CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/Serial Number:	22-244 / 00
Drug Name:	Fospropofol disodium
Indication(s):	sedation in adult patients undergoing diagnostic or therapeutic procedures
Applicant:	MGI Pharma
Date(s):	Letter date: 10/1308
	PDUFA date: 12/12/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
	Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Clinical Team:	Medical Officer: Lex Schultheis, M.D.
	Medical Team Leader: Rigoberto Roca, M.D.
Project Manager:	Allison Meyer

Keywords: New Molecular Entity; NDA review; complete response to NA letter

A new drug application for fospropofol was originally submitted on September 27, 2007 and contained efficacy results from three clinical studies. My statistical review of that application was completed on June 10, 2008. The conclusion was that there was sufficient evidence of efficacy for the 6.5 mg/kg dose of fospropofol disodium for the indication of sedation in adults undergoing diagnostic or therapeutic procedures.

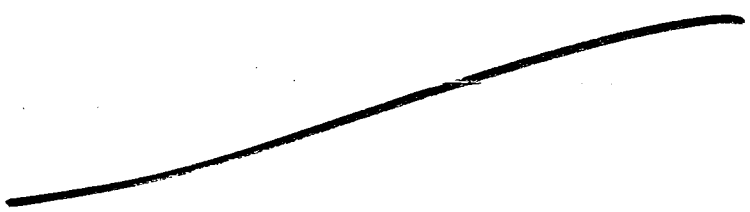
The applicant received a Not Approvable letter on July 23, 2008 from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). The Not Approvable letter specified that the label needed to be revised to adequately inform prescribers about sedating patients with fospropofol. On October 13, 2008, the applicant submitted a complete response with new proposed labeling, but no other changes or new information. My assessment of the clinical efficacy remains the same as in my June, 10, 2008 review of the clinical studies.

The applicant's revised proposed label reports the results from the analysis in the Clinical Studies section. The study design, patient population, and endpoints for the three efficacy studies are appropriately described. I have the following suggestions regarding the reporting of the results:

1.

2.

3.



b(4)

Signatures/Distribution List Page

Katherine B. Meaker, M.S.
Mathematical Statistician

Dionne Price, Ph.D.
Team Leader

Thomas Permutt, Ph.D.
Division Director

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine Meaker
11/25/2008 04:01:35 PM
BIOMETRICS

Dionne Price
11/25/2008 04:33:00 PM
BIOMETRICS
concur

Thomas Permutt
11/25/2008 05:00:12 PM
BIOMETRICS
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-244 / 00
Drug Name:	Fospropofol disodium
Indication(s):	sedation in adult patients undergoing diagnostic or therapeutic procedures
Applicant:	MGI Pharma
Date(s):	Letter date: 9/26/07
	PDUFA date: 7/26/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
	Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Clinical Team:	Medical Officer: Lex Schultheis, M.D.
	Medical Team Leader: Rigoberto Roca, M.D.
Project Manager:	Allison Meyer

Keywords: New Molecular Entity; NDA review

Appears This Way
On Original

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

This application requests consideration of one dose of fospropofol disodium (6.5 mg/kg) for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures. The applicant conducted a dose response study and two confirmatory controlled clinical studies to support the efficacy of fospropofol disodium for use in sedation in adult patients undergoing diagnostic or therapeutic procedures. In all three studies, the results for the fospropofol disodium 6.5 mg/kg dose group demonstrated efficacy as measured by the higher proportion of patients meeting the sedation success criteria. The efficacy of fospropofol disodium 6.5 mg/kg was also evident for secondary endpoints evaluating treatment success, patients' memory of being awake during the procedure, physician satisfaction with the level of sedation, and time to being fully alert after the procedure.

The efficacy and safety results were presented to the Anesthetic and Life Support Drugs Advisory Committee on May 7, 2008. The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) sought advice on the treatment settings, personnel and monitoring appropriate for safe use of fospropofol disodium, if approved. The feedback from the committee members suggested approval with limitations for use similar to propofol (Diprivan®).

1.2 Brief Overview of Clinical Studies

This application includes data from three prospectively planned, controlled, randomized, double-blind clinical studies. A Phase 2 dose response study (Study #520) in patients undergoing colonoscopy included five treatment arms: four doses of fospropofol disodium (2, 5, 6.5, and 8 mg/kg) and a midazolam arm. Based on this study, the 6.5 mg/kg dose was selected as the effective dose for the confirmatory trials and the 2 mg/kg dose was selected as a lower dose active comparator. The Phase 3 study in colonoscopy patients (Study #522) included three treatment arms: fospropofol disodium 2 mg/kg, fospropofol disodium 6.5 mg/kg, and midazolam. In each of these studies, the midazolam arm was included for general information and was not planned or intended for efficacy comparisons. The Phase 3 study in patients undergoing a flexible bronchoscopy (Study #524) included the same two fospropofol disodium doses but did not include a midazolam arm.

In all three studies, the primary endpoint was defined as the sedation success rate. Success required that four criteria be met: (i) 3 consecutive Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scores ≤ 4 after administration of sedative medication and (ii) completing the procedure (iii) without requiring the use of alternative sedative medication and (iv) without requiring manual or mechanical ventilation. The MOAA/S scale has six levels (scores 0-5). A score of 0 denotes non-responsive and 5 denotes fully alert. Important secondary endpoints included treatment success, patients' memory of being awake during the procedure, physician satisfaction with the level of sedation, and time to fully alert after the procedure.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized, received at least one dose of study treatment and had at least one postdose clinical assessment. Only 6 randomized patients were not included in the mITT population (2 in study #522; 4 in study #524).

Support for efficacy was tested by the pairwise comparison of the fospropofol disodium 6.5 mg/kg group to the fospropofol disodium 2.0 mg/kg group. Fisher's Exact test was used for the primary efficacy endpoint.

1.3 Statistical Findings

In all three studies, the 6.5 mg/kg dose was statistically significantly better than the 2 mg/kg dose for the sedation success rate. Success rates in the fospropofol disodium 6.5 mg/kg groups ranged from 69% to 89%, compared to 24% to 28% in the fospropofol disodium 2 mg/kg groups. Additional secondary endpoints also supported efficacy for the 6.5 mg/kg dose. The results are presented in Tables 3, 6, and 9, for studies 520, 522, and 524 respectively, and provide sufficient information to conclude fospropofol disodium 6.5 mg/kg is efficacious for this indication.

2. Introduction

2.1 Overview

Fospropofol disodium is a new molecular entity and is not currently approved for any indication in the United States or other countries. It is an intravenous sedative-hypnotic agent and is a pro-drug of propofol.

The applicant is requesting approval for use in adult patients undergoing diagnostic or therapeutic procedures. The clinical studies assessed its use during two procedures: colonoscopy or bronchoscopy. These were performed in a procedure room, with a person trained in airway management and basic life support equipment immediately available.

The applicant has submitted a Phase 2 dose-response study and two Phase 3 studies to support this application. All three studies are randomized, double-blind, active-controlled, parallel arm studies in adult patients. My statistical review focuses on these three studies, referred to as 520, 522, and 524. The design, endpoints, and patient populations for these studies, and the clinical development plan, were discussed with DAARP at the End-of-Phase 2 meeting (March 31, 2004). The applicant followed the advice received at that meeting in the protocols.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path location \\cdsesub1\nonectd\N22244\N_000\2007-09-26. The information needed for this review was contained in modules 1, 2.5, and 5.3.5.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study 3000-0520 (conducted 8/05 to 10/05)

Design

Study 520 was a randomized, double-blind, parallel arm, multi-center study. This was a Phase 2 dose-response study with four dose levels of fospropofol disodium and an additional arm received midazolam, an approved product. The dose levels are shown in Table 1. The objective was to evaluate the trend for the four fospropofol disodium doses. No direct comparisons to the midazolam arm were planned, which was included as a safety reference therapy group, according to the applicant.

Patients were adults undergoing a colonoscopy procedure. Following pretreatment with fentanyl, an analgesic, patients were randomly assigned to one of the 5 treatment arms. The appropriate dose was prepared by a pharmacist and delivered to the procedure room. Thus, all clinical assessors remained blinded to the dose being administered. The treatment was administered via i.v. infusion, with an initial bolus dose followed by up to 4 supplemental doses as needed to achieve a MOAA/S sedation score ≤4. If adequate sedation was not reached, an alternative sedative medication was used, and the patient was classified as a failure for sedation success.

The primary endpoint was the sedation success rate. This was defined as (i) 3 consecutive Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scores ≤ 4 after administration of sedative medication and (ii) completing the procedure (iii) without requiring the use of alternative sedative medication and (iv) without requiring manual or mechanical ventilation. The MOAA/S scale had six levels (scores 0-5). A score of 0 denoted non-responsive and 5 denotes fully alert. Important secondary endpoints included treatment success, patients' memory of being awake during the procedure, physician satisfaction with the level of sedation, and time to fully alert after the procedure.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized, received at least one dose of study

treatment and had at least one postdose clinical assessment.

Patient Disposition

A total of 127 patients were randomized using a 1:1:1:1:1 ratio to the five treatment arms. Only 2 patients discontinued prior to completing the study, both were recorded as lost to follow-up. However, both discontinued patients had post baseline clinical assessments. Therefore, all the randomized patients met the criteria for inclusion in the modified Intent-to-Treat (mITT) population

Table 1: Patient Disposition (Study 520)

	Fospropofol disodium 2.0 mg/kg	Fospropofol disodium 5.0 mg/kg	Fospropofol disodium 6.5 mg/kg	Fospropofol disodium 8.0 mg/kg	Midazolam 0.02 mg/kg
Randomized	25	26	26	24	26
Discontinued after study drug administered	0	0	1	1	0
mITT	25	26	26	24	26

Source: Clinical Study Report Table 9

Baseline Demographics

The five treatment groups were balanced with respect to relevant demographic and baseline characteristics. These are shown in Table 2.

The randomization plan included strata for the American Society of Anesthesiologists (ASA) Physical Classification System status, with two levels: P1/P2 or P3/P4. The medical descriptions corresponding to P1 through P4 status are no known systemic disease, mild systemic disease, severe systemic disease, and systemic disease that is a constant threat to life, respectively. Of the total 127 patients randomized, only 3 were in the higher P3/P4 strata. The other randomization stratum was age: <65 or ≥65. The 5 groups are similar for the age categories.

Table 2: Demographic Characteristics at Baseline (mITT population; Study 520)

	Fospropofol disodium 2.0 mg/kg N=25	Fospropofol disodium 5.0 mg/kg N=26	Fospropofol disodium 6.5 mg/kg N=26	Fospropofol disodium 8.0 mg/kg N=24	Midazolam 0.02 mg/kg N=26
Age (years)					
Mean (SD)	55 (10)	56 (11)	54 (15)	53 (15)	54 (12)
Range	25, 72	36, 80	21, 75	18, 75	25, 76
Age group:					
18-64 yrs	21 (84%)	21 (81%)	21 (81%)	20 (83%)	22 (85%)
≥65 yrs	4 (16%)	5 (19%)	5 (19%)	4 (17%)	4 (15%)
Gender					
Female	13 (52%)	12 (46%)	15 (58%)	13 (54%)	16 (62%)
Male	12 (48%)	14 (54%)	11 (42%)	11 (46%)	10 (39%)
Race					
Caucasian	17 (68%)	24 (92%)	21 (81%)	22 (92%)	20 (77%)
Black	4 (16%)	1 (4%)	4 (15%)	2 (8%)	3 (12%)
Asian	0	1 (4%)	0	0	2 (8%)
Hisp/Latino	4 (16%)	0	0	0	1 (4%)
Other	0	0	1 (4%)	0	0
Weight (kg)					
Mean (SD)	79 (15)	82 (23)	77 (19)	86 (23)	78 (15)
Range	53, 110	43, 146	48, 113	50, 132	45, 111
Wt. group:					
<60 kg	3 (12%)	4 (16%)	6 (23%)	4 (17%)	1 (4%)
60-90 kg	16 (64%)	15 (58%)	13 (50%)	10 (42%)	19 (73%)
≥90 kg	6 (24%)	7 (27%)	7 (27%)	10 (42%)	6 (23%)
ASA Status					
P1	15 (60%)	10 (39%)	15 (58%)	8 (33%)	12 (46%)
P2	10 (40%)	15 (58%)	11 (42%)	16 (67%)	12 (46%)
P3	0	1 (4%)	0	0	1 (4%)
P4	0	0	0	0	1 (4%)

Sources: Clinical Study Report Table 13 and SAS datasets

Efficacy Results

The planned hypothesis of this study was a trend test for sedation success rate among the four fospropofol doses using Cochran-Armitage test for trend at alpha=0.05. The result indicated a statistically significant trend (p-value < 0.001). Based on the overall results, the applicant selected only the 6.5 mg/kg dose to move forward into the Phase 3 studies. The 2.0 mg/kg dose was selected as a non-placebo comparator in the Phase 3 studies. The sponsor also performed between-group pairwise comparisons among the fospropofol groups using a Fisher's Exact test for the difference in the sedation success rate. There were no planned adjustments for multiple tests.

The results of the analyses are presented in Table 3. The 6.5 mg/kg dose of fospropofol was statistically significantly different from, and superior to, the 2.0 mg/kg fospropofol dose for the sedation success rate. The secondary endpoints were also favorable for the 6.5 mg/kg dose.

Table 3: Study 520 (Phase 2; Colonoscopy) Efficacy Analysis Results

		Fospropofol disodium 2.0 mg/kg n=25	Fospropofol disodium 6.5 mg/kg n=26
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	6/25 24%	18/26 69% 45% p<0.001
Secondary Endpoints:			
Treatment Success Rate	n/N %	9/25 36%	21/26 81%
Proportion of patients who required alternative sedative medication	n/N %	16/25 64%	5/26 19%
Proportion of patients who did not recall being awake	n/N %	10/25 40%	15/26 58%
Proportion of patients who required supplemental analgesic medication	n/N %	19/25 76%	14/26 54%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	3/25 12%	10/26 38%
Proportion of physicians who rated high overall satisfaction at end of procedure	n/N %	2/25 8%	7/26 27%
Time to sedation (minutes)	Mean Median Range	12 12 0, 22	7 6 0, 18
Time to fully alert (minutes)	Mean Median Range	7 5 0, 29	8 7 0, 30

Source: Clinical Study Report 3000-0520 and SAS datasets

Study 3000-0522 (conducted 3/06 to 8/06)

Design

Study 522 was a randomized, double-blind, parallel arm, multi-center study in adult patients undergoing colonoscopy. The primary objective was to evaluate the efficacy of fospropofol 6.5 mg/kg dose in providing minimal-to-moderate sedation in patients undergoing colonoscopy. The study included three treatment arms: fospropofol 2.0 mg/kg, fospropofol 6.5 mg/kg, and midazolam 0.02 mg/kg. Patients were randomized in a 1:3:2 ratio, respectively.

This study had the same design, patient population, endpoints, and analyses as study 520. The main difference was that there were only three treatment arms in study 522.

Patient Disposition

As shown in Table 4, 314 patients were enrolled. There were only two patients who discontinued from the study, both in the fospropofol disodium 6.5 mg/kg dose group and prior to study drug administration. There were no concerns about the disposition across the groups.

Table 4: Patient Disposition (Study 522; Colonoscopy)

	Fospropofol disodium 2.0 mg/kg	Fospropofol disodium 6.5 mg/kg	Midazolam 0.02 mg/kg
Randomized	102	160	52
Discontinued prior to study drug administration	0	2	0
Discontinued after study drug administered	0	0	0
mITT	102	158	52

Source: Clinical Study Report Table 10

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 5.

Table 5: (Study 522; Colonoscopy)

	Fospropofol disodium 2.0 mg/kg N=102	Fospropofol disodium 6.5 mg/kg N=158	Midazolam 0.02 mg/kg N=52
Age (years)			
Mean (SD)	52 (11)	53 (12)	54 (11)
Range	19, 76	18, 85	25, 79
Age group:			
18-64 yrs	88 (86%)	137 (87%)	42 (81%)
≥65 yrs	14 (14%)	21 (13%)	10 (19%)
Gender			
Female	56 (55%)	82 (52%)	18 (35%)
Male	46 (45%)	76 (48%)	34 (65%)
Race			
Caucasian	69 (68%)	133 (84%)	43 (83%)
Black	20 (20%)	11 (7%)	6 (12%)
Asian	3 (3%)	3 (2%)	1 (2%)
Hisp/Latino	9 (9%)	11 (7%)	2 (4%)
Other	1 (1%)	0	0
Weight (kg)			
Mean (SD)	81 (18)	87 (20)	84 (20)
Range	45, 132	48, 147	50, 134
Wt. group:			
<60 kg	13 (13%)	9 (6%)	4 (8%)
60-90 kg	56 (55%)	86 (54%)	31 (60%)
≥90 kg	33 (32%)	63 (40%)	17 (33%)
ASA Status			
P1	27 (27%)	54 (34%)	17 (33%)
P2	71 (70%)	99 (63%)	32 (62%)
P3	4 (4%)	5 (3%)	3 (6%)
P4	0	0	0

Sources: Clinical Study Report Table 14 and SAS datasets

Efficacy Results

For the primary endpoint, the treatment groups were compared using a Fisher's Exact test for the difference in the sedation success rate between the 2.0 mg/kg and 6.5 mg/kg fospropofol groups.

The results of the analyses are presented in Table 6. The 6.5 mg/kg dose of fospropofol was statistically significantly different from, and superior to, the 2.0 mg/kg fospropofol dose for the sedation success rate. The secondary endpoints were also favorable for the 6.5 mg/kg dose.

Table 6: Study 522 (Phase 3; Colonoscopy) Efficacy Analysis Results

		Fospropofol disodium 2.0 mg/kg N=102	Fospropofol disodium 6.5 mg/kg N=158
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	26/102 25%	137/158 87% 61% $p < 0.001$
Secondary Endpoints:			
Treatment Success Rate	n/N %	29/102 28%	139/158 88%
Proportion of patients who required alternative sedative medication	n/N %	73/102 72%	19/158 12%
Proportion of patients who did not recall being awake	n/N %	45/102 44%	83/158 53%
Proportion of patients who required supplemental analgesic medication	n/N %	78/102 76%	87/158 55%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	4/102 4%	61/158 39%

Proportion of physicians who rated high overall satisfaction at end of procedure	n/N %	15/102 15%	82/158 52%
Time to sedation (minutes)	Mean Median Range	17 18 0, 34	9 8 2, 28
Time to fully alert (minutes)	Mean Median Range	7 3 0, 54	7 5 0, 47

Source: Clinical Study Report 3000-0522 Tables 16-19 and 23; SAS datasets

Study 3000-0524 (conducted 4/06 to 2/07)

Design

Study 524 was a randomized, double-blind, parallel arm, multi-center study. The objective was to evaluate the efficacy of fospropofol 6.5 mg/kg dose in providing minimal-to-moderate sedation in patients undergoing flexible bronchoscopy. The study included two treatment arms: fospropofol 2.0 mg/kg, and fospropofol 6.5 mg/kg. Patients were randomized using a 2:3 ratio, respectively.

This study used the same design endpoints, and analyses as studies 520 and 522. The main difference was the patient population. In study 524, patients were adult males and females undergoing a flexible bronchoscopy procedure, and on average were older and had more baseline medical issues (ASA categories P3/P4) than the colonoscopy patients (see Table 8).

Patient Disposition

As shown in Table 7, a total of 256 patients were enrolled in this study. Four patients discontinued prior to study drug administration, and none discontinued after study drug was administered. The two groups were similar in terms of their disposition.

Table 7: Patient Disposition (Study 524; Bronchoscopy)

	Fospropofol disodium 2.0 mg/kg	Fospropofol disodium 6.5 mg/kg
Randomized	103	153
Discontinued prior to study drug administration	1	3
Discontinued after study drug administered	0	0
mITT	102	150

Source: Clinical Study Report Table 10

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 8.

Table 8: Patient Demographics (Study 524; Bronchoscopy)

	Fospropofol disodium 2.0 mg/kg N=102	Fospropofol disodium 6.5 mg/kg N=150
Age (years)		
Mean (SD)	60 (14)	61 (13)
Range	22, 84	25, 83
Age group:		
18-64 yrs	60 (59%)	89 (59%)
≥65 yrs	42 (41%)	61 (41%)
Gender		
Female	48 (47%)	64 (43%)
Male	54 (53%)	86 (57%)
Race		
Caucasian	84 (82%)	130 (87%)
Black	14 (14%)	16 (11%)
Asian	0	1 (1%)
Hisp./Latino	3 (3%)	3 (2%)
Other	1 (1%)	0
Weight (kg)		
Mean (SD)	79 (23)	79 (23)
Range	43, 136	37, 154
Wt. group:		
<60 kg	19 (19%)	27 (18%)
60-90 kg	51 (50%)	81 (54%)
≥90 kg	32 (31%)	42 (28%)
ASA Status		
P1	6 (6%)	7 (5%)
P2	58 (57%)	74 (49%)
P3	31 (30%)	61 (41%)
P4	7 (7%)	8 (5%)

Sources: Clinical Study Report Table 14 and SAS datasets

Efficacy Results

For the primary endpoint, the treatment groups were compared using a Fisher's Exact test for the difference in the sedation success rate between the 2.0 mg/kg and 6.5 mg/kg fospropofol groups.

The results of the analyses are presented in Table 9. The 6.5 mg/kg dose of fospropofol was statistically significantly different from, and superior to, the 2.0 mg/kg fospropofol dose for the sedation success rate. The secondary endpoints were also favorable for the 6.5 mg/kg dose.

Table 9: Study 524 (Flexible Bronchoscopy) Efficacy Analysis Results

		Fospropofol disodium 2.0 mg/kg n=102	Fospropofol disodium 6.5 mg/kg n=150
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	28/102 27%	133/150 89% 61% p<0.001
Secondary Endpoints:			
Treatment Success Rate	n/N %	42/102 41%	137/150 91%
Proportion of patients who required alternative sedative medication	n/N %	60/102 59%	12/150 8%
Proportion of patients who did not recall being awake	n/N %	56/101 55%	125/150 83%
Proportion of patients who required supplemental analgesic medication	n/N %	38/102 37%	25/150 17%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	12/102 112%	83/150 55%

Proportion of physicians who rated high overall satisfaction at end pf procedure	n/N %	23/102 23%	93/150 62%
Time to sedation (minutes)	Mean Median Range	14 18 0, 30	6 4 2, 22
Time to fully alert (minutes)	Mean Median Range	9 3 0, 114	8 6 0, 61

Source: Clinical Study Report 3000-0524 Tables 16, 17, 19, 20 and 22 and SAS datasets

3.2 Evaluation of Safety

Dr. Schultheis requested additional information on the number of patients in each study who reached sedation levels deeper than intended for the protocols, and the length of time patients remained at those levels. Table 10 provides descriptive information on the number of patients in the three efficacy studies who had Modified OAA/S scores of 1 or 0 at any time after the first dose of study medication. A score of 1 denotes "Responds only after painful trapezius squeeze" and a score of 0 denotes "Did not respond to painful trapezius squeeze." Sedation in the 2-4 range (responds to name or mild stimulus) was preferred during the procedures in the clinical studies. The results for the midazolam arm in each study are included for descriptive purposes only. The studies were not designed for any comparisons of fospropofol disodium treatment groups to the midazolam groups.

Table 10: Patients Who had MOAA/S Scores of 0 or 1

		Fospropofol disodium 6.5 mg/kg	Fospropofol disodium 2.0 mg/kg	Midazolam 0.02 mg/kg
Study #520	n/N % Time at 0 or 1	1/26 4% 4 minutes	2/25 8% 2 to 4 mins.	1/26 4% 8 minutes
Study #522	n/N % Time at 0 or 1	6/158 4% 2 to 16 mins.	1/102 1% 2 minutes	0/52 0%
Study #524	n/N % Time at 0 or 1	24/150 16% 2 to 20 mins.	8/102 8% 2 to 52 mins.	NA

Source: SAS datasets

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

I reviewed exploratory analyses for the primary endpoint by age groups, gender, and race. There were no notable differences in the responder rates for the treatments across any of these subgroups. Results for gender and race are shown in Table 11. The results for age are shown in Table 12 in the next section.

Table 11: Subgroup Analyses

Primary Endpoint: Sedation Success Rate n (%)	Study 520 Colonoscopy		Study 522 Colonoscopy		Study 524 Bronchoscopy	
Fospropofol dose:	2.0 mg/kg N=25	6.5 mg/kg N=26	2.0 mg/kg N=102	6.5 mg/kg N=158	2.0 mg/kg N=102	6.5 mg/kg N=150
Gender						
Female	3/13 (23)	9/15 (60)	14/56 (25)	73/82 (89)	16/48 (33)	59/64 (92)
Male	3/12 (25)	9/11 (82)	12/46 (26)	64/76 (84)	12/54 (22)	74/86 (86)
Race						
Caucasian	2/17 (12)	14/21 (67)	13/69 (19)	114/133 (86)	24/84 (29)	114/130 (88)
Non-Caucasian	4/8 (50)	4/5 (80)	13/33 (39)	23/25 (92)	4/18 (22)	19/20 (95)

Sources: SAS datasets

4.2 Other Special/Subgroup Populations

Dr. Schultheis requested subgroup analyses for three groups who may be at higher risk for complications during anesthesia. His safety analysis will cover these same groups, and he asked for the corresponding efficacy results. The groups of interest were elderly (age ≥ 65), existing health problems (ASA status P3/P4), or body weight < 60 kg. The results for the primary efficacy endpoint for these subgroups are presented in Table 12. There were no notable differences in efficacy for these subsets of patients.

Table 12: Additional Subgroup Analyses

Primary Endpoint: Sedation Success Rate n (%)	Study 520 Colonoscopy		Study 522 Colonoscopy		Study 524 Bronchoscopy	
Fospropofol dose:	2.0 mg/kg N=25	6.5 mg/kg N=26	2.0 mg/kg N=102	6.5 mg/kg N=158	2.0 mg/kg N=102	6.5 mg/kg N=150
Age groups						
18-64 years	6/21 (29)	15/21 (71)	24/88 (27)	119/137 (87)	17/60 (28)	77/89 (87)
≥65 years	0/4 (0)	3/5 (60)	2/14 (14)	18/21 (86)	11/42 (26)	56/61 (92)
Weight groups						
<60 kg	0/3 (0)	4/6 (67)	2/13 (15)	9/9 (100)	7/19 (37)	25/27 (93)
60-90 kg	5/16 (31)	9/13 (69)	13/56 (23)	72/86 (84)	14/51 (27)	75/81 (93)
≥90 kg	1/6 (17)	5/7 (71)	11/33 (33)	56/63 (89)	7/32 (22)	33/42 (79)
ASA Status						
P1 / P2	6/25 (24)	18/26 (69)	26/98 (27)	133/153 (87)	18/64 (28)	71/81 (88)
P3 / P4	No pts.	No pts.	0/4 (0)	4/5 (80)	10/38 (26)	62/69 (90)

Sources: SAS datasets

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There were no additional statistical issues identified during the review. The studies were conducted as planned, and any protocol amendments did not impact the analysis or interpretation of the results. Dropouts were not a concern, and missing data was handled appropriately.

5.2 Label Issues

The applicant's proposed label reports the results from the analysis in the Clinical Studies section. The study design, patient population, and endpoints for the three efficacy studies are appropriately described. I have the following suggestions regarding the reporting of the results;

1. [redacted]

2. [redacted]

b(4)

3. [redacted] b(4)

5.3 Conclusions and Recommendations

The goal of these three studies was to investigate the efficacy of the 6.5 mg/kg dose of fospropofol disodium for sedation in adults undergoing diagnostic or therapeutic procedures. In all three studies, results indicated that the 6.5 mg/kg dose was statistically superior to the 2.0 mg/kg dose of fospropofol disodium for sedation success. Additional clinically relevant secondary endpoints provided supportive evidence that the 6.5 mg/kg dose was favorable. Based on my review of these studies, I conclude there is sufficient evidence of efficacy for the 6.5 mg/kg dose of fospropofol disodium for this indication.

Signatures/Distribution List Page

Katherine B. Meaker, M.S.
Mathematical Statistician

Dionne Price, Ph.D.
Team Leader

Thomas Permutt, Ph.D.
Division Director

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine Meaker
6/10/2008 03:02:39 PM
BIOMETRICS

I found and changed the capitalization Tom mentioned.

Dionne Price
6/10/2008 04:57:50 PM
BIOMETRICS
Concur.

Thomas Permutt
6/10/2008 05:05:13 PM
BIOMETRICS
concur