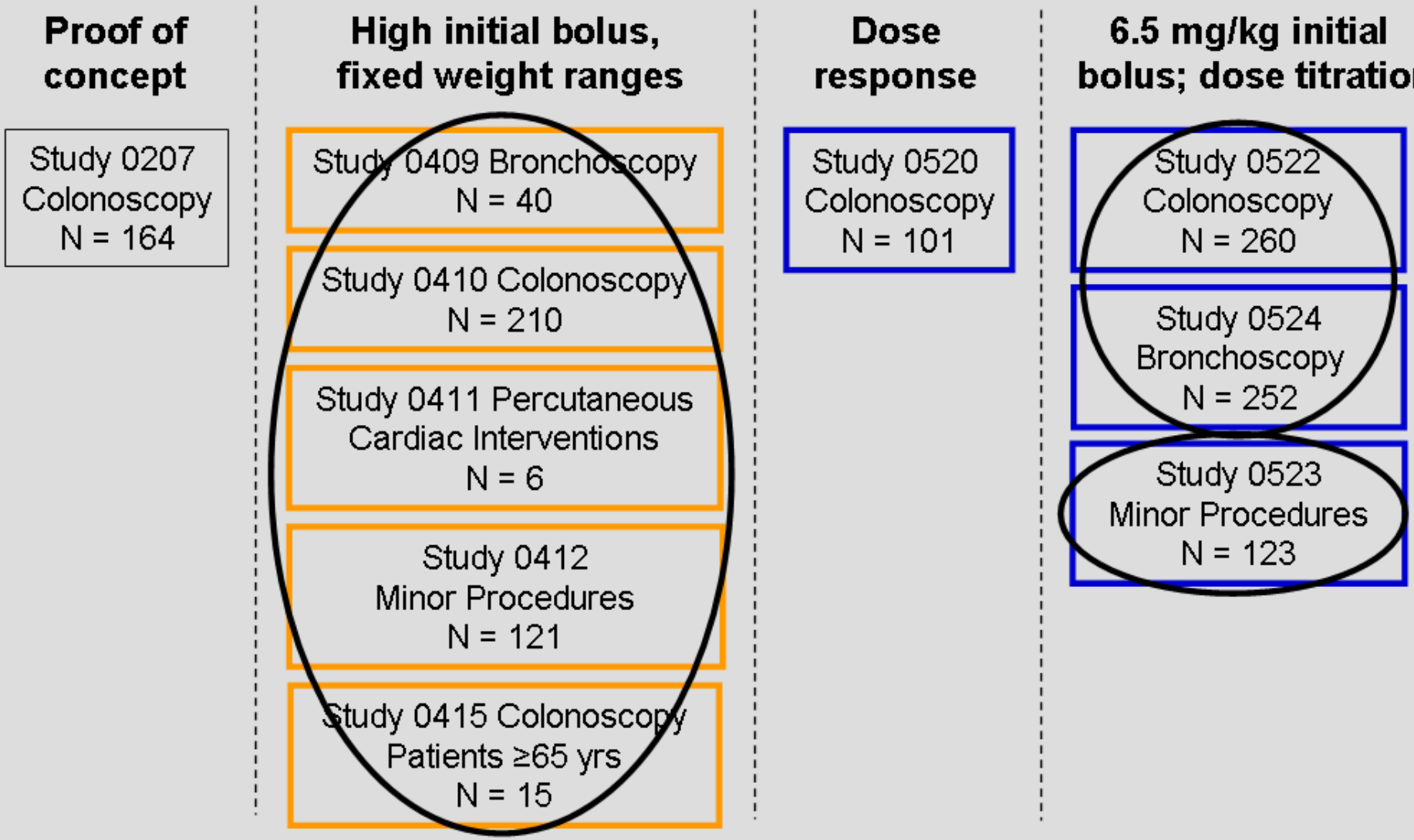
Safety Data Supports Administration of Fospropofol by Nonanesthesia Professionals

- Sedation-related adverse events
  - Occur at a frequency consistent with the expectations of procedural sedation practitioners
  - Can be managed by nonanesthesia professionals
- Sedation-related adverse events resolved without sequelae

Safety Overview

- Exposure and Demographics
- Adverse Events (AE)
  - Serious Adverse Events (SAE)
  - Deaths
  - Sedation-Related Adverse Events (SRAE)
  - Subgroup Analyses
- Experience in Minor Procedures
- Experience At Higher Doses (Fixed Dose Studies)

Sedation for Diagnostic & Therapeutic Procedures—Clinical Development Program



Exposure to Fospropofol All Subjects—All Studies

	Subjects, n (%) N = 1611	Total fospropofol dose, mg
Proposed dose titration regimen (6.5 mg/kg)	455 (28.2)	280-1593
Low-dose control (2.0 mg/kg)	232 (14.4)	105-425
Fixed dose regimen	556 (34.5)	450-1680
Other doses (5.0 and 8.0 mg/kg)	49 (3.0)	315-1225
Prolonged exposure (ICU)	46 (2.9)	155-6981
Healthy subjects	273 (16.9)	224-3532

Fospropofol Exposure by Procedure

	Patients, n (%)		
	Colonoscopy N = 750	Minor procedures N = 250	Bronchoscopy N = 292
6.5 mg/kg	183 (24.4)	123 (49.2)	149 (51.0)
2.0 mg/kg	129 (17.2)	0	103 (35.3)
5.0 and 8.0 mg/kg	49 (6.5)	0	0
Fixed dose	389 (51.9)	127 (50.8)	40 (13.7)

Total Study Drug Exposure in Phase 3 Studies

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Study drug					
Median, mg	262.5	778.8	4.3	227.5	577.5
min, max	140, 420	298, 1278	1.6, 9.6	123, 385	280, 1558
Fentanyl					
Median, mcg	75	75	75	50	50
min, max	50, 250	50, 150	50, 150	50, 400	0, 450

Patients Receiving Midazolam as an Alternative Sedative

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Patients, n (%)	71 (69.6)	19 (12.0)	10 (19.2)	60 (58.8)	12 (8.0)
Median dose, mg	3	2	4	4	2
min, max	1, 7	1, 8	1, 9.5	1, 14	1, 10

Demographics (Age, ASA, Weight)
Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Age, yr					
≥ 65	14 (13.7)	21 (13.3)	10 (19.2)	42 (41.2)	61 (40.7)
ASA					
P3	4 (3.9)	5 (3.2)	3 (5.8)	31 (30.4)	61 (40.7)
P4	0	0	0	7 (6.9)	8 (5.3)
Weight, kg					
< 60	13 (12.7)	9 (5.7)	4 (7.7)	19 (18.6)	27 (18.0)
≥ 90	33 (32.4)	63 (39.9)	17 (32.7)	32 (31.4)	42 (28.0)

Most Frequently Reported Significant Cardiac/Respiratory Medical History

Study 0524 Bronchoscopy

System organ class Preferred term	Patients, n (%) Bronchoscopy Fospropofol 6.5 mg/kg N = 149
Cardiac disorders	**42 (28.2)**
Coronary artery disease	26 (17.4)
Myocardial infarction	13 (8.7)
Atrial fibrillation	9 (6.0)
Cardiac failure congestive	9 (6.0)
Respiratory, thoracic, and mediastinal disorders	**139 (93.3)**
Chronic obstructive pulmonary disease	84 (56.4)
Hemoptysis	23 (15.4)
Pulmonary mass	23 (15.4)
Lung neoplasm	16 (10.7)

Summary of Adverse Events
Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Treatment-emergent AEs	89 (87.3)	145 (91.8)	31 (59.6)	79 (76.7)	124 (83.2)
Severe TEAE	1 (1.0)	4 (2.5)	0	13 (12.6)	22 (14.8)
Serious AE	1 (1.0)	0	1 (1.9)	13 (12.6)	15 (10.1)
Related SAEs	0	0	0	0	1 (0.7)
Deaths	0	0	0	2 (1.9)	3 (2.0)
Related deaths	0	0	0	0	0

Paresthesia and Pruritus

- Most patients receiving fospropofol reported paresthesia/pruritus
- Known effect of phosphate containing drugs (dexamethasone and fosphenytoin)
- No dose response
- Transient and self limited; 98% mild to moderate
  - 1 patient discontinued use of study drug due to severe paresthesia
- 95% of patients were willing to be treated again with fospropofol

Patient Incidence of Treatment-Emergent Adverse Events in ≥ 5% of Patients

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
Preferred term	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Paresthesia	61 (59.8)	108 (68.4)	0	46 (44.7)	74 (49.7)
Pruritus	26 (25.5)	25 (15.8)	0	15 (14.6)	22 (14.8)
Procedural pain	57 (55.9)	83 (52.5)	31 (59.6)	12 (11.7)	18 (12.1)
Cough	0	0	0	4 (3.9)	13 (8.7)
Hypoxemia	0	1 (0.6)	0	14 (13.6)	26 (17.4)
Hypotension	2 (2.0)	3 (1.9)	1 (1.9)	2 (1.9)	12 (8.1)

Summary of Serious Adverse Events

- Reported SAEs in fospropofol subjects
  - 58/1611 (3.6%)
- Colonoscopy (Study 0522)
  - 2.0 mg/kg 1/102 (1.0%)
  - 6.5 mg/kg 0/158
  - Midazolam 1/52 (1.9%)
- Bronchoscopy (Study 0524)
  - 2.0 mg/kg 13/103 (12.6%)
  - 6.5 mg/kg 16/149 (10.7%)

Serious Adverse Events Within 24 Hrs of Fospropofol Exposure

Study 0524 Bronchoscopy

Preferred term	Patients, n (%) Fospropofol (mg/kg) 2.0 N = 103	6.5 N = 149
Bronchitis acute (worsening)	0	1 (0.7)
Chronic obstructive pulmonary disease (exacerbation)	1 (1.0)	2 (1.3)
Hypoxemia	0	1 (0.7)
Lung infection pseudomonas	0	1 (0.7)
Lung neoplasm malignant	0	2 (1.3)
Lung squamous cell carcinoma	0	1 (0.7)
Pneumothorax	1 (1.0)	0

Summary of Deaths

- Ten deaths occurred in clinical program
- No death considered related to study drug
- Five deaths in ICU ventilator study (prolonged exposure)
  - One patient received propofol lipid emulsion only
  - Critically ill patients
  - Related to underlying disease
  - 1 to 31 days post exposure to drug
- Five deaths occurred in phase 3 bronchoscopy study
  - Related to underlying disease
  - 4 to 23 days post exposure to drug

Deaths in Phase 3 Bronchoscopy Study 0524

Demographics (age, sex, ASA)	Medical history	Randomized fospropofol dose	Primary cause of death	Interval from dose to **onset** of fatal event
46, Male, ASA P2	HIV, Cryptococcal Meningitis	6.5 mg/kg	Anoxic encephalopathy	3 days
61, Male, ASA P4	Lung cancer, endobronchial stent, liver metastases	2.0 mg/kg	Respiratory arrest	11 days
67, Male, ASA P2	Metastatic prostate cancer, neutropenia 2^0 to chemotherapy, sepsis	2.0 mg/kg	Septic shock	17 days
77, Male, ASA P3	Lung cancer, pulmonary embolism	6.5 mg/kg	Malignant lung neoplasm	Lung cancer diagnosed during bronchoscopy (Died 19 days later)
70, Female, ASA P2	Lung cancer, pneumonia	6.5 mg/kg	Pneumonia	Lung cancer diagnosed during bronchoscopy (Died 23 days later)

Definitions of Sedation-Related Adverse Events

Event	Definition
Apnea	Lack of spontaneous breathing > 30 sec
Hypoxemia	O_2 saturation < 90% for > 30 sec
Hypotension	Systolic BP < 90 mm Hg and required medical intervention
Bradycardia	Heart rate < 50 beats per minute and required medical intervention

Sedation-Related Adverse Events
Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Patients with ≥ 1 SRAE	2 (2.0)	3 (1.9)	1 (1.9)	13 (12.6)	30 (20.1)†
Apnea	0	0	0	0	1 (0.7)
Hypoxemia	0	1 (0.6)	0	13 (12.6)	23 (15.4)
Hypotension	2 (2.0)	2 (1.3)	1 (1.9)	0	8 (5.4)‡
Bradycardia	0	0	0	0	0

† 1 patient experienced apnea, hypoxemia, and hypotension.
‡ 2 of 8 treated with airway assistance; 6 of 8 treated with IV fluids.

Airway Assistance for Sedation-Related Adverse Events

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
Patients with ≥ 1 type of airway assistance†	0	1 (0.6)	0	11 (10.7)	25 (16.8)
Increased O_2 flow	0	0	0	11 (10.7)	21 (14.1)
Patient repositioning	0	0	0	0	2 (1.3)
Tactile/Verbal stimulation	0	1 (0.6)	0	2 (1.9)	6 (4.0)
Face mask (100% O_2)	0	0	0	1 (1.0)	0
Jaw thrust	0	0	0	2 (1.9)	2 (1.3)
Chin lift	0	0	0	0	3 (2.0)
Nasal trumpet	0	0	0	0	0
Oral airway	0	0	0	0	0
Suction	0	0	0	0	2 (1.3)
Manual ventilation (bag-valve-mask)	0	0	0	0	1 (0.7)
Mechanical ventilation (intubation)	0	0	0	0	0

† Some patients may have received more than 1 type of airway assistance.

Sedation-Related Adverse Events by Subgroup at Proposed Dosage Regimen

Study 0522 Colonoscopy

	Patients, n/N (%)
Age, yrs	
18 - < 65	4/137 (2.9)
≥ 65	0/21
≥ 75†	0/4
ASA	
P1/2	3/153 (2.0)
P3	1/5 (20.0)
P4	0
Weight, kg	
< 60	1/9 (11.1)
60 - < 90	2/86 (2.3)
≥ 90	1/63 (1.6)

† Patients in the ≥ 75 yrs category are also included in the ≥ 65 yrs category.

Sedation-Related Adverse Events by Subgroup at Proposed Dosage Regimen

Study 0524 Bronchoscopy

	Patients, n/N (%)
Age, yrs	
18 - < 65	17/87 (19.1)
≥ 65	16/60 (26.7)
≥ 75†	7/19 (36.8)
ASA	
P1/2	19/81 (23.5)
P3	13/61 (21.3)
P4	1/7 (14.3)
Weight, kg	
< 60	7/27 (25.9)
60 - < 90	16/81 (19.8)
≥ 90	10/41 (24.4)

† Patients in the ≥ 75 yrs category are also included in the ≥ 65 yrs category.

Patients who Reached MOAA/S Scores of 1 or 0 at any time

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Patients, n (%)				
	Colonoscopy			Bronchoscopy	
	Fospropofol mg/kg		Midazolam mg/kg	Fospropofol mg/kg	
	2.0 N = 102	6.5 N = 158	0.02 N = 52	2.0 N = 103	6.5 N = 149
MOAA/S 1	1 (1.0)†	3 (1.9)†	0	8 (7.8)†	22 (14.8)§
MOAA/S 0	0	5 (3.2)‡	0	0	3 (2.0)
MOAA/S 0 or 1	1 (1.0)	6 (3.8)	0	8 (7.8)	24 (16.1)

† All patients went to MOAA/S 1 or 0 after receiving midazolam as an alternative sedative.
‡ 4/5 patients went to MOAA/S 1 or 0 after receiving midazolam as an alternative sedative.
§ 1/22 patients went to MOAA/S 1 or 0 after receiving midazolam as an alternative sedative.

Airway Assistance for Sedation-Related AEs in Patients with MOAA/S 1 or 0

Study 0522 Colonoscopy, 0524 Bronchoscopy

Sedation-related AE Airway assistance	Patients, n (%) Fospropofol 2.0 & 6.5 mg/kg MOAA/S 1 N = 34	 MOAA/S 0 N = 8
Patients with ≥ 1 sedation-related AE†	11 (32.4)	3 (37.5)
Apnea	1 (2.9)	0
Tactile stimulation	1 (2.9)	0
Chin lift	1 (2.9)	0
Hypoxemia	10 (29.4)	3 (37.5)
Increased oxygen flow	10 (29.4)	2 (25.0)
Patient repositioning	2 (5.9)	0
Verbal stimulation	1 (2.9)	1 (12.5)
Jaw thrust	3 (8.8)	0
Suction	1 (2.9)	0
Manual ventilation	1 (2.9)	1 (12.5)
Hypotension	2 (5.9)	0
Verbal/tactile stimulation	1 (2.9)	0
Chin lift	1 (2.9)	0

† 1 patient experienced apnea, hypoxemia, and hypotension.

Procedures Performed in Minor Procedures Study 0523

Procedure	Patients, n (%) Fospropofol 6.5 mg/kg N = 123
Esophagogastroduodenoscopy	27 (22.0)
Arthroscopy	22 (17.9)
Hysteroscopy	21 (17.1)
Bunionectomy	18 (14.6)
Transesophageal echocardiogram	13 (10.6)
Ureteroscopy	10 (8.1)
Lithotripsy	8 (6.5)
Dilatation & Curettage	3 (2.4)
Arteriovenous shunt	1 (0.8)

Summary of Adverse Events in Minor Procedures Study 0523

	Patients, n (%)
	Fospropofol 6.5 mg/kg N = 123
Treatment-emergent AEs	111 (90.2)
Severe TEAEs	11 (8.9)
Serious AEs	4 (3.3)
Related SAEs	0
Sedation-related AEs	5 (4.1)
SRAEs requiring airway assistance	1 (0.8)†

† Hypoxemia.

Summary of Airway Assistance For Sedation-Related Adverse Events at 6.5 mg/kg

Study 0522 Colonoscopy, 0523 Minor Procedures, 0524 Bronchoscopy

Sedation-related AE Airway assistance	Colonoscopy N = 158	Minor procedures N = 123	Bronchoscopy N = 149
Apnea	0	0	1 (0.7)
Tactile stimulation	0	0	1 (0.7)
Chin lift	0	0	1 (0.7)
Hypoxemia	1 (0.6)	1 (0.8)	23 (15.4)
Increased O_2 flow	0	0	21 (14.1)
Patient repositioning	0	0	2 (1.3)
Tactile/verbal stimulation	1 (0.6)	1 (0.8)	6 (4.0)
Face mask	0	0	1 (0.7)
Jaw thrust	0	0	2 (1.3)
Chin lift	0	1 (0.8)	3 (2.0)
Suction	0	0	2 (1.3)
Manual ventilation (bag-valve-mask)	0	0	1 (0.7)
Hypotension	0	0	2 (1.3)
Increased O_2 flow	0	0	1 (0.7)
Verbal stimulation	0	0	1 (0.7)

Experience with Higher Fixed Doses ~ 2 times the Proposed Dose of 6.5 mg/kg

- Fixed dose studies included initial bolus doses based on 3 different weight groups
  - 241/556 (43.3%) received initial bolus dose ≥ 11 mg/kg
  - 249/556 (44.9%) received initial bolus dose between 8 and 11 mg/kg
- 11 mg/kg bolus dose is equivalent to an initial bolus dose of 6.5 mg/kg + 3 supplements given simultaneously

Sedation-Related Adverse Events in Higher Fixed Dose Studies

- Incidence of SRAEs
  - Apnea: 16/556 (2.9%)
  - Hypoxemia: 97/556 (17.4%)
- Airway assistance
  - Most were simple maneuvers (increased O_2, verbal/tactile stimulation, chin lift)
  - 8 (1.4%) patients with manually assisted ventilation, and 1 (0.2%) patient with intubation
  - All managed by the physician
- No long-term sequelae for patients who received high fixed doses of fospropofol

Safe Sedation with Fospropofol by Nonanesthesia Professionals

- Administration of fospropofol by the proposed dose titration regimen provides safe sedation in a range of patients
  - Age, ASA status, and weight

  Undergoing a range of procedures
  - Colonoscopy, minor procedures, bronchoscopy

  In settings where procedural sedation is performed
  - Hospitals, ambulatory surgical centers, and office practices

Safe Sedation with Fospropofol by Nonanesthesia Professionals

- Sedation-related adverse events were manageable by the nonanesthesia professionals performing these studies
  - Most events were managed with simple airway maneuvers (increased oxygen flow, verbal/tactile stimulation, chin lift)
  - No patient experienced sequelae

Safe Sedation with Fospropofol by Nonanesthesia Professionals in Clinical Studies

- Nonanesthesia professionals utilized fospropofol to provide safe sedation for patients by ensuring
  - Pre-procedure patient evaluation
  - Appropriate dosing and titration to effect
  - The presence of a designated health care professional, not performing the procedure, who monitored patients

Package Insert Aligned with ASA Guidelines

- Appropriate patient assessment
  - Suitability for procedural sedation
  - Determine which patients require an anesthesia professional
- Appropriate dose selection
  - Dose reductions
- Designated health care professional to monitor
  - Responsiveness, ventilatory effort, oxygen saturation, hemodynamics

American Society of Anesthesiologists, Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists; Anesthesiology; 2002.

Agenda

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Clinical Pharmacology	**Stephen J. Waters, PhD** VP Science & Technology, MGI PHARMA, INC.
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Clinical Safety	**Michael T. Cullen, MD** Chief Medical Officer, MGI PHARMA, INC.
Risk/Benefit Summary	**John B. Leslie, MD** Consulting Professor of Anesthesiology Mayo Clinic, Scottsdale, AZ
Conclusion	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.

Benefit/Risk Assessment

John B. Leslie, MD MBA

Professor of Anesthesiology
Mayo Clinic College of Medicine
Mayo Clinic Hospital, Scottsdale

AQUAVAN Proposed Indication

- AQUAVAN is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures

Benefits of Sedation with Fospropofol

- Pro-drug approach provides
  - For gradual increase in plasma propofol concentration and onset of sedation
  - Benefits of propofol wake up experience
- Pro-drug propofol approach avoids
  - Pain on injection
  - Risk for contamination associated with lipid carrier

Benefits of Sedation with Fospropofol

- Successful procedural sedation experience
  - Successful sedation: 88 to 95%
  - Few procedure or drug discontinuations
  - Rate of sedation related adverse events that is in line with the experience and expectations of those performing procedural sedation
- Rapid sedation recovery experience
  - Median time to fully alert: 5 min
  - Median time to Aldrete ≥ 9: < 10 min
  - Potential for reduced duration of monitoring and burden on patient care team

Benefits of Sedation with Fospropofol

- Most patients did not recall
  - Being awake during the procedure
  - Pain or discomfort
  - Disagreeable aspects of the procedure
- High level of patient and physician satisfaction with the drug and sedation experience using the proposed dosing regimen
  - 95% of patients would receive fospropofol again
  - Physicians rated it 9 out of 10 on satisfaction scale

Risks of Sedation with Fospropofol

- Sedation related AEs
  - Apnea, hypoxia, hypotension, bradycardia
- Requirement for
  - Pre-procedure patient evaluation
  - Appropriate dosing and monitoring

Target Sedation Level: Minimal to Moderate

	Minimal sedation (Anxiolysis)	*Moderate Sedation/ Analgesia ("Conscious Sedation")*	*Deep Sedation/ Analgesia*	*General Anesthesia*
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimuli
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

** Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

Anesthesiology 2002;96:1004-17 – Amended Oct 2004.
http://www.asahq.org/publicationsAndServices/sgstoc.htm

Risks of Sedation with Fospropofol

Sedation-related adverse events

- Dose regimen based on ASA status, weight and age
- Dose adjustments based on patient parameters and purposeful response (thumbs up)
- Severely compromised and medically unstable patients

Risks of Sedation with Fospropofol

- No reversal agent
- Appropriate dosing
  - Sedation onset less rapid
  - 4-min dose interval
  - Need for additional doses to control patient
  - Propofol wake-up experience, but not propofol onset of action

Addressing the Risks

- Preprocedure patient evaluation
  - Good clinical practice
  - Exclude patients with difficult airways
  - Exclude patients who are medically unstable or severely compromised
- Physician who is adept at performing minimal to moderate sedation in the patient population they routinely treat.

Addressing the Risks

Minimization of misdosing in clinical practice

- Appropriate labeling that is aligned with ASA guidelines for minimal to moderate sedation
- Dosing cards and charts clarifying modified dosing and dosing time intervals
- Fospropofol specific training and support materials for associations and proceduralists
- Support of training programs provided by professional associations that will train nonanesthesia professionals to perform minimal to moderate sedation

Regulatory Approval of Fospropofol

- Approval of fospropofol is not a substitute for MAC sedation
  - Severely compromised and medically unstable patients should receive MAC sedation
  - Patients who desire and need the services of anesthesia professionals should receive this care
- Fospropofol should be utilized by physicians who are skilled in providing minimal to moderate sedation to the population they treat on a routine basis

Conclusions: Benefits vs Risks for Fospropofol

- Sedative agent that can be safely administered by nonanesthesia professionals to provide minimal to moderate sedation of patients undergoing procedures
- The proposed dosing regimen optimizes the balance of safety and efficacy
- Fospropofol is a valuable and needed addition to the procedural sedation armamentarium

Introduction	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.
Medical Need	**Lawrence B. Cohen, MD** Associate Clinical Professor Mount Sinai Hospital, New York, NY
Clinical Pharmacology	**Stephen J. Waters, PhD** VP Science & Technology, MGI PHARMA, INC.
Clinical Efficacy	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.
Clinical Safety	**Michael T. Cullen, MD** Chief Medical Officer, MGI PHARMA, INC.
Risk/Benefit Summary	**John B. Leslie, MD** Consulting Professor of Anesthesiology Mayo Clinic, Scottsdale, AZ
Conclusion	**Jacqueline M. Kline, PhD** Director Regulatory Affairs, MGI PHARMA, INC.

Conclusions

Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Overall Conclusions

- Prodrug of propofol with gradual onset and titratable, dose-related depth of sedation
- Successfully achieves moderate sedation, enabling completion of procedures
- SRAEs as expected and easily managed by proceduralists without sequelae
- Benefit/Risk clearly positive for use by nonanesthesiologists
- Important addition to the moderate sedation armamentarium

Purposeful Response

- Reliable indicator of depth of sedation
  - Virtually 100% of purposeful responses occurred during minimal to moderate sedation
- Important component of overall patient condition to guide supplemental dosing
  - Must be considered in context of overall patient status

Populations of Special Interest

- At the recommended dose sedation success met by all subgroups and SRAEs were managed using basic airway maneuvers
- Geriatric patients
  - Known to be more susceptible to SRAEs
  - Studied at and above recommended doses
  - Experience with fospropofol consistent with other agents
- Cardiopulmonary morbidities
  - Prospectively studied by ASA Physical Classification status
  - When controlled for procedure, no difference in rates of SRAEs
- Low body weight
  - Prospectively studied
  - Confounded by comorbidities
  - Well-founded based on clinical pharmacology

Safe Administration by Nonanesthesiology Professionals

- Safety of fospropofol in the hands of nonanesthesiologists is a testable proposition
- Data are compelling
  - Sedation and treatment success
  - Safety profile as expected
  - SRAEs manageable, even when misdosed at two times the recommended dose
- MGI Pharma/Eisai committed to safe implementation, consistent with existing guidelines

AQUAVAN® (fospropofol disodium) Injection Proposed Indication

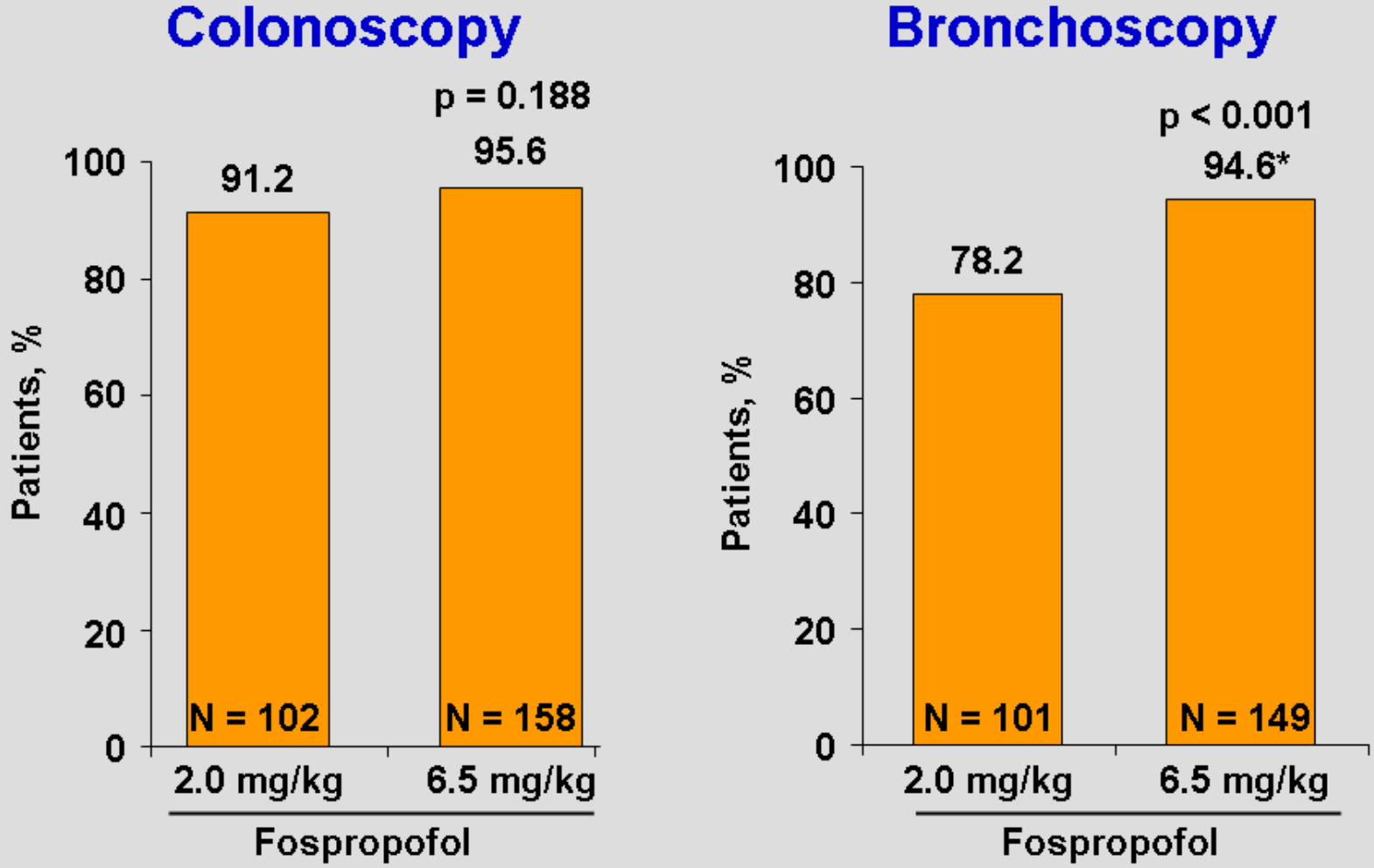
AQUAVAN is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures.

List of Additional Respondents

Joel V. Brill, MD, AGAF, FASGE, FACG, CHCQM	Assistant Clinical Professor of Medicine University of Arizona School of Medicine
Keith Candiotti, MD	Associate Professor of Clinical Anesthesiology and Medicine University of Miami, Jackson Memorial Hospital, Miami, FL
Lawrence B. Cohen, MD	Associate Clinical Professor Mount Sinai Hospital, New York, NY
John B. Leslie, MD	Consulting Professor of Anesthesiology Mayo Clinic, Scottsdale, AZ
Gerard Silvestri, MD, FCCP	Consulting Pulmonologist/Professor of Medicine Medical University of South Carolina

Patients Willing to Be Treated Again With Same Study Sedative

Study 0522 Colonoscopy, 0524 Bronchoscopy



*Statistically different from 2.0 mg/kg (Fisher's exact test).

Fospropofol Education Emphasis

- Pre-procedure patient assessment
  - ASA status
  - Airway difficulty
- Proper dosing and administration
  - 6.5 mg/kg bolus, 1.6 mg/kg supplemental
  - 4 min dosing interval
  - Dose reductions ≥ 65, ASA 3 & 4
- Monitoring expectations
  - Dedicated HCP only assisting in minor tasks
  - What to monitor

Sponsor Fospropofol Training

- Fospropofol intended for use by physicians routinely performing moderate sedation procedures
- Numerous societies and organizations publish sedation guidelines and/or offer sedation training
  - Upon approval, sponsor will proactively supply comprehensive, fospropofol information
  - Sponsor Medical Affairs will follow-up individually with more detailed discussions and collaboration
- Sponsor drug specific training initiatives will include
  - Dosing guidelines, patient assessment and monitoring tools, on-line resources, CME support, simulation training, educational programs and symposia, etc.

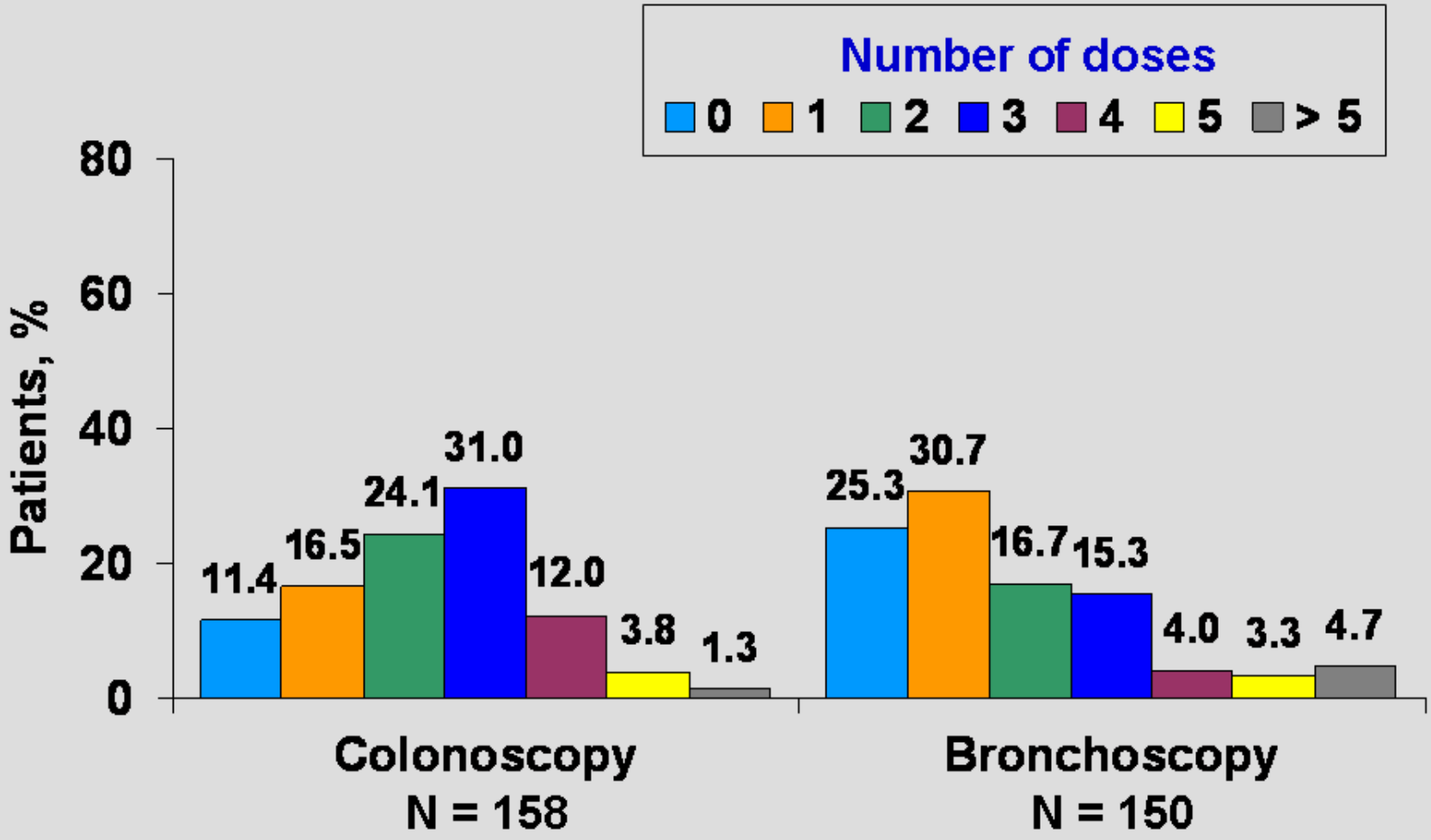
Fospropofol and Difficult Airways

- The exclusion of patients with difficult airways is consistent with ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists†
- Preprocedure patient assessment should identify whether patient is candidate for minimal to moderate sedation performed by nonanesthesiologists

*Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 2002; 96:1004-17.

Supplemental Doses of Study Sedative Medication Administered (6.5 mg/kg Dose)

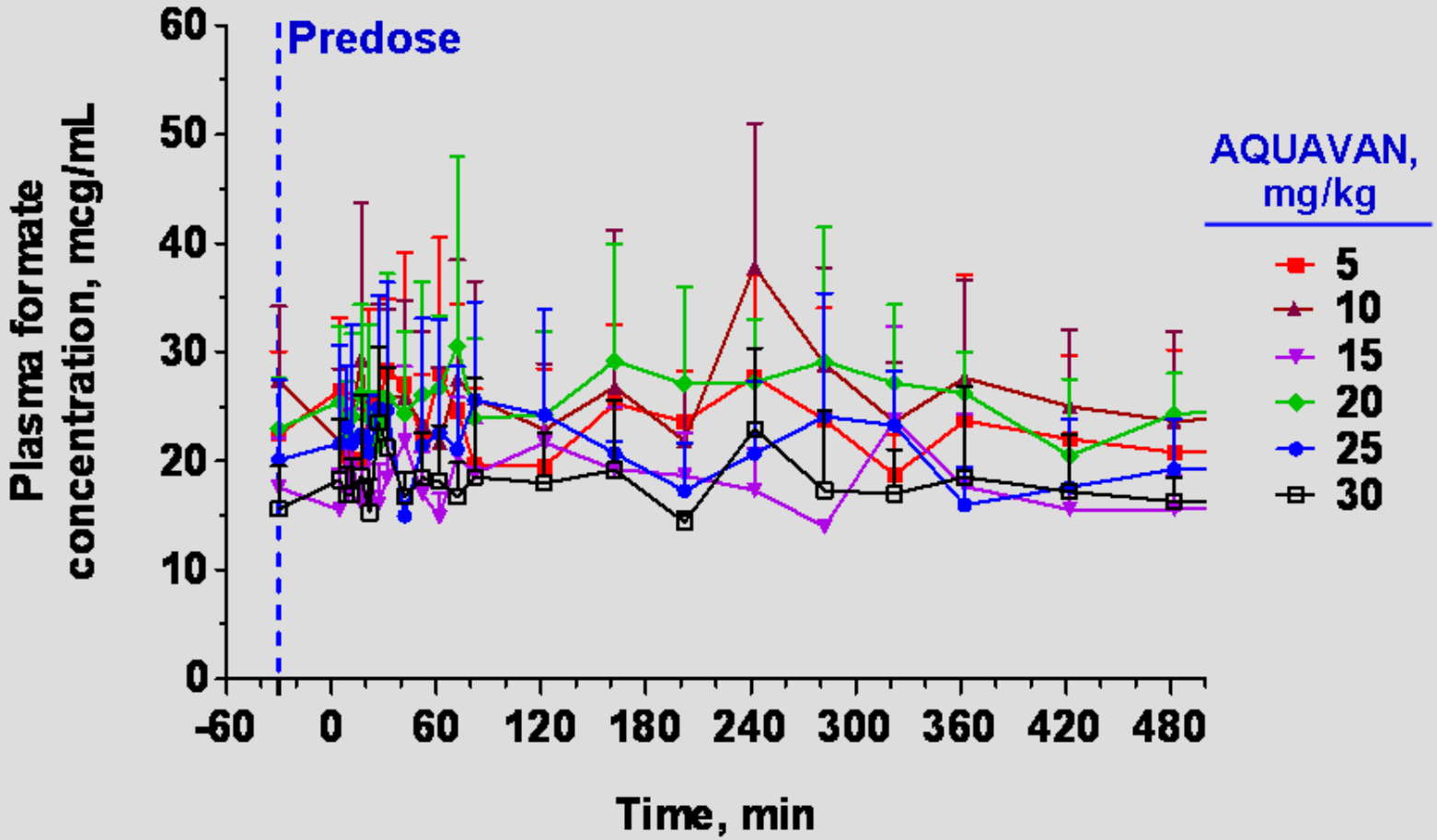
Study 0522 Colonoscopy, 0524 Bronchoscopy



Safety Profile of Patients with Moderate to Severe Hepatic Impairment and Severe Renal Impairment

	Patients, n (%)	
	Hepatic impairment N = 8	Renal impairment N = 7
Treatment-emergent AEs	5 (62.5)	6 (85.7)
Treatment-related AEs	5 (62.5)	4 (57.1)
Adverse events leading to airway assistance	1 (12.5)	0
Adverse events leading to discontinuation of procedure	0	0
Adverse events leading to discontinuation of study drug	0	0
Adverse events leading to discontinuation from the study	0	0
SAEs (treatment-emergent)	2 (25)	1 (14.3)
Deaths	1 (12.5)	0

Formate Plasma Concentrations
Study 0103

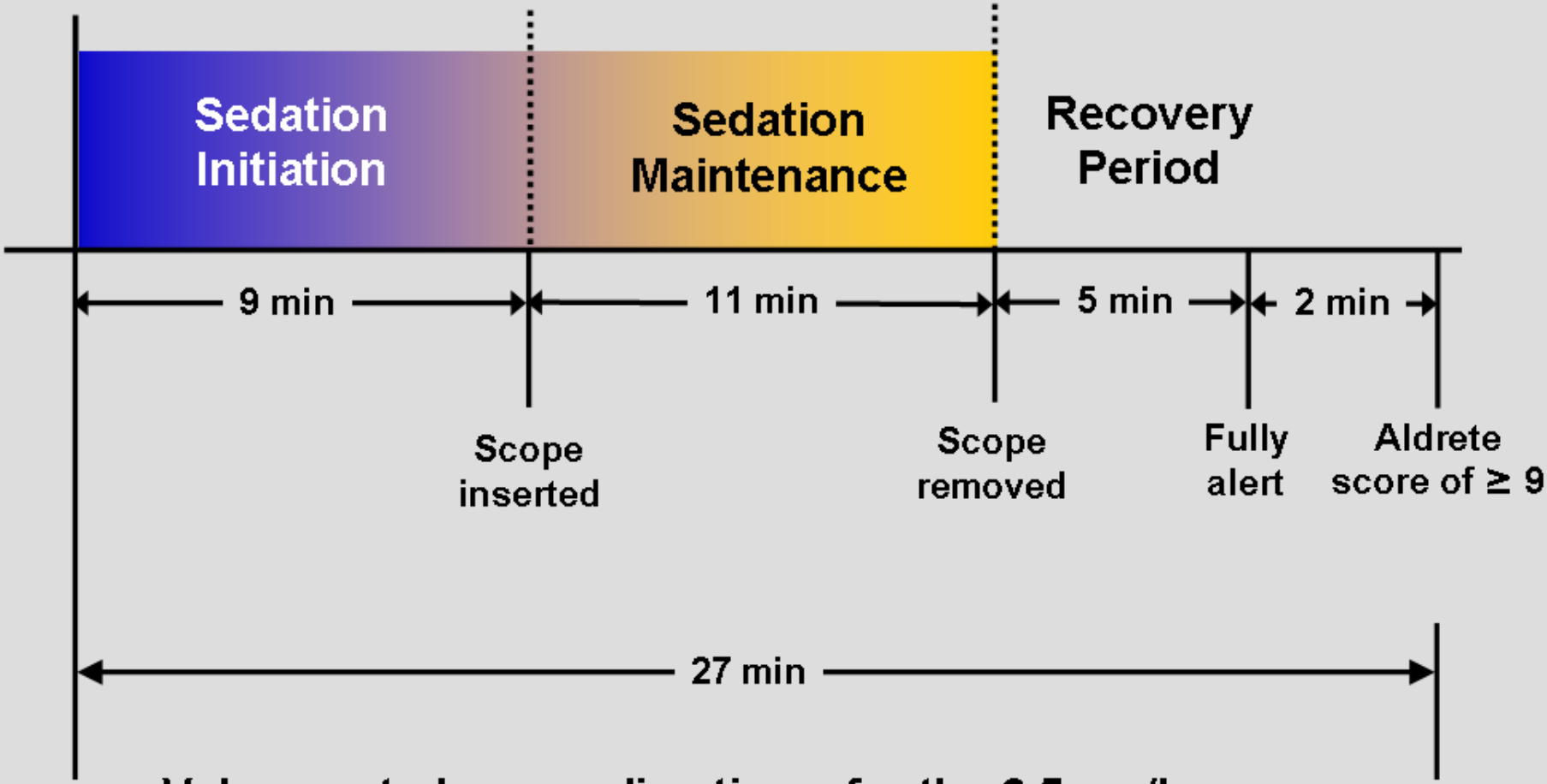


Mean ± SD (N = 6 subjects per dose).

Screening Failure
Study 0522 Colonoscopy

	Total, n (%)
Number of patients screened	345
Number of screen failures	31 (9.0)
Primary reason for screen failure	
Patient did not meet inclusion/exclusion criteria	2 (0.6)
Adverse events	0 (0.0)
Patient withdrew consent	15 (4.3)
Investigator's discretion	4 (1.2)
Other	10 (2.9)
Abnormal labs	2 (0.6)
Insurance reasons	2 (0.6)
Protocol related	4 (1.2)
Target enrollment reached	2 (0.6)

Time to Procedural Milestones
Study 0522 Colonoscopy



Values noted are median times for the 6.5 mg/kg group.

Hopkins Verbal Learning Test-Revised™ HVLT-R™

- Used to assess verbal learning and memory recall
- Initial test – 15 min after end of procedure
  - Patient listens to a series of 12 words and then recites as many as they can remember
  - Repeats 3 times in a row
  - No explanation that the patient will be retested at a later point
- 20 min later
  - Patient asked to recite as many words as they can recall
  - Patient listens to a series of words and indicates if they were on the original list

Retention Score—Hopkins Verbal Learning Test-Revised (HVLT-R™)—Recovery Period

Study 0522 Colonoscopy, 0524 Bronchoscopy

	Fospropofol mg/kg		Midazolam mg/kg
Retention percentage	2.0 N = 102	6.5 N = 158	0.02 N = 52
Study 0522	n = 102	n = 158	n = 51
mean ± SD	59.2 ± 36.3	67.0 ± 33.2	41.0 ± 32.0
Retention percentage	2.0 N = 102	6.5 N = 150	N/A
Study 0524	n = 98	n = 145	
mean ± SD	63.6 ± 42.3	64.2 ± 51.7	

Sedation-Related Adverse Event Rate per 100 Patient-minute Exposure of Purposeful Response

Studies 0520, 0522, 0524 (6.5 mg/kg)

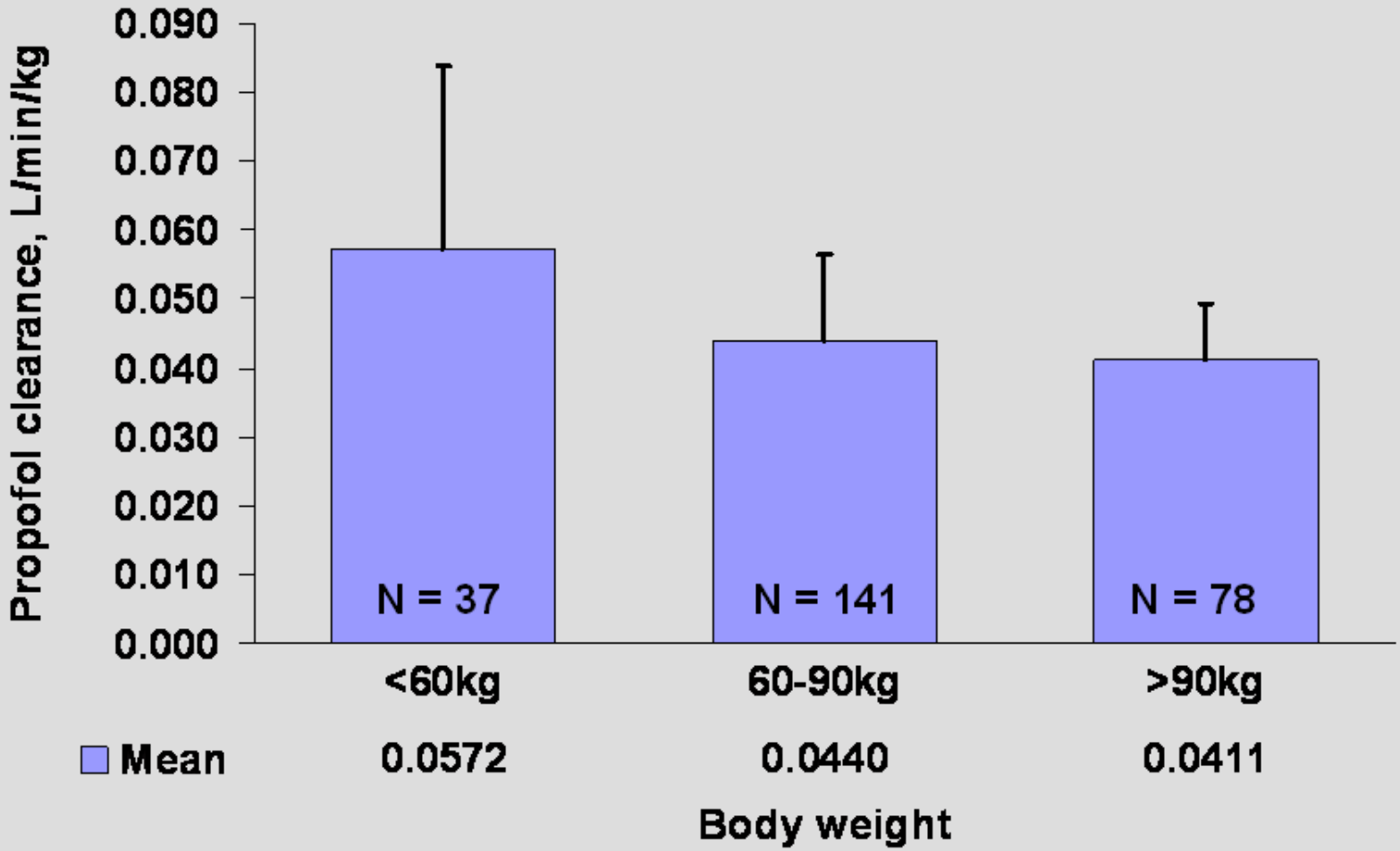
SRAE requiring management	No purposeful response			Purposeful response		
	Exposure	Events	Rate	Exposure	Events	Rate
Any	1156	12	1.04	19032	49	0.25
Apnea		0	0		1	0.01
Hypotension		4	0.35		14	0.07
Hypoxia		8	0.69		34	0.18

Exposure is measured by minutes. All SRAE are time-matched with purposeful/no purposeful response.

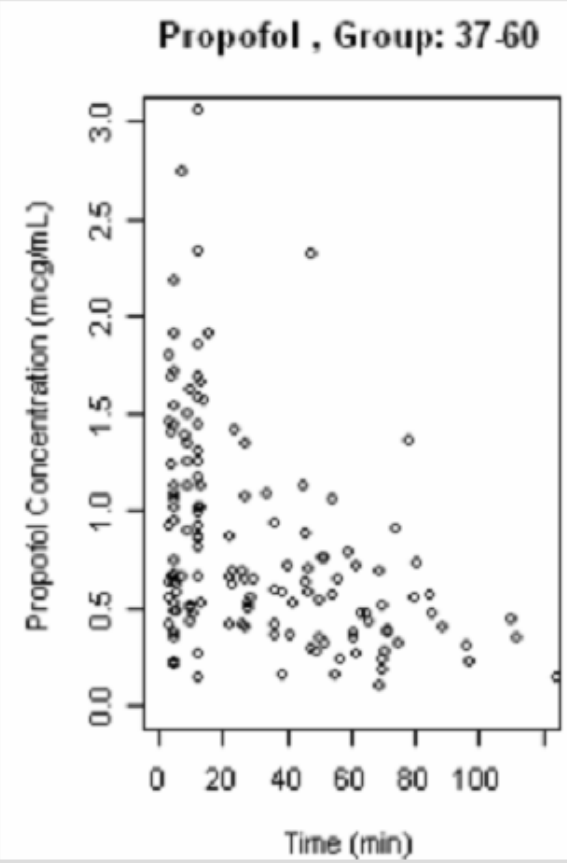
Post Marketing Surveillance

- Clinical Outcomes Research Initiative (CORI)
  - Leading endoscopic research/data repository
  - 86 sites—community and academic
  - Created to study outcomes and practice patterns of endoscopic procedures in "real life" setting
- Sponsor will work with CORI to assess fospropofol patterns of use
  - Feedback for training
  - Compare in market use with clinical trial outcomes
  - Rapid detection of safety issues should they arise

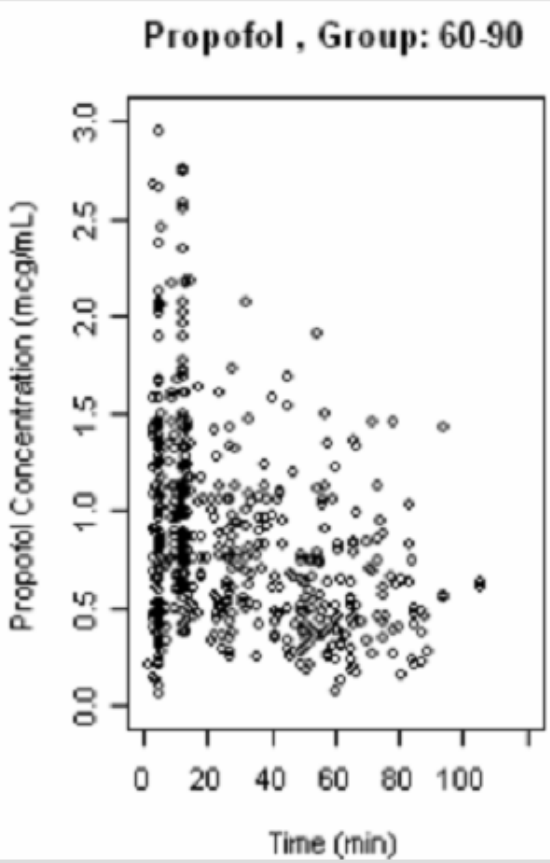
Propofol Clearance vs Weight



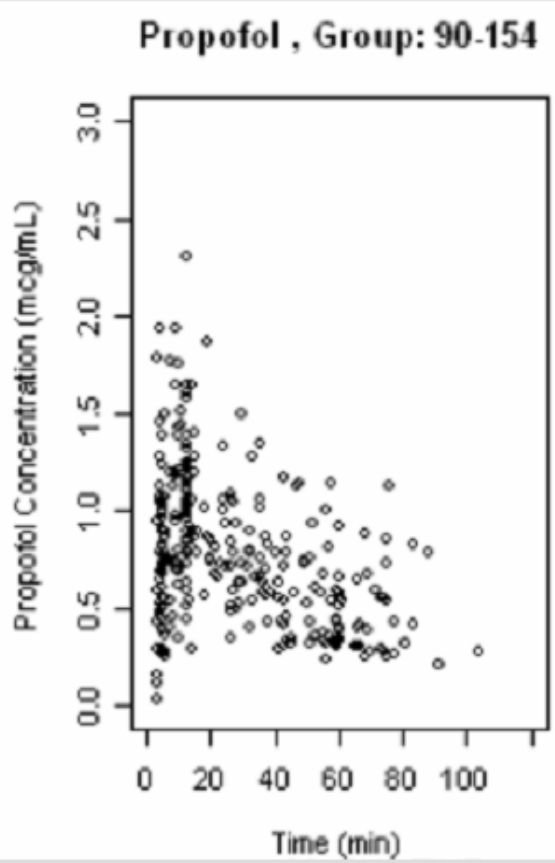
Observed Plasma Propofol Concentrations by Weight Groups (Studies 0522, 0523, 0524) 6.5 mg/kg



N = 37



N = 141



N = 78

Drug Interaction Study (Healthy Volunteers)
Study 0414

- Randomized, double-blind, placebo-controlled, single-center, parallel-design study
- Designed to estimate the adjustment in the cumulative dose of fospropofol required to achieve targeted sedative effect when preceded by typical medications used for minimal-to-moderate sedation
- Initial fospropofol dose 8 mg/kg (N = 60)
- Supplemental fospropofol dose 2 mg/kg (up to 4)
- Placebo (N = 12); Fentanyl 1 mcg/kg (N = 12); Midazolam 0.01 mg/kg (N = 12); Meperidine 0.75 mg/kg (N = 12); Morphine 0.1 mg/kg (N = 12)
- Plasma concentrations and PK parameters for fospropofol were similar in all treatment groups
- Comparisons among placebo and active premedication groups showed no overall statistically significant effect of premedication on the cumulative dose of fospropofol

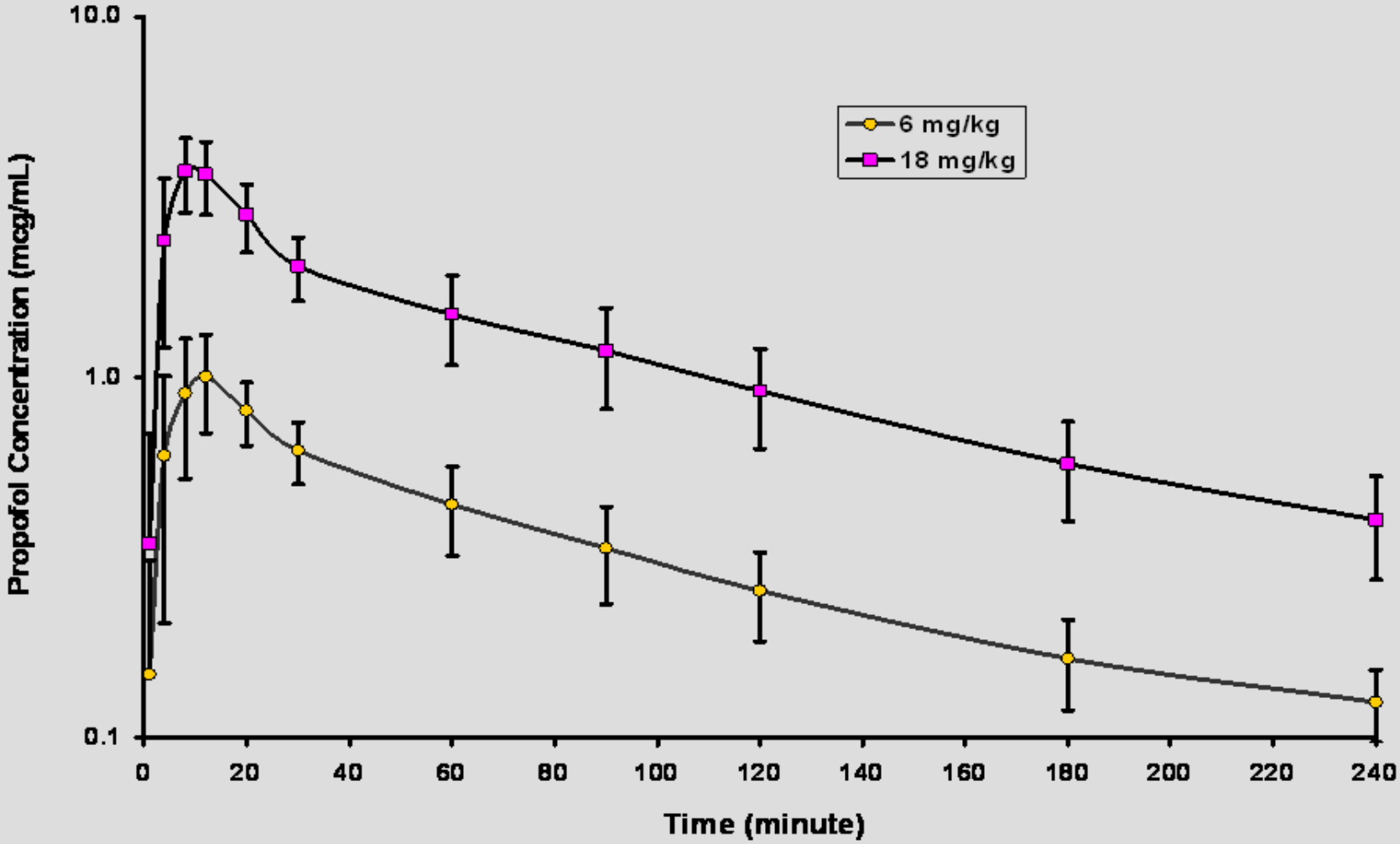
Fospropofol PK and PK-PD Results

- Inter-individual variability
  - Plasma concentration and PK parameter variability is low (coefficient of variation < 30%)
- Dose proportionality
  - C_{max} and AUC proportional over a wide range of doses (6 - 18 mg/kg) in subjects and in patients
- Bioavailability
  - Complete metabolic conversion of fospropofol to propofol based on metabolism and clearance studies
- Pharmacodynamics
  - Propofol PK-PD relationship independent of source; EC_{50} value consistent with propofol literature

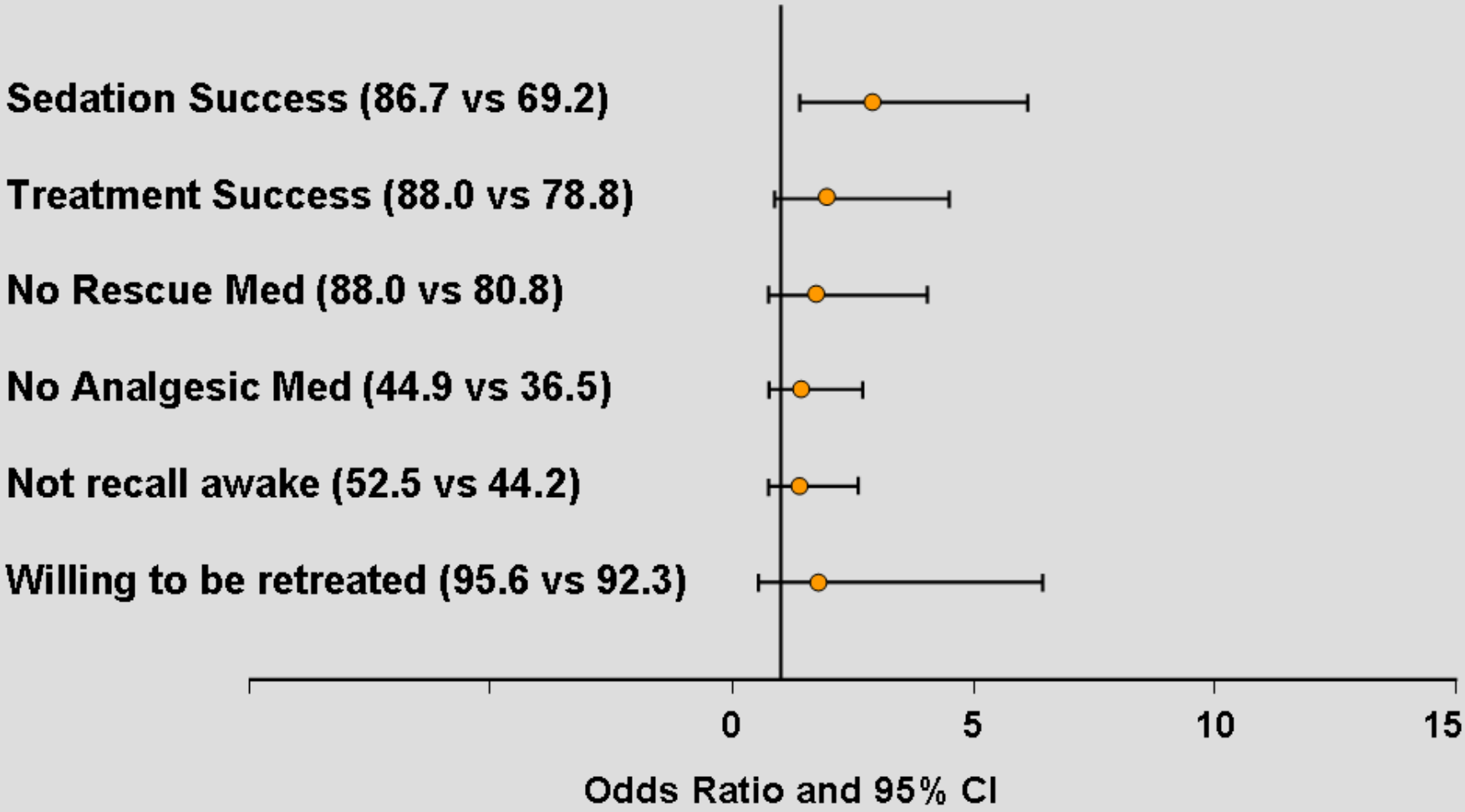
PK and PK-PD Presentations

- Differential PK/PD of Propofol After Intravenous Fospropofol and Diprivan® in Healthy Subjects. Shah, Fechner, Struys and Mistry. Presented at the 2007 American Society of Anesthesiologists Annual Meeting; October 13–17, 2007
- Fospropofol Intravenous Injection for Procedural Sedation: A Population Pharmacokinetic Model. Shah and Gibiansky. Presented at the 2007 American Society of Anesthesiologists Annual Meeting; October 13–17, 2007
- Assessment of Dose Proportionality and Gender Differences in Pharmacokinetics (PK) of Fospropofol (FP) and Propofol (PFP) Following IV Administration of FP in Healthy Subjects. Mistry and Shah. Presented at American Association of Pharmaceutical Scientists; November 11–15, 2007
- Pharmacokinetic-Pharmacodynamic Study of Fospropofol Injection versus Propofol in Healthy Volunteers: Results of an Open-Label, Single-Dose Crossover Study. Shah, Fechner, Struys and Mistry. Presented at the American Society of Health-System Pharmacists Midyear Clinical Meeting; December 2-6, 2007
- Gibiansky, Gastonguay, and Shah. Simultaneous Population Pharmacokinetic–Pharmacodynamic Modeling of Fospropofol Injection (Propofol Prodrug) and Propofol Emulsion in Healthy Volunteers. Gibiansky, Gastonguay, and Shah. Presented at American Conference on Pharmacometrics, March 9-12, 2008

Plasma Propofol Concentrations
Study 3000-0521

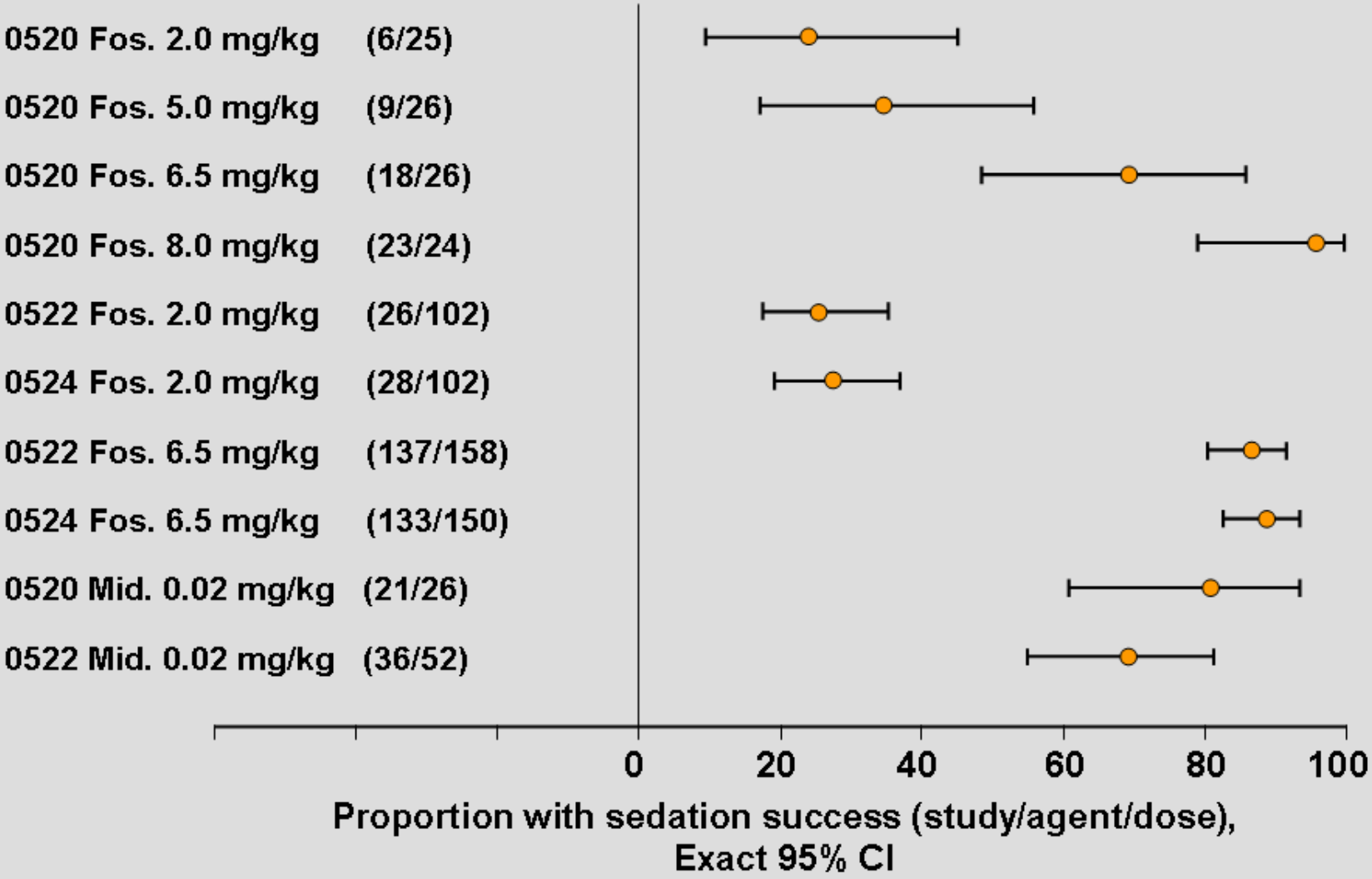


Fospropofol 6.5 mg/kg vs Midazolam 0.02 mg/kg
Primary and Secondary Endpoints
Study 0522 Colonoscopy



Sedation Success – 95% CI

Study 0520, 0522, 0524



"Sufficient Sedation"?

- Studies 0522 and 0524
  - Designed for 2.0 vs 6.5 mg/kg comparison
  - Easy bar, robust P values observed
- Has "sufficient sedation" been observed?
  - Refer to external standards
  - Midazolam arm provides internal sedation reference