

# Clinical trial: a dose–response study of fospropofol disodium for moderate sedation during colonoscopy

L. B. COHEN

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The Mount Sinai School of Medicine,  
New York, NY, USA

Correspondence to:  
Dr L. B. Cohen, 311 E. 79th Street,  
Suite 2A, New York, NY 10021, USA.  
E-mail: lawrence.cohen@nyga.md

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## SUMMARY

### Background

An effective agent is needed that provides rapid onset of sedation and quick recovery for patients undergoing colonoscopy.

### Aim

To assess the efficacy and safety of fospropofol disodium in providing sedation in patients undergoing colonoscopy.

### Methods

A randomized, double-blind, multicentre trial evaluated 127 adult patients who received fospropofol (2, 5, 6.5 or 8 mg/kg) or midazolam 0.02 mg/kg following pre-treatment with fentanyl. Supplemental doses of study medication were allowed to reach a Modified Observer's Assessment of Alertness/Sedation scale score  $\leq 4$ . Efficacy end points included sedation success, measures of clinical benefit, sedation, and recovery as well as patient- and doctor-rated satisfaction.

### Results

Fospropofol produced a significant dose-dependent increase in sedation success from 24% (2 mg/kg), 35% (5 mg/kg) and 69% (6.5 mg/kg) to 96% (8 mg/kg;  $P < 0.001$ ). There were also dose-dependent trends for time to sedation, requirements for alternative sedative medication, supplemental doses of sedative and fentanyl, time to ready for discharge and doctor-rated satisfaction scores. Fospropofol was well tolerated, with most adverse events mild-to-moderate in severity.

### Conclusion

The 6.5 mg/kg dose of fospropofol provides the ideal balance of efficacy and safety for patients undergoing colonoscopy and has been selected for phase 3 clinical development.

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## INTRODUCTION

Gastroenterologists commonly use benzodiazepines and opioids to produce moderate sedation with analgesia during colonoscopy.<sup>1</sup> Not all patients are readily sedated with commonly used doses of midazolam (1–2 mg) combined with opioids, and these drugs are not suitable for certain patients undergoing endoscopy who are at a higher risk for sedation-related complications, e.g. morbid obesity, short thyromental distance ('short neck'), alcohol or substance abuse, unstable cervical spines and those with psychiatric illnesses who may require evaluation and sedation care under the direction of an anaesthesiologist. Lipid emulsion propofol, used as a rate-controlled infusion for procedures, has pharmacokinetic (PK) and pharmacodynamic (PD) properties, such as rapid attainment of maximum plasma concentration ( $C_{max}$ ), that can induce levels of deep sedation, and occasionally even general anaesthesia. Although propofol can be highly effective for moderate sedation during procedures such as endoscopy, it may require the presence of an anaesthesia specialist. Therefore, a sedative agent that provided the benefits of propofol, but which could more readily, reliably and safely be titrated to target a moderate level of sedation on individual patient basis, would be useful for patients undergoing diagnostic and therapeutic procedures performed by a variety of medical and surgical specialists, including gastroenterologists.

Fospropofol disodium (AQUAVAN Injection; MGI PHARMA, Inc., Bloomington, MN, USA) is a water-soluble prodrug of propofol that is undergoing evaluation as a sedative agent for diagnostic and therapeutic procedures. Fospropofol disodium is rapidly hydrolysed by alkaline phosphatases to release propofol, as well as phosphate and formaldehyde (which is rapidly converted to formate). These metabolites do not accumulate above endogenous levels.<sup>2</sup> The safety profile and PK/PD properties of fospropofol disodium have been evaluated in preliminary clinical trials and support its use as a sedative during diagnostic procedures such as colonoscopy.<sup>3, 4</sup> Following intravenous (i.v.) administration of fospropofol, the plasma concentration profile of fospropofol-derived propofol is characterized by a smooth and predictable rise and decline, rather than a rapid spike similar to that observed following administration of the lipid-emulsion formulation of propofol (Diprivan, AstraZeneca SpA, Caponago, Italy).<sup>4</sup> The elimination kinetics of propofol are similar, regardless of whether propofol is derived from fospropofol or

Diprivan. The purpose of this dose-ranging trial was to determine the efficacy and safety of various dosing regimens of fospropofol disodium intended to target moderate sedation, to avoid deep levels of sedation and to provide an acceptable safety profile for patients undergoing colonoscopy.

## MATERIALS AND METHODS

### Study objectives and design

The primary objective of this randomized, double-blind, multicentre trial was to evaluate the dose-response relationship of fospropofol disodium with sedation success in patients undergoing elective colonoscopy. Measures of sedation, recovery, memory retention, patient- and doctor-rated satisfaction, safety and tolerability were also evaluated.

Patients were randomized to one of the four fospropofol disodium treatment arms: 2, 5, 6.5 or 8 mg/kg. The lowest fospropofol dose was included to serve as a surrogate for a placebo group. A fifth treatment group, serving as a sensitivity reference for measurements of efficacy and clinical benefit, received midazolam 0.02 mg/kg (Table 1). All patients received a dose of fentanyl, an opioid analgesic, prior to the study treatment.

### Patient selection

The study population included male and female patients  $\geq 18$  years of age with an American Society of Anaesthesiologists (ASA) physical status of P1 to P4 undergoing elective colonoscopy.<sup>5</sup> Study exclusion criteria included: history of allergic reaction or hypersensitivity to any anaesthetic agent, opioid or benzodiazepine; any contraindication relative to the use of fentanyl or midazolam; the presence of a difficult airway as evidenced by a Mallampati Classification Score of 4, or a Mallampati Classification Score of 3 and a thyromental distance of  $\leq 4$  cm; and participation in an investigational drug study within the previous 30 days. All participants gave written informed consent to participate in this study, which was approved by the institutional review board at each participating site.

### Study procedures

A detailed medical history, physical examination, blood chemistries and general assessments including

Table 1. Dosing protocol

	Fentanyl 50 µg				Midazolam dose*	
	Fospropofol dose					
	FP 2.0 (2 mg/kg; n = 25)	FP 5.0 (5 mg/kg; n = 26)	FP 6.5 (6.5 mg/kg; n = 26)	FP 8.0 (8 mg/kg; n = 24)	[MD (0.02 mg/kg; n = 26)]	
Pre-treatment						
Sedation initiation†						
Initial bolus dose (range)	2 mg/kg (120–180 mg)	5 mg/kg (300–450 mg)	6.5 mg/kg (390–585 mg)	8 mg/kg (480–720 mg)	0.02 mg/kg (≤2.5 mg)	
Supplemental doses (range)	0.5 mg/kg (30–45 mg)	1.3 mg/kg (75–113 mg)	1.6 mg/kg (97.5–146 mg)	2 mg/kg (120–180 mg)	1 mg	
Maintenance‡						
Supplemental doses (range)	0.5 mg/kg (30–45 mg)	1.3 mg/kg (75–113 mg)	1.6 mg/kg (97.5–146 mg)	2 mg/kg (120–180 mg)	1 mg	
Supplemental doses of fentanyl‡ 25 µg prn for pain.						
Patients ≥65 years or ASA = 4: doses reduced by 25%. ASA = 3: doses reduced at discretion of principal investigator. Dosing was bounded by weight (<60, 60 to 90 and >90 kg).						
* Midazolam dosing for sedation initiation was weight based (mg/kg); supplemental doses were given in 1-mg increments; † Period between the first dose of study drug and the start of the procedure; ‡ Period between the start of the procedure and the end of the procedure.						

ASA status and Hopkins Verbal Learning Test-Revised (HVLT-R) were performed during the screening visit. Concomitant medication usage, 12-lead electrocardiogram (ECG) and weight were assessed at baseline. Vital signs, oxygen saturation, electrocardiography and adverse events (AEs) were assessed at baseline and then continuously until full recovery. Sedation was assessed using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scale 1 min following pre-treatment with fentanyl and at 2-min intervals thereafter. Patients were monitored and treated during the sedation and recovery phases in facilities staffed and equipped to manage hypotension, hypoxaemia and airway obstruction and/or apnoea, including cardiac dysrhythmias or bradycardia known to occur with sedative-hypnotic agents. In addition to the gastroenterologist and research staff, another healthcare professional who was not performing the colonoscopy was required to be present during the procedure.

### Drug formulations

MGI PHARMA supplied fospropofol disodium to the study centres as a sterile solution containing 35 mg/mL of active agent ready for i.v. administration. Midazolam, a water-soluble benzodiazepine ready for i.v. administration, and fentanyl, an opioid analgesic available for i.v. administration, were obtained commercially by the study centre. Fospropofol disodium, midazolam and saline were indistinguishable by physical appearance.

### Dosage

**Sedation initiation phase.** All patients received fentanyl 50 µg 5 min prior to administration of the initial dose of sedative medication. All patients were placed on supplemental oxygen via nasal cannula (4 L/min) prior to administration of study drug and continuing until the patient was determined to be 'ready for discharge', as per routine clinical site policy for the colonoscopy procedure.

Patients were stratified by age and ASA status (≤65 years and ASA = P1–P3 vs. ≥65 years or ASA = P4) into one of five treatment groups at an equal allocation ratio (Table 1). Patients were randomized to receive either fospropofol (2, 5, 6.5 or 8 mg/kg) or midazolam 0.02 mg/kg. The randomization was carried out centrally via the Internet with a block size of 5. The sponsor and all study personnel

were blinded to the treatment, with the exception of the pharmacist who prepared the study drug. Identical syringes and drug volumes were used in all treatment groups to ensure that the study was blinded. Patients aged  $\geq 65$  years or those with ASA class P4 received initial and supplemental doses of fospropofol or midazolam that were reduced by 25% from the randomized dose. Patients who had an ASA score of P3 may have received initial and supplemental doses reduced by 25% at the discretion of the investigator. Dosing of fospropofol was bounded by weight (<60, 60 to <90 and >90 kg; i.e. adults who weighed >90 kg were dosed as if they weighed 90 kg; adults who weighed <60 kg were dosed as if they were 60 kg). After the initial bolus dose of study drug was given, a maximum of two supplemental doses of fospropofol at 25% of the initial dose (0.5, 1.3, 1.6 or 2 mg/kg) were permitted. Four supplemental doses of midazolam (1 mg) were permitted. Midazolam supplements were administered every 2 min, and fospropofol supplements were administered every 4 min; the fospropofol-treated patients received a corresponding volume of sterile saline at 2 and 6 min to maintain blinding. To further ensure the blind, the syringes were prepared as equal volumes. A MOAA/S score  $\leq 4$  was required for initiation of the procedure. Sedation failure was defined by failure to achieve a MOAA/S score of  $\leq 4$  following administration of all initiation supplements permitted per-protocol. When a patient was declared a sedation failure, alternative sedation medication was provided per-protocol, permitting completion of colonoscopy.

**Sedation maintenance phase.** The patient entered the sedation maintenance phase following successful induction of sedation, defined as MOAA/S score  $\leq 4$  and initiation of procedure (defined as insertion of the endoscope). Supplemental maintenance doses of study medication (Table 1) were permitted if a patient had a MOAA/S score  $\geq 4$  and demonstrated purposeful response. Patients were permitted to receive supplemental doses of fentanyl 25  $\mu\text{g}$  for pain or discomfort during the procedure. A minimum of 10 min was required between supplemental doses of fentanyl.

## Assessments

**Cognitive assessment.** The HVLT-R, a validated neurocognitive assessment that evaluates one's ability to recognize and recall words through verbal learning

and memory, was used to assess cognitive skills.<sup>6,7</sup> During this test, patients are asked to remember a list of 12 words after each of three readings of the list. Following a 20-min delay, patients are asked to recall as many words as possible. The HVLT-R was performed at screening and recovery (approximately 15 min following the end of the procedure). Clear-headed recovery, in this case, is a measurement of the percentage of memory retention of verbal learning in the HVLT-R.

**Depth of sedation.** Level of sedation was assessed using the MOAA/S scale (Table 2).<sup>8</sup> The MOAA/S level was assessed 1 min before the initial dose of fentanyl, 1 min following fentanyl and at 2-min intervals thereafter until fully alert. Patients were considered to be fully alert after the first of three consecutive MOAA/S scores of five following completion of the procedure. Patients were considered to be ready for discharge after scoring 9 or more on the Aldrete Discharge Scale.<sup>9</sup>

**Patient/doctor satisfaction.** Prior to discharge, patients completed a 9-item survey consisting of questions pertaining to their satisfaction with the endoscopic experience and sedation (Supplementary Table S1). Patients were also asked to participate in a telephonic survey the day after their procedure. The 24-h assessment consisted of seven questions regarding postprocedural recovery and patients' willingness to receive the same sedation for colonoscopy during a subsequent examination (Supplementary Table S2a). Investigators received a 16-question survey; four questions pertained to the induction of sedation and 12 questions evaluated overall satisfaction with sedation, level of sedation, control of patient discomfort and anxiety and willingness to use the sedation drug again

**Table 2.** Modified Observer's Assessment of Alertness/Sedation (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

(Supplementary Table S2b). Doctors and patients rated their level of satisfaction on a scale of 1–10 (1 = dissatisfied, 10 = highly satisfied).

### Efficacy end points

The primary efficacy end point, sedation success, was defined as (i) three consecutive MOAA/S scores of  $\leq 4$  after administration of sedative medication, (ii) completion of procedure without use of alternative sedative medications and (iii) no requirement for either manual or mechanical ventilation. An additional analysis assessed treatment success, defined as completion of the procedure without requiring alternative sedative medications and without requiring manual or mechanical ventilation.

Secondary efficacy end points included time to sedation, number of doses of study medication and fentanyl, percentage of patients requiring alternative sedative medication, time to ready for discharge, MOAA/S scores over time, percentage of patients with mean MOAA/S scores of 2–4 and 0–1 during the procedure, and patient- and doctor-rated satisfaction with level of sedation and memory recall.

### Safety monitoring

All patients who received at least one dose of fospropofol or midazolam were included in the safety analyses. Safety was assessed by evaluating AEs, clinical laboratory test results (serum chemistry, haematology and urinalysis), vital sign measurements, ECGs, oxygen saturation and the need for pharmacological intervention or ventilatory support. Patients were evaluated for AEs at baseline (predosing) and during the 24-h (day 1) follow-up telephonic interview. If new or continuing AEs were noted during the telephonic follow-up on day 1, additional follow-up was performed on days 2–5.

Potential sedation-related AEs were also evaluated. Sedation-related AEs included apnoea (lack of spontaneous breathing  $>30$  s), hypoxaemia (oxygen saturation  $<90\%$  for  $>30$  s), bradycardia (heart rate  $<50$  bpm and requiring medical intervention) and hypotension (systolic blood pressure  $<90$  mmHg and requiring medical intervention).

### Statistical analysis

Two efficacy populations [modified intent-to-treat (mITT) and per-protocol 2 (pP<sub>2</sub>)] and one safety popu-

lation were used in the presented analyses. The mITT population included all randomized patients who received at least one dose of study drug and had at least one postdose clinical assessment. Because those patients declared as sedation failures received alternative sedative, the pP<sub>2</sub> population allowed for exploring the treatment effects of the assigned sedative without the confounding effect of alternative sedative medications. This population included only patients in the mITT population who did not receive alternative sedative medication during the study. The safety population included all randomized patients who received at least one dose of fospropofol or midazolam. For efficacy end points, the primary analyses were based on the mITT population. Patients in the mITT population were analysed by the study group to which they were randomized. Patients in the pP<sub>2</sub> and safety populations were analyzed according to the study drug they received.

Summary statistics (mean, standard deviation, median, minimum and maximum values) were calculated for all end points. The number and proportion of patients considered a sedation success was calculated for each treatment group and for the between-group differences in the sedation success rate. Using the Fisher's exact test, pairwise *P*-values for the between-group differences are provided. The trend in the sedation success rate over different fospropofol doses was tested using the Cochran–Armitage trend test. Sample size was determined to show a difference between the 8, 6.5 and 5 mg/kg dosing groups compared with the 2 mg/kg group based on the primary analysis of sedation success.

For analyses of categorical variables, Fisher's exact test was used to assess whether there was overall significant difference among fospropofol groups, and pairwise comparisons were performed if the overall *P*-value was  $\leq 0.05$ . For continuous variables, Wilcoxon rank sum test was used to assess whether there was overall significant difference among fospropofol groups, and pairwise comparisons were performed if the overall *P*-value was  $\leq 0.05$ .

## RESULTS

### Patient population

A total of 127 patients from 16 sites were enrolled in the trial. Of the 34 patients who were screening failures, 18 patients withdrew consent before randomization,

three were ineligible because they did not meet inclusion or exclusion criteria, nine were not randomized because the sponsor closed enrollment upon reaching the target sample size and four patients had the date of their randomization visit outside the 14-day window. All enrolled patients received study medication and were included in the efficacy/safety evaluations. Twenty-three of 127 (18%) randomized patients were  $\geq 65$  years of age or had an ASA status of P4. Demographic and baseline characteristics were similar among treatment groups (Table 3).

### Efficacy assessments

**Sedation success.** Sedation success was dose-dependent across fospropofol treatment groups (Figure 1). There was also a highly significant dose-dependent increase in treatment success across the fospropofol dosing groups. Both sedation success and treatment success rates in the fospropofol groups FP 6.5 and FP 8.0 were significantly higher than in the fospropofol groups FP 2.0 and FP 5.0 ( $P \leq 0.001$ ). There were also

dose-dependent trends across the fospropofol dosing groups for median time to sedation, use of alternative sedative medication, number of supplemental doses of study sedative and mean number of doses of fentanyl administered (Table 4). There was an inverse relationship between fospropofol dose and use of alternative sedative medications.

The mean cumulative doses of fospropofol were as follows: 234 mg for the FP 2.0 group, 590 mg for the FP 5.0 group, 710 mg for the FP 6.5 group and 780 mg for the FP 8.0 group. There was a trend towards a higher total dose of fentanyl administered to patients in the groups receiving lower doses of fospropofol: 83.5  $\mu\text{g}$  for the FP 2.0 group and 84.6  $\mu\text{g}$  for the FP 5.0 group compared with 66.0  $\mu\text{g}$  for the FP 6.5 group and 62.0  $\mu\text{g}$  for the FP 8.0 group. The mean cumulative dose of midazolam was 4.2 mg, and patients in the MD group received a mean dose of 65.4  $\mu\text{g}$  of fentanyl.

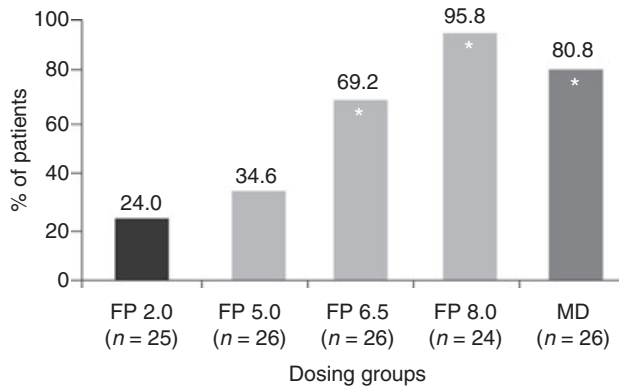
**Depth of sedation.** The majority of patients in each of the fospropofol treatment groups had mean

Table 3. Patient demographics\*

Characteristic	Fospropofol				Midazolam (n = 26)
	FP 2.0 (n = 25)	FP 5.0 (n = 26)	FP 6.5 (n = 26)	FP 8.0 (n = 24)	
Age (years)					
Mean ( $\pm$ s.d.)	54.6 ( $\pm$ 10.4)	55.5 ( $\pm$ 11.1)	54.2 ( $\pm$ 15.2)	53.4 ( $\pm$ 14.5)	53.9 ( $\pm$ 11.9)
$\geq 65$	4 (16)	5 (19)	5 (19)	4 (17)	4 (15)
Males	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)
Hispanic/Latino	4 (16)	0	0	0	1 (4)
Other	0	0	1 (4)	0	0
Weight group (kg)					
<60	3 (12)	4 (15)	6 (23)	4 (17)	1 (4)
60 to <90	16 (64)	15 (58)	13 (50)	10 (42)	19 (73)
$\geq 90$	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)

\* Data expressed as n (%) unless otherwise indicated.

P-value between groups not significant for any variable.



**Figure 1.** Sedation success. The primary end point of this study was sedation success, where a highly significant dose-dependent trend was observed across fospropofol dosing groups in the modified intent-to-treat population ( $P < 0.001$  by Cochran–Armitage trend test). The sedation success rates were 24%, 35%, 69% and 96% in the FP 2.0, FP 5.0, FP 6.5 and FP 8.0 groups respectively. \* $P < 0.05$  vs. FP 2.0 and FP 5.0.

MOAA/S scores ranging from 2 to 4 during the procedure (Figure 2). One patient in group FP 2.0 entered deep sedation (mean MOAA/S score of 0 or 1) during the procedure. A greater number of patients in group FP 8.0 ( $n = 6/24$ , 25%) had MOAA/S scores of 0 or 1 at any time after the first dose of sedation agent compared with those in groups FP 2.0 ( $n = 2/27$ , 8%), FP 5.0 ( $n = 1/26$ , 4%) and FP 6.5 ( $n = 1/25$ , 4%).

**Memory retention.** Memory retention, as evidenced by HVLt-R results at screening and recovery, is summarized by treatment group in Figure 3. Although it was not significant, during the recovery period, the mean percentage of memory retention was higher in the fospropofol 6.5 mg/kg group (99%) compared with the other fospropofol treatment groups (71%, 90% and 76% for 2, 5 and 8 mg/kg, respectively; see Recovery, mITT; Figure 3). The lower retention rate for patients in group FP 2.0 (71%) was likely due to the confounding influence of alternative sedatives that were used in the majority (64%) of patients in this group. When patients who received alternative sedative medications were removed from the analysis (pP<sub>2</sub>), the percentage of retention for patients in group FP 2.0 increased (86%). The percentage of retention was similar in the mITT and pP<sub>2</sub> populations for the other groups.

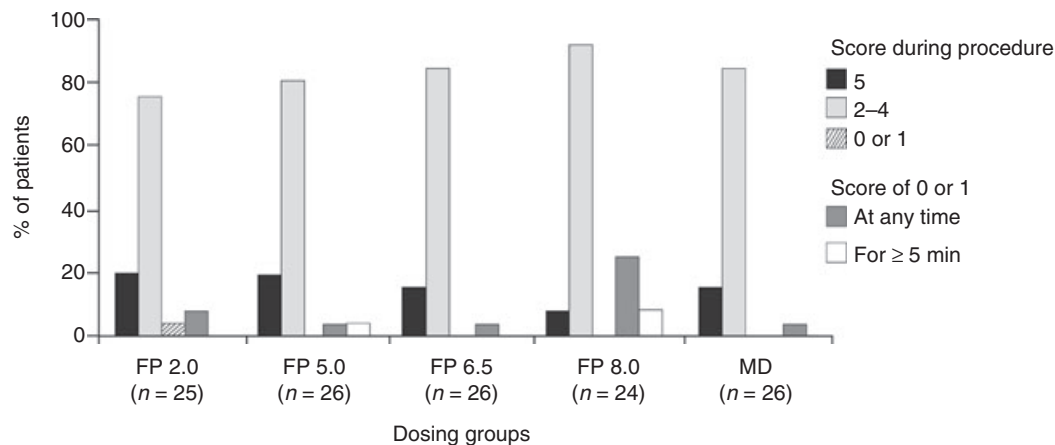
Mean percentage of retention was >100% for patients in the FP 2.0 group at the screening visit and in the FP 6.5 group pP<sub>2</sub> population during recovery. This occurred when patients recalled more words after the 20-min delay than they did after the first reading.

**Patient satisfaction.** Patients in the 6.5 mg/kg group reported a higher overall satisfaction with the entire procedure than patients in the other fospropofol groups. There was also a trend towards a higher percentage of patients willing to use the study drug

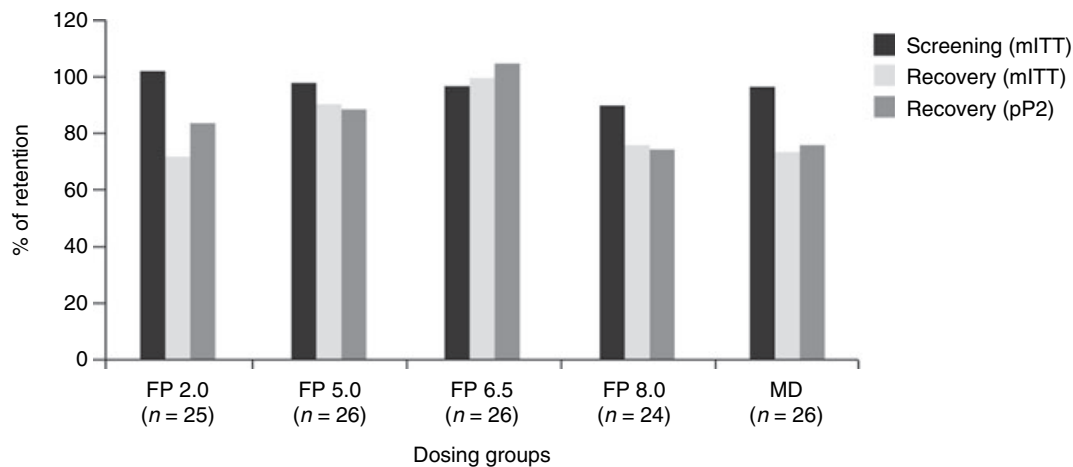
**Table 4.** Measures of clinical benefit and recovery (modified intent-to-treat population)

Parameter	Fospropofol				Midazolam (n = 26)
	FP 2.0 (n = 25)	FP 5.0 (n = 26)	FP 6.5 (n = 26)	FP 8.0 (n = 24)	
Treatment success, n (%)	9 (36)	11 (42)	21 (81)*	23 (96)†	23 (89)†
Time to sedation, mean (±s.d.; min)	12.4 (±5.0)	11.0 (±6.9)	6.5 (±4.5)	4.7 (±2.4)	5.0 (±4.2)
Received alternative sedative, n (%)	16 (64)	15 (58)	5 (19)	1 (4)	2 (8)
Number of supplemental doses of sedative, mean (±s.d.)	2.4 (±1.3)	2.3 (±1.2)	2.1 (±1.2)	1.3 (±1.2)	3.3 (±1.7)
Number of supplemental doses of fentanyl, mean (±s.d.)	1.0 (±0.7)	0.9 (±0.7)	0.7 (±0.7)	0.5 (±0.6)	0.6 (±0.6)
Time to ready for discharge from the end of the procedure, mean (±s.d.; min)	15.0 (±19.6)	7.8 (±10.5)	9.1 (±7.8)	14.2 (±13.4)	10.2 (±14.1)

P-value not significant except where indicated: \*  $P = 0.002$  vs. fospropofol 2 mg/kg; †  $P < 0.001$  vs. fospropofol 2 mg/kg.



**Figure 2.** Depth of sedation (modified intent-to-treat population). Fospropofol produced a satisfactory depth and duration of sedation for patients undergoing colonoscopy. Results of depth of sedation evaluated according to the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scale are presented in this graph. Mean MOAA/S scores during the procedure: most patients in the fospropofol arms had mean MOAA/S scores of 2-4 during the procedure, ranging from 76% in the FP 2.0 group to 92% in the FP 8.0 group. Of the patients in the MD group, 85% had MOAA/S scores in the range of 2-4. Mean MOAA/S scores  $\leq 1$ : MOAA/S scores of 0 or 1 are indicative of deeper sedation. Slightly more patients in the FP 8.0 group (25%) had MOAA/S scores of 0 or 1 (dark grey bars) at any time after the first dose of sedation agent compared with the other fospropofol groups. Of the patients with MOAA/S scores in this range, one patient in the FP 5.0 group had a score of 0 or 1 for  $\geq 5$  min (white bar) and this patient had received alternative sedative medication (midazolam). Two patients in the FP 8.0 group also had scores of 0 or 1 for  $\geq 5$  min (white bar).



**Figure 3.** Mean percentage retention [Hopkins Verbal Learning Test-Revised (HVLT-R) results]. The mean percentage of memory retention at screening and recovery by treatment group are summarized in this figure. The mean retention percentage was similar among the five groups at screening. Patients in the FP 6.5 group demonstrated the highest memory retention during recovery, with a mean of 99%. Groups FP 2.0, FP 5.0 and FP 8.0 had mean memory retention of 71%, 90% and 76%, respectively. Patients in the MD group had a mean retention of 73%. However, as the use of alternative sedatives may confound these analyses, the HVLT-R data are also presented for the per-protocol 2 (pP<sub>2</sub>) population, which excluded those patients who received alternative sedatives. Patients in the FP 6.5 group tended to have higher mean percentage of memory retention than patients in the other groups. The mean scores for the pP<sub>2</sub> analysis were as follows: 83%, 88%, 104%, 74% and 76% for the FP 2.0, FP 5.0, FP 6.5, FP 8.0 and MD groups, respectively.

Table 5. Patient and doctor ratings of success (modified intent-to-treat)

Parameter	Fospropofol				Overall <i>P</i> -value among fospropofol groups	Midazolam ( <i>n</i> = 26)
	FP 2.0 ( <i>n</i> = 25)	FP 5.0 ( <i>n</i> = 26)	FP 6.5 ( <i>n</i> = 26)	FP 8.0 ( <i>n</i> = 24)		
<b>Patient satisfaction</b>						
Patient overall satisfaction rated as high (9–10; %)	72.0	84.0	92.3	79.2	0.2793	69.2
Percent of patients remembering being awake	58.3	52.0	42.3	33.3	0.3356	65.4
Percent who would be treated with this sedative again	80.0	84.0	96.2	91.7	0.2832	100
<b>Doctor satisfaction</b>						
Doctor overall satisfaction rated as high (9–10; %)	8.0	11.5	26.9	50.0	0.0028	11.5
Believe patient was adequately sedated	32.0	38.5	80.8	83.3	<0.001	65.4
Percent who would use this sedative again	24.0	57.7	92.3	83.3	<0.001	76.9

again among patients in the fospropofol 6.5 mg/kg group. The patient satisfaction scores (mean  $\pm$  s.d.) were  $8.9 \pm 1.6$ ,  $9.4 \pm 1.3$ ,  $9.5 \pm 0.6$  and  $9.2 \pm 1.5$ , respectively, in the fospropofol groups FP 2.0, FP 5.0, FP 6.5 and FP 8.0; overall  $P = 0.6200$ . The proportion of patients who rated their overall satisfaction very high (9 or 10 on a 10-point scale) ranged from 72% (FP 2.0) to 92% (FP 6.5) among those receiving fospropofol, overall  $P = 0.2793$  (Table 5). The proportion of patients who reported an adequate level of sedation was 76%, 81%, 100% and 83%, respectively, in the fospropofol groups FP 2.0, FP 5.0, FP 6.5 and FP 8.0 (overall  $P = 0.04$ , FP 2.0 vs. FP 6.5:  $P = 0.0098$ ). Fospropofol exhibited an amnestic effect, with the proportion of patients remembering being awake during the procedure decreasing with increasing doses of fospropofol.

**Doctor satisfaction.** Doctor ratings of overall satisfaction with the entire procedure were dose dependent in the fospropofol group. The mean scores ( $\pm$  s.d.) for doctor level of satisfaction with the study medication at end of procedure were  $3.5 \pm 2.7$ ,  $4.7 \pm 3.0$ ,  $6.8 \pm 2.3$  and  $7.7 \pm 2.8$ , respectively, in the fospropofol groups FP 2.0, FP 5.0, FP 6.5 and FP 8.0, overall  $P < 0.0001$ ; FP 2.0 vs. FP 6.5,  $P = 0.0004$ ; FP 5.0 vs. FP 6.5,  $P = 0.0157$ . The proportion of doctors who expressed a high level of satisfaction (9 or 10 on a

10-point scale) ranged from 8% (FP 2.0) to 50% (FP 8.0), overall  $P = 0.0028$  (Table 5).

## Safety

Fospropofol was well tolerated, and there were no major treatment-emergent AEs (Table 6). There were no serious AEs or deaths during the study, and only one event led to discontinuation of the procedure (MD group).

Adverse events were primarily mild to moderate in severity, transient and self-limited. The most common treatment-related AE (TRAE) experienced by patients in the fospropofol groups was paraesthesia (Table 6). Paraesthesia refers to all AEs characterized as burning sensations and tingling that occurred between the administration of the first dose of study medication and the start of the procedure. Paraesthesias generally occurred in the perianal and perineal area and were usually described as mild in intensity, were transient and self-limited, and typically lasted for 1–2 min.

Four patients receiving fospropofol experienced sedation-related AEs including mild hypotension [FP 5.0 ( $n = 1$ ) and FP 6.5 ( $n = 1$ )] and hypoxaemia [FP 6.5 ( $n = 2$ ); one classified as mild hypotension and one classified as moderate hypotension]. Of these four patients, one patient (FP 6.5 group) required airway assistance (verbal stimulation) for the treatment of hypoxaemia.

Table 6. Safety overview (safety population)

Parameter, <i>n</i> (%)	Fospropofol				All fospropofol groups ( <i>n</i> = 101)	Midazolam ( <i>n</i> = 26)
	FP 2.0 ( <i>n</i> = 27)	FP 5.0 ( <i>n</i> = 26)	FP 6.5 ( <i>n</i> = 25)	FP 8.0 ( <i>n</i> = 23)		
Treatment-emergent AEs	22 (82)	22 (85)	24 (96)	17 (74)	85 (84)	16 (62)
TRAEs	14 (52)	19 (73)	19 (76)	10 (44)	62 (61)	2 (8)
Paraesthesia*	13 (48)	15 (58)	14 (56)	7 (30)	49 (49)	1 (4)
Pruritus†	1 (4)	3 (12)	2 (8)	3 (13)	9 (9)	0
Hypotension	0	1 (4)	1 (4)	0	2 (2)	0
Hypoxaemia	0	0	2 (8)	0	2 (2)	0
Abdominal pain	0	0	0	1 (4)	1 (1)	0
AE-related discontinuation of procedure	0	0	0	0	0	1 (4)
Sedation-related AEs‡	0	1 (4)	3 (12)	0	4 (4)	0
Hypotension	0	1 (4)	1 (4)	0	2 (2)	0
Hypoxaemia	0	0	2 (8)	0	2 (2)	0

AEs, adverse events; TRAEs, treatment-related adverse events.

\* Paraesthesia includes all TRAEs characterized as burning sensations and tingling.

† Pruritus includes all TRAEs characterized as genital pruritus male, genital pruritus female, pruritus, pruritus ani, pruritus generalized, pruritus genital or nasal itching.

‡ Hypotension, hypoxaemia, bradycardia and apnoea.

Comparing the safety profile of the midazolam arm with that of the 8 mg/kg fospropofol group, the highest dose of fospropofol in this study, neither group experienced an episode of hypotension or hypoxaemia, and there were no serious AEs.

## DISCUSSION

The findings of this study demonstrate a highly significant dose-dependent effect of sedation across the fospropofol dosing groups, with the 6.5 and 8 mg/kg dosing groups producing superior sedation compared with the 2 mg/kg group. A similar trend was observed for depth of sedation, time to sedation, supplemental doses of study medication, alternative sedation medication and supplemental fentanyl. Significant differences were observed between the 6.5 and 8 mg/kg dosing groups in depth of sedation, however. Within the 6.5 mg/kg dose group, there were no recorded episodes of deep sedation during procedures, and only a single, brief episode of deep sedation was observed during the recovery period. In contrast, 25% of those patients receiving 8 mg/kg experienced deep sedation during the study. Further, doctors as well as patients preferred 6.5 mg/kg over the other doses of fospropofol, with all of the patients in the 6.5 mg/kg dosing group reporting they were adequately sedated.

Fospropofol was safe and well tolerated by patients in all fospropofol dosing arms. The majority of treatment-emergent AEs were categorized as mild or moderate. Paraesthesia, the most common AE, was transient and self-limited, generally lasting for 1–2 min, and was usually described as mild to moderate in intensity. The mechanism of this AE is not understood but has been noted with other i.v. administered drugs that contain phosphate esters, e.g. dexamethasone and fosphenytoin.<sup>10–14</sup> Four sedation-related AEs were reported during this study. Two patients experienced mild hypotension and two patients experienced hypoxaemia (mild, *n* = 1 and moderate, *n* = 1). There were no deaths and no patient withdrew from participation in the study.

Currently, midazolam is the most widely used sedative hypnotic agent for endoscopy in the United States.<sup>1</sup> Therefore, this study was designed to include a midazolam treatment arm, using the FDA-approved dose, which served as a reference therapy. It is important to point out that this study was neither intended nor designed to compare the efficacy of fospropofol to midazolam, as used in current practice. With that caveat, it is worth noting that the sedation success rates for patients in both groups were high, while overall patient satisfaction, the feeling of adequate sedation and memory retention were generally higher

in the fospropofol 6.5 mg/kg dosing group than with midazolam.

In clinical practice, the standard combination of benzodiazepine and opioid often results in a level of sedation that is deeper than that intended in this study.<sup>15</sup> This may be due to the treatment effect of these agents when used in combination, along with the lack of standardized methods (such as MOAA/S) to assess the depth of sedation patients experience. In a recent study by Patel *et al.*, 68% of patients undergoing endoscopy, including 45% of all patients having colonoscopies with meperidine and midazolam, were deeply sedated at least transiently during examination.<sup>15</sup> In this study, we targeted moderate sedation and used the MOAA/S levels to help direct the titration of the study drugs. In doing so we observed a significant amnesic effect with moderate sedation, accounting for the high satisfaction scores among patients receiving 6.5 mg/kg of fospropofol. Consequently, we conclude that patients do not necessarily need to undergo the risks associated with deep levels of sedation to experience the clinical benefits of sedation.<sup>16–20</sup>

Benzodiazepines and opioid analgesics are the drugs most often used for sedation during colonoscopy.<sup>1, 21</sup> These agents, although effective for the majority of patients, have several undesirable features, including slow to variable onset of action and an extended duration of effect.<sup>21, 22</sup> Additionally, midazolam is a selective substrate of CYP3A4 and CYP3A5, so there is significant potential for drug–drug interactions and a wide interpatient metabolic variability (approximately 4-fold)<sup>23</sup> that can result in the need for very large doses of midazolam in some patients. Full recovery from the effects of these agents may require up to 3–6 h or more,<sup>1</sup> and patients are instructed to abstain from work or their usual activities for up to 24 h post-procedure. For these reasons, many gastroenterologists prefer propofol. However, propofol administration under the direction of gastroenterologists has been limited, largely due to the FDA-approved product label, which indicates that its use should be restricted to personnel ‘trained in the administration of general anaesthesia’.<sup>24</sup> Fospropofol may be an appealing alternative for these practitioners of endoscopic sedation.

In conclusion, the results of this study demonstrate that administration of fospropofol disodium results in

a level of sedation that is safe and effective for patients undergoing colonoscopy. On the basis of this study, we believe that the 6.5 mg/kg dose of fospropofol provides the ideal balance of efficacy and safety. Additional studies are planned to evaluate this weight-based initial dose of fospropofol. This study also demonstrates that the safety profile of fospropofol compares favourably with that of other sedatives such as midazolam. If the results of this study are supported by the findings of a phase 3 trial, fospropofol could provide a useful alternative to the agents currently in use for endoscopic sedation.

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## SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article:

Table S1. Patient satisfaction survey day of colonoscopy procedure

Table S2a. Physician satisfaction surveys

Table S2b. Physician satisfaction survey at the end of the procedure

This material is available as part of the online article from:

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1365-2036.2008.03598.x>

(This link will take you to the article abstract).

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## REFERENCES

- 1 Rex DK. Review article: moderate sedation for endoscopy: sedation regimens for non-anaesthesiologists. *Aliment Pharmacol Ther* 2006; **24**: 163–71.
- 2 Fechner J, Ihmsen H, Hatterscheid D, *et al.* Pharmacokinetics and clinical pharmacodynamics of the new propofol prodrug GPI 15715 in volunteers. *Anesthesiology* 2003; **99**: 303–13.
- 3 Weinstein ML, Hinson J, Wang C, Gibiansky E, Cohen LB. Aquavan injection for sedation in patients undergoing elective colonoscopy: results of a phase 2 dose-ranging study. *Surg Endosc* 2006; **20** (Suppl. 1): P165.
- 4 Shah A, Fechner J, Struys M, *et al.* Differential PK/PD of propofol after intravenous fospropofol and Diprivan in healthy subjects [abstract]. *Anesthesiology* 2007; A46.
- 5 Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology* 1978; **49**: 239–43.
- 6 Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test-Revised. *Clin Neuropsychol* 1999; **13**: 348–58.
- 7 Lacritz LH, Cullum CM, Weiner MF, Rosenberg RN. Comparison of the Hopkins Verbal Learning Test-Revised to the California Verbal Learning Test in Alzheimer's disease. *Appl Neuropsychol* 2001; **8**: 180–4.
- 8 Chernik DA, Gillings D, Laine H, *et al.* Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; **10**: 244–51.
- 9 Chung F, Chan VW, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. *J Clin Anesth* 1995; **7**: 500–6.
- 10 Rasche H, Meier CR, Schneider J, Groticke J, Schonhofer P. Cutaneous paresthesia in high-dose intravenous dexamethasone therapy in oncology. *Dtsch Med Wochenschr* 1986; **111**: 1406–7.
- 11 Luer MS. Fosphenytoin. *Neurol Res* 1998; **20**: 178–82.
- 12 Cerebyx®. *Package Insert*. NY: Parke-Davis, Division of Pfizer, Inc. NY, 2002.
- 13 Perron G, Dolbec P, Germain J, Bechard P. Perineal pruritus after i.v. dexamethasone administration. *Can J Anaesth* 2003; **50**: 749–50.
- 14 Dexamethasone. *Package Insert*. Schaumburg, IL: American Pharmaceutical Partners, 2004.
- 15 Patel S, Vargo JJ, Khandwala F, *et al.* Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol* 2005; **100**: 2689–95.
- 16 Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004; **59**: 795–803.
- 17 Bright E, Roseveare C, Dalgleish D, Kimble J, Elliott J, Shepherd H. Patient-controlled sedation for colonoscopy: a randomized trial comparing patient-controlled administration of propofol and alfentanil with physician-administered midazolam and pethidine. *Endoscopy* 2003; **35**: 683–7.
- 18 Kucukyavuz Z, Cambazoglu M. Effects of low-dose midazolam with propofol in patient-controlled sedation (PCS) for apicectomy. *Br J Oral Maxillofac Surg* 2004; **42**: 215–20.
- 19 Ulmer BJ, Hansen JJ, Overley CA, *et al.* Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; **1**: 425–32.
- 20 Sipe BW, Scheidler M, Baluyut A, Wright B. A prospective safety study of a low-dose propofol sedation protocol for colonoscopy. *Clin Gastroenterol Hepatol* 2007; **5**: 563–566.
- 21 Cohen LB, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: a protocol for safe and effective administration by the gastroenterologist. *Gastrointest Endosc* 2003; **58**: 725–32.
- 22 Gan TJ. Pharmacokinetic and pharmacodynamic characteristics of medications used for moderate sedation. *Clin Pharmacokinet* 2006; **45**: 855–69.
- 23 Floyd MD, Gervasini G, Masica AL, *et al.* Genotype-phenotype associations for common CYP3A4 and CYP3A5 variants in the basal and induced metabolism of midazolam in European- and African-American men and women. *Pharmacogenetics* 2003; **13**: 595–606.
- 24 Diprivan®. *Full Prescribing Information*. LP: AstraZeneca Pharmaceuticals, 2004.