A Phase 1, Single-center, Double-blind, Placebo-controlled Study in Healthy Subjects to Assess the Safety, Tolerability, Clinical Effects, and Pharmacokinetics–Pharmacodynamics of Intravenous Cyclopropyl-methoxycarbonylmetomidate (ABP-700) after a Single Ascending Bolus Dose


ABSTRACT

Background: Cyclopropyl-methoxycarbonylmetomidate (ABP-700) is a new “soft” etomidate analog. The primary objectives of this first-in-human study were to describe the safety and efficacy of ABP-700 and to determine its maximum tolerated dose. Secondary objectives were to characterize the pharmacokinetics of ABP-700 and its primary metabolite (cyclopropyl-methoxyacarbonyl acid), to assess the clinical effects of ABP-700, and to investigate the dose–response and pharmacokinetic/pharmacodynamic relationships.

Methods: Sixty subjects were divided into 10 cohorts and received an increasing, single bolus of either ABP-700 or placebo. Safety was assessed by clinical laboratory evaluations, infusion-site reactions, continuous monitoring of vital signs, physical examination, adverse event monitoring, and adrenocorticotropic hormone stimulation testing. Clinical effects were assessed with modified observer’s assessment of alertness/sedation and Bispectral Index monitoring. Pharmacokinetic parameters were calculated.

Results: Stopping criteria were met at 1.00 mg/kg dose. No serious adverse events were reported. Adverse events were dose-dependent and comprised involuntary muscle movement, tachycardia, and ventilatory effects. Adrenocorticotropic hormone stimulation evoked a physiologic cortisol response in all subjects, no different from placebo. Pharmacokinetics were dose-proportional. A three-compartment pharmacokinetic model described the data well. A rapid onset of anesthesia/sedation after bolus administration and also a rapid recovery were observed. A quantitative concentration–effect relationship was described for the modified observer’s assessment of alertness/sedation and Bispectral Index.

Conclusions: This first-in-human study of ABP-700 shows that ABP-700 was safe and well tolerated after single-bolus injections up to 1.00 mg/kg. Bolus doses of 0.25 and 0.35 mg/kg were found to provide the most beneficial clinical effect versus side-effect profile. (ANESTHESIOLOGY 2017; XXX:00-00)
the compound. This approach also is being applied to sedative-
hypnotics to create so-called “soft analogs” that show faster
pharmacokinetics and a high therapeutic index.5,4

Etomidate was introduced into clinical practice to induce and maintain the hypnotic component of anesthesia while preserving hemodynamic and respiratory stability.5 However, large population variability in recovery times and significant suppression of adrenocortical steroid synthesis has limited its clinical use.6 In an attempt to eliminate these side effects while retaining its beneficial cardiovascular and respiratory profile, various new analogs of etomidate have been synthesized and tested in preclinical and animal settings.7 Of these, ABP-700 showed promising pharmacology in rats.7 When tested in beagle dogs, it was observed that recovery after ABP-700 was rapid both after single-bolus and continuous infusion.1 Also, adrenocortical recovery occurred within approximately 90 min, which is not significantly different from propofol.1

In this article, results from a first-in-human, Phase 1, single-center, double-blind, placebo-controlled study of ABP-700 after a single ascending bolus dose are reported. The primary objectives were to describe the safety and efficacy of ABP-700 and to determine its maximum tolerated dose (MTD). Secondary objectives were to characterize the pharmacokinetics of ABP-700 and its primary metabolite (CPM acid), to assess the clinical effects of ABP-700, and to investigate the pharmacokinetic-pharmacodynamic relationships. We also tested the influence of a single-dose fentanyl pre-treatment on the clinical and side effect profile with two of the most promising ABP-700 dosages.

Materials and Methods

Study Management and Registration

This trial was conducted at the QPS early Phase 1 unit, Groningen, The Netherlands, in cooperation with the Department of Anesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, in compliance with good clinical practice and applicable regulatory requirements. Ethics committee approval was obtained (Medische Ethische Toetsings Commissie Stichting Bebo, Assen, The Netherlands).

Timothy Brennan, Ph.D., M.D., served as Handling Editor for this article. M.M.R.F.S. and B.I.V. contributed equally to this article and should both be considered as first authors. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal’s Web site (www.anesthesiology.org).

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Study Execution

This study was set up as a Phase 1, single-center, double-blind, placebo-controlled, single ascending-dose study of ABP-700. In total, 60 volunteers were divided into 10 cohorts. In each cohort, six subjects received a single IV bolus dose of ABP-700 or placebo in a 5:1 ratio. The actual dosages of ABP-700 were 0.03, 0.10, 0.25, 0.35, 0.50, 0.75, and 1 mg/kg. The starting dose of 0.03 mg/kg was chosen as a conservative starting point based on preclinical efficacy and toxicology data and following guidelines from the European Medicines Agency (London, United Kingdom). Two cohorts of six volunteers received a single IV bolus dose of 0.25 or 0.35 mg/kg ABP-700 or placebo preceded by 1 µg/kg fentanyl in a 5:1 ratio. An additional cohort (cohort 10) of six volunteers was added, receiving a single IV bolus dose of ABP-700, 0.175 mg/kg or placebo in a 5:1 ratio to fine-tune the dose–response relationship.

Subjects were admitted to the clinical pharmacology unit 1 day before study drug administration. Subjects were required to fast for a minimum of 8 h overnight before study drug administration and continued to fast for at least 4 h thereafter. Water was not permitted from 2 h before until 1 h after dosing. Consumption of foods and beverages containing caffeine, alcohol, or grapefruit was prohibited 24 h, 48 h, and 10 days before dosing, respectively. Further details regarding dietary restriction were provided in the informed consent document and Companion Study Management and Registration.

Subjects

Healthy nonsmoking men and women aged between 18 and 45 yr with a body mass index (BMI) between 17.5 and 30 kg/m², American Society of Anesthesiologists physical status of I or II, and without risk of a difficult airway (modified Mallampati score 1 or II) were eligible for this study. Women were included if they were of nonchildbearing potential, i.e., had to have undergone one of the following sterilization procedures at least 6 months before the first dose: hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, bilateral oophorectomy, or be postmenopausal with amenorrhea for at least 1 yr before the first dose and have follicle-stimulating hormone serum levels consistent with postmenopausal status (follicle-stimulating hormone levels of less than 30 IU/l). Subjects were excluded in case of a history or presence of significant disease or disease risk. In addition, volunteers must have refrained from, or not anticipate, the use of any medication, alcohol, or (illicit) drug abuse. Participants should not have had surgery within 90 days before drug dosing, a history of febrile illness within 5 days before dosing, not have participated in another clinical trial within 90 days before dosing, and not be pregnant or lactating. Subjects with a history or presence of adrenal insufficiency as defined by serum cortisol level less than 6 µg/dl at screening also were excluded from participation.

Subjects and Methods

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dosing, respectively, and throughout subjects’ admission to the study facility. Before dosing, all subjects were transported to a dedicated treatment room equipped similarly to an operating room used in the University Medical Center Groningen that included monitoring equipment as well as respiratory support, including a tracheal intubation kit, anesthesia machine (Primus®; Dräger, Germany), and a fully equipped emergency “crash” cart immediately available. Subjects breathed room air before, during, and postdosing of ABP-700. In the event that an oxygen saturation (SpO₂) level less than 90% was not resolved by stimulation or jaw thrust, additional oxygen (5 l/min) was delivered via nasal prongs (Microstream®; Medtronic, Ireland).

If required, brief manual ventilatory support was allowed with the use of a tight-fitting face mask. Before drug administration, two intravenous cannulas were inserted. The intravenous cannula for study drug administration was placed downstream of the arterial sampling and monitoring cannula, which was inserted into the radial artery after local anesthesia. The second intravenous cannula was placed in the opposite arm to draw the venous blood samples. All subjects received minimal crystalloid intravenous fluids during the drug administration period via the cannula for drug administration.

Because ABP-700 is derived from etomidate, a drug associated with involuntary muscle movements (IMMs), and because of the preclinical findings that ABP-700 also is associated with IMMs, including myoclonic jerking,1 midazolam was delivered via nasal prongs (Microstream®; Medtronic, Ireland). If required, brief manual ventilatory support was allowed with the use of a tight-fitting face mask. Before drug administration, two intravenous cannulas were inserted. The intravenous cannula for study drug administration was placed downstream of the arterial sampling and monitoring cannula, which was inserted into the radial artery after local anesthesia. The second intravenous cannula was placed in the opposite arm to draw the venous blood samples. All subjects received minimal crystalloid intravenous fluids during the drug administration period via the cannula for drug administration.

Because ABP-700 is derived from etomidate, a drug associated with involuntary muscle movements (IMMs), and because of the preclinical findings that ABP-700 also is associated with IMMs, including myoclonic jerking,1 midazolam was made available as safety medication at an initial 1-mg bolus dose for amelioration of severe myoclonus if observed. Additional midazolam doses of 1 mg could be administered at the discretion of the anesthesiologist-investigator. During the conduct of the study, a board-certified anesthesiologist was present throughout the dosing period until full recovery of the subject.

Subjects remained supine until recovery and were supine or semirecumbent in bed until the removal of the arterial line. When supine or semirecumbent, subjects were allowed to rise for brief periods under supervision. Subjects did not engage in strenuous activity at any time during the confinement period. Subjects were asked to avoid exercise 72 h before clinical laboratory tests at screening, check-in (1 day before dosing), and follow-up. Subjects remained in the clinic through completion of all scheduled postdose procedures on day 2 and returned for a follow-up visit 4 to 6 days after dosing.

After each cohort, the principal investigator (PI), sponsor, and ethics committee evaluated all available data relevant to the safety, tolerability, pharmacokinetics, and clinical effects of ABP-700 to proceed to the next dose level. Once an MTD was identified, no further dose escalation occurred. Stopping criteria for dose escalation were a grade 3 or higher dose-limiting toxicity event as defined in the September 2007 Food and Drug Administration Guidance; SpO₂ less than 90% not resolved by simple stimulation, jaw thrust, or supplemental oxygen administered via nasal prongs; any serious adverse events (AEs) that were considered by the PI to be related to study drug; and any clinically significant AEs that the sponsor and PI considered a safety concern. Because methanol is a byproduct of the ABP-700 metabolism and was detected during animal studies (data on file), it was indicated to search for significant changes in clinical or laboratory parameters indicative of methanol exposure with the potential for toxicity including, but not limited to, evidence of metabolic acidosis.

**Primary Study Endpoints**

Safety and tolerability of ABP-700 were assessed by evaluation of AEs, physical examination, safety laboratory tests (serum chemistry, hematology, arterial blood gas, urinalysis, and coagulation), serum methanol concentration, intermittent 12-lead electrocardiograms, temperature, and infusion-site reaction monitoring. Electrocardiograms were evaluated for PR interval, QRS interval, and QTcF interval. AEs were defined as the incidences of treatment-emergent adverse experiences per system organ class according to MedDRA (version 16.1; MedDRA MSSO, USA) from the period of arrival at the clinic up to the follow-up visit.

All volunteers were monitored continuously with a Philips MP50 monitor (Philips, The Netherlands) measuring continuous three-lead electrocardiogram and for heart rate, continuous pulse oximetry, noninvasive blood pressure every minute (at lower limb level), continuous invasive blood pressure via the radial artery cannula, respiration rate, respiration pattern, and end-tidal carbon dioxide (Microstream; Medtronic). High-frequency electronic data were captured from 1 min predose until 15 min after full recovery.

An adrenocorticotropic hormone (ACTH) stimulation test was performed to evaluate the effect of ABP-700 on adrenal function. Screening and baseline cortisol levels were attained before 9:00 AM after 1-h rest in the supine position and after at least an 8-h fast. Adrenocortical stimulation commenced with an IV bolus administration of 250 µg synthetic ACTH 60 min after ABP-700 administration. Cortisol levels were measured at 1 and 2 h after ACTH administration. The MTD was reached when two or more volunteers met stopping criteria in any particular dosing cohort.

**Secondary Study Endpoints**

The clinical hypnotic–anesthetic drug effect of ABP-700 was evaluated by means of the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) score, as shown in table 1. Clinical effect was defined as a MOAA/S less than 5. Onset of deep sedation/anesthesia was defined as the first postdose transition to a MOAA/S value less than 3 and offset of deep sedation/anesthesia as the transition to a MOAA/S value greater than 2. Duration of sedation/anesthesia was defined as the time between onset and offset. MOAA/S scoring was performed 1 min before dosing and at approximately 15 s, 30 s, 1 min postdose, and every minute thereafter for a
Minimum of 15 min after full recovery. Subjects were considered recovered when three consecutive MOAA/S scores of 5 were obtained. In addition, a processed electroencephalographic measure, the Bispectral Index (BIS), was applied as a continuous measure of cerebral drug effect. BIS (software revision 1.13; Medtronic) was derived from two-channel frontal electroencephalogram using an Fpz-F7 and Fpz-F8 referential montage and calculated with the BIS-VISTA monitor (Medtronic) using the bilateral electrodes BIS® Sensor electrodes (Medtronic). An average BIS value was calculated by use of data from the left and right BIS values. Electrode impedance was less than 5 kΩhm. The smoothing interval of the BIS® monitor (Medtronic) was set at 15 s. BIS values range from 100 to 0, with lower values denoting more drug effect.

**Pharmacokinetic–Pharmacodynamic and Clinical Effect Evaluation**

The pharmacokinetics of ABP-700 and its metabolite (CPM acid) were studied. Arterial and venous blood samples were collected. Arterial samples were drawn before ABP-700 injection and at 0.5, 1, 2, 3, 4, 8, 12, 20, 30, 45, 60, 90, 120, and 180 min after ABP-700 injection. Venous samples were drawn predose, 1.5, 3.5, 7, 13, 21, 35, 75, 125, 185, 240 min and 6, 8, and 12 h postdosing. Blood samples were collected in prechilled Vacutainers (Becton Dickinson, USA) containing NaF/Na₂EDTA to inhibit nonspecific esterase activity (BD cat. No. 367587; Becton Dickinson). Samples were stored on wet ice for no longer than 30 min until centrifuged at 5°C for 7 min at 1,800g to separate the plasma. Plasma was transferred by the use of disposable pipettes into cryovials and placed immediately on dry ice until transferred to a –80°C freezer within a total allotted time of 60 min.

Plasma concentrations of ABP-700 and metabolite CPM acid were measured by high-performance liquid chromatography with tandem mass spectrometric detection using the SCIEX API 4000 LC/MS/MS System with a TurboIonSpray® interface (AB SCIEX, Canada) in positive mode at QPS. Deuterium-labeled D5-ABP-700 and D5-CPM-acid were used as internal standards. To 0.05 ml plasma, the internal standard solution and acetonitrile were added. After mixing and centrifuging, part of the supernatant was transferred onto the Ostro Protein Precipitation and Phospholipid Removal Plate, 25 mg (Waters Chromatography B.V., The Netherlands). By the use of positive pressure, the supernatant was eluted and collected in a 96-well plate. Before analysis, a dilution step with Milli-Q ultrapure water (Merck Millipore, The Netherlands) and acetonitrile was applied. Liquid chromatography was performed on a C18 column (50 x 3.0 mm, 5 µm; Advanced Chromatography Technologies Ltd, UK) mounted in line with a 4 x 3.0-mm C18 guard column (Advanced Chromatography Technologies Ltd) on an Agilent 1100/1200 LC system (Agilent Technologies, USA). The column temperature was maintained at 50°C. The mobile phase A was 0.1% formic acid in water, and the mobile phase B was 0.1% formic acid in 50% acetonitrile. For sample elution, a gradient of 30 to 95% B was applied over a period of 1 min at a flow rate of 1 ml/min. The approximate elution times for ABP-700 and CPM acid were 2.1 and 1.7 min, respectively. The nominal mass transitions monitored were 315.2 to 211.1 and 301.3 to 197.0 m/z for ABP-700 and CPM acid, respectively. The method was validated over a concentration range of 5.00 to 1,250 ng/ml for ABP700 and 25.0 to 6,250 ng/ml for CPM acid. Precision and accuracy were demonstrated for the validation samples within a single run of six aliquots (within-run for repeatability) and between different runs (between-run for reproducibility) distributed over at least 2 days. Validation samples were prepared in blank human NaF/Na₂EDTA plasma by spiking known concentrations of ABP-700 and CPM acid. For precision, acceptance criteria of coefficient of variation (CV%) not to exceed 20.0% at lower limit of quantification (LLOQ) or 15% at all other levels was met for all samples. For accuracy, acceptance criteria of percentage of relative error not to exceed 20.0% at LLOQ or 15% at all other levels was met for all samples. LLOQ for ABP-700 and CPM acid was determined at 5 and 25 ng/ml, respectively.

Noncompartmental pharmacokinetic analyses of concentration–time data of both arterial and venous plasma ABP-700 and its primary metabolite (CPM acid) were conducted with Phoenix® WinNonlin®, version 6.3 (Pharsight Corporation, USA). Only plasma pharmacokinetic profiles that contained more than five consecutive data points with a quantifiable concentration value were considered evaluable. Actual elapsed times from dosing were used to estimate all individual plasma pharmacokinetic parameters for evaluable subjects. Observed predose concentrations were set as missing to generate C₀ values, which were calculated as the extrapolated concentration at time 0 (computed for parent only). Systematic exposure was calculated with the area under the drug concentration–time curve. More detailed information on the applied methods to analyze the noncompartmental pharmacokinetics of the concentration–time data of plasma ABP-700 (both arterial and venous) and its primary metabolite can be found in Supplemental Digital Content 1 (http://links.lww.com/ALN/B437).

In addition, compartmental pharmacokinetic and pharmacodynamic models were developed with NONMEM (Icon Development Solutions, USA). The time course of ABP-700

### Table 1. Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) score

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Responds readily to name spoken in normal tone</td>
<td>5 (alert)</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>4</td>
</tr>
<tr>
<td>Responds only after name is called loudly and/or repeatedly</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after mild prodding or shaking</td>
<td>2</td>
</tr>
<tr>
<td>Responds only after painful trapezius squeeze</td>
<td>1</td>
</tr>
<tr>
<td>Does not respond to painful trapezius squeeze</td>
<td>0</td>
</tr>
</tbody>
</table>
was modeled with a three-compartmental pharmacokinetic model with volumes $V_1$, $V_2$, $V_3$; elimination clearance $CL$; and intercompartmental clearances $Q_2$ and $Q_3$. Arterial observations were related to the central compartment. Venous and metabolite concentrations were not used. All parameters were scaled linearly with total body weight. Mixing delay for the pharmacokinetic was set to 15 s. Residual error in pharmacokinetic observations was assumed to be proportional to the predicted concentration. Pharmacokinetic observations reported as lower than the LLOQ were ignored.

We modeled BIS using a sigmoidal $E_{max}$ model driven by an effect compartment concentration ($Ce$) connected to the plasma compartment by a first-order rate constant ($k_{e0,BIS}$). The equation of the pharmacodynamic model was as follows:

$$\frac{dCe}{dt} = k_{e0,BIS} \cdot (C - Ce)$$

$$\text{Effect} = E_0 \cdot \left(\frac{E_{max} - E_0}{Ce^{\gamma} + Ce^{\gamma}} + \varepsilon\right)$$

Where $C$ and $Ce$ are the concentrations in the central ($V_1$) and effect compartments, $E_0$ is the baseline pharmacodynamic measure when no drug is present, $E_{max}$ is the maximum possible drug effect, $Ce_{50}$ is the $Ce$ associated with 50% of the maximum effect, $\gamma$ is the steepness of the concentration versus response relation, and $\varepsilon$ represents additive residual error to the pharmacodynamic observations. Signal delay in the BIS due to epoch generation and smoothing also was set to 15 s.

MOAA/S observations were treated as ordered categorical responses and modeled with a proportional-odds method. The model estimates the cumulative probabilities of MOAA/S scores. Let $S$ denote an observed score, the logits $b_s$, of the probabilities that $S = 0, 1, 2, 3, 4$, are:

$$l_{s=0} = b_0 + \text{DEFF} \cdot Ce$$
$$l_{s=1} = b_1 + b_0 + \text{DEFF} \cdot Ce$$
$$l_{s=2} = b_2 + b_1 + b_0 + \text{DEFF} \cdot Ce$$
$$l_{s=3} = b_3 + b_2 + b_1 + b_0 + \text{DEFF} \cdot Ce$$
$$l_{s=4} = b_4 + b_3 + b_2 + b_1 + b_0 + \text{DEFF} \cdot Ce$$

Where the $b_0$ is a fixed-effect parameter representing the logit of the probability for score 0 and $b_s$ represent the difference in logits between the scores. DEFF is also a fixed-effect parameter for the model, and $Ce$ represents the effect-site concentration of ABP-700, calculated with a first-order rate constant ($k_{e0,MOAA/S}$) in a similar manner as done for BIS. The corresponding probabilities are given by:

$$PC_s = \frac{e^{l_s}}{1 + e^{l_s}}$$

The actual probabilities, $P_s$, of observing a particular score are:

$$P_{s=0} = PC_{s=0} \cdot PC_{s=1} \cdot PC_{s=2} \cdot PC_{s=3} \cdot PC_{s=4} \cdot PC_{s=5}$$

For BIS and MOAA/S PD model estimation, the individual predicted plasma concentrations were used as the driving force for the effect compartment. This is known as the sequential method, also known as the Individual Pharmacokinetic Parameters (IPP) method. Covariate search was not performed due to the limited variability in age, weight, sex, and BMI in the studied individuals.

Model parameters were assumed to be log-normally distributed or constant across the population. For estimates of logarithmic interindividual variability, we report the estimated variance and the coefficient of variation.

Uncertainty in estimated model parameters was evaluated by estimating the upper and lower 95% confidence limits by spline-interpolation of the likelihood profiles. We determined what increase/decrease in each parameter is required to increase NONMEM objective function by 3.84.

To quantify the pharmacokinetic predictive performance for an observation, we calculated the performance error ($PE_{pk}$) and absolute performance error ($APE_{pk}$) as follows:

$$PE_{pk} = \frac{C_{predicted} - C_{observed}}{C_{predicted}} \times 100\%$$

$$APE_{pk} = PE_{pk}$$

For these measures, the median values are reported. The median $PE_{pk}$ ($MdPE_{pk}$) indicated bias, and median $APE_{pk}$ ($MdAPE_{pk}$) indicates precision.

**Clinical Observations**

This study was intended to define a MTD for ABP-700. However, it was reasoned that well-tolerated doses would need to be assessed for potential further clinical testing. Therefore, to evaluate the potential clinical utility of every specific dose, we analyzed various relevant clinical observations described by the attending anesthesiologist during the dosing together with a visual inspection of the individual vital signs trends.

IMMs were anticipated with clinical testing of ABP-700 based both on preclinical observations and also by virtue of the parent compound etomidate’s known effects on muscle movement in humans. No standardized nomenclature or scoring system was implemented to characterize IMM, as it has not been done for etomidate in the past. Instead, we described the extensiveness of the observed IMMs, rather than their nature. As such, “extensive movements” are movements defined as IMMs that involve the whole body or a considerable part of it. “Few movements” are movements that occur in few body parts, such as both arms or the face.

Breathing was monitored by means of capnography (end-tidal carbon dioxide) and capnography-derived respiratory rate monitoring. Apnea was defined as an absence of breathing for 20s or more. Tachypnea was defined as a breathing frequency of 20 breaths/min or more. Sinus tachycardia was defined as a heart rate of 100 beats/min or more and if this meant a significant change from baseline (due to possible volunteer stress). Increased blood pressure was defined as a mean arterial pressure greater than 110 mmHg if this meant a significant change from baseline. Desaturation was defined as a decrease of $SpO_2$ less than 95%.
Data Recording and Statistics
All vital signs data, MOAA/S, BIS, respiratory function, comments, and a subset of pharmacokinetic sampling time were stored electronically with a dedicated and validated electronic data capturing device (Rugloop II; DEMED, Belgium). Visual and computerized methods of data validation were applied to ensure accurate, consistent, and reliable data for the subsequent statistical analysis.

The sample size was based on previous investigations adequately studying safety, efficacy, clinical effect, and pharmacokinetic–pharmacodynamic behavior of new compounds while minimizing the exposure of volunteers to the compound. Descriptive statistics are displayed as mean ± SD or geometrical mean ± 95% CI unless indicated otherwise.

Results
Subjects
In total, 154 subjects were screened by the contract research organization (QPS, The Netherlands). Of these, 60 subjects were admitted to the study, of whom 50 received ABP-700 and 10 received a placebo. All subjects who were enrolled completed the study; no subject withdrew from the study. Mean height, weight, BMI, and age were similar among the groups, as shown in table 2.

Safety and Tolerability
Treatment-emergent adverse experiences were reported in 41 subjects, with 94 AEs reported in total (table 3). Of these, three subjects (30%) in the placebo group reported at least one AE. The majority of AEs were of mild intensity (93.7%). The number and severity of reported AEs increased with ascending doses of ABP-700. No volunteers withdrew from the study due to AEs. Of the 41 subjects experiencing at least one AE, all had at least one AE of mild intensity. Three subjects also experienced at least one AE of moderate intensity. No AEs of severe intensity were reported. AEs that were "possibly" related to the study treatment were reported for 37 subjects. Four subjects had AEs that were unlikely related, and 15 subjects experienced AEs that were unrelated to the study medication.

For each cohort, figure 1 presents the hemodynamic and respiratory data. More information on vital signs data can be found in Supplemental Digital Content 2 (http://links.lww.com/ALN/B438), which are figures plotting the individual data on heart rate, SpO2, mean arterial blood pressure measured using a noninvasive blood pressure cuff, mean arterial blood pressure using an invasive blood pressure method, respiratory rate, frontal muscles electromyographic activity and BIS measured by the Vista Monitor (Medtronic, Ireland), and end-tidal carbon dioxide for each volunteer receiving ABP-700 or placebo.

Table 2. Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N = 10)</th>
<th>ABP-700 (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (100)</td>
<td>49 (98)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>23 (3.7)</td>
<td>25 (3.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>10 (100)</td>
<td>49 (98.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>White</td>
<td>9 (90)</td>
<td>47 (94)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10 (100)</td>
<td>58 (96.7)</td>
</tr>
<tr>
<td>Stopped</td>
<td>0 (0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>If yes, subject quit smoking &gt;6 months ago? Yes</td>
<td>0 (0)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>182 (6)</td>
<td>182 (7)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>74 (7)</td>
<td>76 (7)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>22 (1.8)</td>
<td>23 (1.8)</td>
</tr>
<tr>
<td>Alcohol consumption, units/week, median (range)</td>
<td>4.5 (0–12)</td>
<td>7 (0–14)</td>
</tr>
</tbody>
</table>

ABP-700 = cyclopropyl-methoxycarbonylmethylidate.

Table 3. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>ABP-700 (N = 50)</th>
<th>Placebo (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle twitching</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Apnea</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Hyperventilation*</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Catheter site–related reaction</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Eye disorder†</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal respiration‡</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Decreased oxygen saturation</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic anesthetic complication§</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hiccups</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Presyncope║</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Listing of adverse events occurring in two or more ABP-700–treated subjects: *verbatim term: breathing disorder and paradoxical chest wall movements; †verbatim terms: rhythmic movement of eyes, eye lid flutting, and eye lid twitching; ‡verbatim term: sigh; §verbatim term: emergence delirium; and ||verbatim term: vasovagal reaction (during placement of arterial line).

ABP-700 = cyclopropyl-methoxycarbonylmethylidate.

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or hypotension after bolus injection. In the higher dosing cohorts, an increase in heart rate and mean arterial blood pressure was observed after similar time course as the cerebral drug effect of ABP-700.

Decreased SpO₂ was reported by seven subjects in the highest dose cohorts and was considered mild and self-limiting (fig. 1). Depression in respiratory rate as measured by capnography, mostly related to IMM resulting in short-lasting and self-limiting upper airway obstruction, was found in 13 volunteers and was dose-related (table 4). Short-lasting chin lift was required in four of these higher dose volunteers to maintain a patent airway. Except in the two highest dosages, where tachypnea was seen, overall respiration rate did not change during the study period, as shown in figure 1.

ABP-700 was not tolerated by three subjects because of the occurrence of severe IMM accompanied by hemodynamic disturbances. One of these subjects had received 0.75 mg/kg ABP-700, and the other two subjects had received 1.00 mg/kg ABP-700. Per protocol, midazolam was given in these three subjects. Total dosages of midazolam ranged from 2 to 5 mg. As such, in the group of 1.00 mg/kg ABP-700 the stopping criteria of the study were met, and it was concluded that 1.00 mg/kg of ABP-700 was the MTD.

Serum chemistry, hematology, urinalysis, coagulation, serum methanol concentration, and temperature did not change during the study period (data not shown). In particular, serum methanol levels were not detectable at all doses tested. Arterial blood gas parameters (pH, PaCO₂, PaO₂, HCO₃⁻, Na⁺, Cl⁻, anion gap) did not change significantly between baseline and 15 min postdose (see Supplemental Digital Content 3, http://links.lww.com/ALN/B439, a table with the arterial blood gas sampling values at baseline and 15 min postdose for each ABP-700 dosing cohort and placebo).

On the 12-lead electrocardiogram, a small decrease in the PR interval and QRS interval was observed after bolus injection of ABP-700 of all dosing groups. The changes are not dose-dependent and not clinically significant. A minor increase in the QTcF interval can be seen after bolus injection of ABP-700 (all dosing groups) without dose

---

**Fig. 1.** Vital signs. (A) Heart rate. (B) Oxygen saturation (SpO₂). (C) Mean arterial pressure as measured by no-invasive blood pressure monitoring (NIBP MAP). (D) Mean arterial blood pressure as measured by invasive arterial blood pressure monitoring (INV MAP). (E) Respiration rate. Data are presented as geometrical means per cohort. Fen = fentanyl.
dependency or clinical significance. ACTH stimulation evoked an adrenal cortisol response in all subjects treated with ABP-700. Plasma cortisol concentrations increased by at least 200 nM/l at 60 or 120 min post-ACTH stimulation, indicating no adrenal suppression (fig. 2). There was no difference observed between placebo and the ABP-700 dose levels, other than differences that would be considered with the normal variability of the test.

ACTH testing was not performed for the cohorts that received fentanyl as a pretreatment, because these cohorts were repeats of previous dose levels. Cortisol levels of cohort 10, which received 0.175 mg/kg ABP-700, were not analyzed because an ACTH-stimulation test in previous cohorts that received a higher dose of ABP-700 (0.25, 0.35, 0.50, 0.75, and 1.00 mg/kg) did not reveal any adrenocortical suppression.

Table 4. Evaluation of Tolerability of ABP-700 Given to Healthy Volunteers

<table>
<thead>
<tr>
<th>Placebo</th>
<th>0.03 mg/kg</th>
<th>0.10 mg/kg</th>
<th>0.175 mg/kg</th>
<th>0.25 mg/kg</th>
<th>0.25 mg/kg + fen</th>
<th>0.35 mg/kg</th>
<th>0.35 mg/kg + fen</th>
<th>0.50 mg/kg</th>
<th>0.75 mg/kg</th>
<th>1.00 mg/kg</th>
<th>Total</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Involuntary muscle movements</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No movements</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Few movements</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Extensive movement</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>5</td>
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<table>
<thead>
<tr>
<th>Ventilation</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Tachypnea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
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<td>Desaturation</td>
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<td>0</td>
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<table>
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<tr>
<th>Vital signs</th>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Tachycardia</td>
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<td>0</td>
<td>2</td>
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<td>Bradycardia</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<table>
<thead>
<tr>
<th>Catheter site–related reactions</th>
<th></th>
<th></th>
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<th></th>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ventilation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Values are number of volunteers. ABP-700 = cyclopropyl-methoxycarbonylmetomidate; fen = fentanyl.

Fig. 2. Human adrenocortical response to adrenocorticotropic hormone (ACTH) stimulation after bolus administration of cyclopropyl-methoxycarbonylmetomidate (ABP-700) (0.03 to 1.0 mg/kg) or placebo. Adrenocortical response before and after administration of 250 μg synthetic ACTH 1 h after bolus ABP-700. Predose cortisol reference levels were obtained before 9 AM on the day of ABP-700 administration. Values are mean cortisol levels (± SD) for ABP-700 and placebo groups. n = 5 by ABP-700 dose and n = 7 for placebo.
Noncompartmental Pharmacokinetics
For each cohort, the time courses of the arterial and venous concentrations of ABP-700 and of the arterial of CPM acid are displayed in figure 3. The most important noncompartmental pharmacokinetic parameter values for ABP-700 (both arterial and venous) and its metabolite CPM acid are shown as tables in Supplemental Digital Content 1 (http://links.lww.com/ALN/B437). Overall, pharmacokinetics were dose-proportional. Clear differences between arterial and venous concentrations and pharmacokinetic parameters were observed.

Compartmental Pharmacokinetics
No significant covariate relationships with age, weight, height, or sex were found. The weight linear scaled model achieved an Akaike information criterion of −2,700.61 with a median absolute percentage error of 1.98 (24.5)%.

Summarized equations of the final pharmacokinetic model are as follows:

\[
\text{SIZE} = \frac{\text{WGT}}{70\text{kg}}
\]

\[
V1(L) = V_{1\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_1)
\]

\[
V2(L) = V_{2\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_2)
\]

\[
V3(L) = V_{3\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_3)
\]

\[
CL(L \cdot \text{min}^{-1}) = CL_{\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_4)
\]

\[
Q2(L \cdot \text{min}^{-1}) = Q_{2\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_5)
\]

\[
Q3(L \cdot \text{min}^{-1}) = Q_{3\text{ref}} \cdot \text{SIZE} \cdot \exp(\eta_6)
\]

Symbols \(V_{1\text{ref}}, V_{2\text{ref}}, V_{3\text{ref}}, CL_{\text{ref}}, Q_{2\text{ref}}, \) and \(Q_{3\text{ref}}\) are the estimated compartmental volumes and clearances for a 70-kg individual, and symbols \(\eta_1\) to \(\eta_6\) represent random variances. Estimated parameters are shown in table 5. The population and individual predictions versus time and observed concentrations are shown in figure 3.
ABP-700 arterial concentrations and the likelihood profiles are documented as figures in Supplemental Digital Content 4 (http://links.lww.com/ALN/B440) and 5 (http://links.lww.com/ALN/B441), respectively.

### Clinical Effects and Pharmacodynamics

For each cohort, the time course of the BIS and frontal electromyographic activity are plotted in figure 4. At the lowest dose of ABP-700 administered (0.03 mg/kg), there was no observed effect on BIS. Subjects receiving dose levels of 0.1 mg/kg ABP-700 or greater showed a dose-dependent response to the treatment, as indicated by the rapidly decreasing BIS values (within 1 to 2 min). Duration of cerebral drug effect was longer in higher dosing cohorts. Due to increased electromyographic activity,14 as shown in figure 4, the decrease in BIS in the 0.75 mg/kg cohort paradoxically was delayed. For BIS model development, $C_e$ and $k_e$ were assumed and log-normally distributed across the population. Estimating baseline BIS resulted in numerical instability, and its value was fixed to 90.

The duration of both the clinical effect and sedation increased with escalating dose. Neither the time to onset of clinical effect nor the time to onset of deep sedation/anesthesia was dose-related. For MOAA/S PD model development, we assumed log-normally distributed population variability in drug effect.

### Symbols

Symbols $DEFF$ and $k_{e_0,MOAA}$ represent estimated model parameters in the individual, $DEFF_{TYP}$ and $k_{e_0,MOAA,TYP}$ represent the typical population model parameters, and $\eta_1$ represents population variance. For the final model, the estimated parameters are shown in table 7. The population and individual predictions versus time and MOAA/S and the likelihood profiles for the model parameters are shown as figures in Supplemental Digital Content 8 (http://links.lww.com/ALN/B444) and 9 (http://links.lww.com/ALN/B445).

### Influence of Fentanyl

After completion of the preplanned cohorts and evaluation for tolerability and potential clinical utility, the 0.25- and 0.35-mg/kg doses of ABP-700 were considered as the two most promising doses and were repeated in the presence of fentanyl pretreatment (1 μg/kg). The administration of fentanyl resulted in decrease in the incidence and extent of IMM and also in less tachycardia when compared with the ABP-700 dose without fentanyl (table 4). Fentanyl pretreatment did not alter the time to onset of clinical effect or onset of sedation, nor did it alter the duration of sedation or clinical effect (data not shown). As shown in figure 4, a more pronounced clinical effect of ABP-700 as measured by BIS was observed with fentanyl pretreatment than without, although this did not result in a significant covariate in the pharmacodynamic model parameters. Fentanyl did result in somewhat higher frequency of respiratory depression and desaturation events. The administration of fentanyl did not result in a substantial alteration of the pharmacokinetics of either ABP-700 or its metabolite CPM acid, as shown by both noncompartmental and compartmental modeling (analysis not shown).

### Discussion

Cyclopropyl-methoxycarbonylmethomidate, or ABP-700, is a short-acting, soft analog of etomidate and was developed to avoid the adrenocortical suppression while preserving

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### Table 5. Estimated Model Parameters and Population Variances in the Final Pharmacokinetic Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated Value</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V1_{ref}$</td>
<td>0.527</td>
<td>0.427</td>
<td>0.649</td>
</tr>
<tr>
<td>$V2_{ref}$</td>
<td>3.02</td>
<td>2.47</td>
<td>3.71</td>
</tr>
<tr>
<td>$V3_{ref}$</td>
<td>5.18</td>
<td>4.59</td>
<td>5.85</td>
</tr>
<tr>
<td>$CL_{ref}$</td>
<td>1.66</td>
<td>1.57</td>
<td>1.77</td>
</tr>
<tr>
<td>$Q2_{ref}$</td>
<td>1.14</td>
<td>0.951</td>
<td>1.41</td>
</tr>
<tr>
<td>$Q3_{ref}$</td>
<td>0.336</td>
<td>0.297</td>
<td>0.382</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variance, $\omega^2$</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\eta_1$</td>
<td>0.323</td>
<td>61.8</td>
</tr>
<tr>
<td>$\eta_2$</td>
<td>0.352</td>
<td>64.9</td>
</tr>
<tr>
<td>$\eta_3$</td>
<td>0.106</td>
<td>33.5</td>
</tr>
<tr>
<td>$\eta_4$</td>
<td>0.0178</td>
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</tr>
<tr>
<td>$\eta_5$</td>
<td>0.249</td>
<td>53.2</td>
</tr>
<tr>
<td>$\eta_6$</td>
<td>0.0804</td>
<td>28.9</td>
</tr>
</tbody>
</table>

| Residual error (SD) | 0.103 |

$V1_{ref}$, $V2_{ref}$, $V3_{ref}$, $CL_{ref}$, $Q2_{ref}$, and $Q3_{ref}$ are the estimated compartmental volumes and clearances for a 70-kg individual, and symbols $\eta_1$ to $\eta_6$ represent random variances.

$CV = \text{coefficient of variation.}$

$DEFF = DEFF_{TYP} \cdot \exp(\eta_1)$

$k_{e_0,MOAA} = k_{e_0,MOAA,TYP}$

Symbols $DEFF$ and $k_{e_0,MOAA}$ represent estimated model parameters in the individual, $DEFF_{TYP}$ and $k_{e_0,MOAA,TYP}$ represent the typical population model parameters, and $\eta_1$ represents population variance. For the final model, the estimated parameters are shown in table 7. The population and individual predictions versus time and MOAA/S and the likelihood profiles for the model parameters are shown as figures in Supplemental Digital Content 8 (http://links.lww.com/ALN/B444) and 9 (http://links.lww.com/ALN/B445).
the beneficial dose–response profile of etomidate.\textsuperscript{5} In this first-in-human study, we found that ABP-700 was safe and well-tolerated after single-bolus injections of up to a maximum of 1.0 mg/kg. The two most promising dosages for potential clinical utility as a bolus induction agent were thought to be 0.25 and 0.35 mg/kg.

As expected, based on the preclinical studies,\textsuperscript{2,7,15} ABP-700 demonstrated hypnotic–anesthetic properties. Clinical effect was first seen after a bolus dose of 0.175 mg/kg of ABP-700 (in four out of five volunteers). At doses of 0.25 mg/kg and greater, a decrease in MOAA/S score to 0 was observed in all subjects. The time to onset of deep sedation/anesthesia was found to be dose-independent and extremely short, around 30 s after bolus injection, which is somewhat shorter than etomidate and thiopental\textsuperscript{16} and significantly shorter than propofol.\textsuperscript{17} Duration of deep sedation/anesthesia was dose-dependent. Offset of deep sedation/anesthesia was characterized by an abrupt and rapid return to a MOAA/S score of 5 in most of the volunteers.

There were very few recorded instances of MOAA/S 2 or 3 during either induction or emergence from deep sedation/anesthesia. BIS profiles showed a similar time course of drug effect to MOAA/S scores, characterized by a rapid, dose-independent decline, with lowest value between 45 and 55, except for the cohort that received a bolus of 0.75 mg/kg ABP-700, due to possible electromyographic artifacts (fig. 4).\textsuperscript{14}

Pharmacodynamic modeling for both MOAA/S and BIS illustrate the steep relation between the ABP-700 effect-site concentration and the cerebral drug effect. Although possibly influenced by the intermittent nature of MOAA/S scores in this study, figure 6 clearly shows the small range in effect-site concentrations between the probabilities for different MOAA/S scores. It is remarkable that the difference in ABP-700 effect-site concentration between 50% probability of MOAA/S score 5 and 0 is only around 500 ng/ml. The steepness also is evident in the large $\gamma$ found in the BIS sigmoid pharmacodynamic model. The effect-site

\*Fig. 4. Hypnotic effect of cyclopropyl-methoxy carbonylmetomidate. (A) Depth of sedation and anesthesia, as measured by the Bispectral Index and (B) frontal electromyographic activity (EMG). Fen = fentanyl.
ABP-700 did not cause cardiovascular depression, as seen in figure 1 and table 4. However, increases in heart rate and blood pressure were observed in the higher dosing groups and followed a similar time course as the clinical effect. Increases in heart rate with stable blood pressure have been reported previously for etomidate\(^{23}\) and also with the inhaled agent desflurane.\(^{24}\) Some short-lasting episodes of increased blood pressures (mean arterial blood pressure greater than 110 mmHg) were found, but without any requirement for treatment.

ABP-700 has a remarkably stable respiratory profile. No centrally induced respiratory depression was recorded. Decreases in amplitude and frequency of respiration rate were induced mostly by the IMM, resulting in a brief and self-limiting upper airway obstruction. Per protocol, brief chin lift was applied in four volunteers after 20 s of airway obstruction to maintain a patent airway. Two of these volunteers had received 0.75 mg/kg ABP-700, and two had received 1.00 mg/kg. Tachypnea was observed in parallel with the hypnotic-anesthetic effect in the two highest dosing groups, receiving 0.75 and 1.00 mg/kg AB-700 boluses. Self-limiting changes in SpO\(_2\) were only recorded occasionally. The notion that deep sedation/anesthesia is possible without any appreciable respiratory depression is obviously of potential clinical importance. Etomidate is associated with less respiratory depression than propofol but at deep sedation/anesthesia doses, both decrease medullary respiratory drive and right-shift the hypercarbic ventilator response.\(^{25,26}\) Although the stable respiratory rate and arterial carbon dioxide levels seen with ABP-700 are suggestive of preservation of respiratory drive, this MTD dose study was not intended to thoroughly evaluate ABP-700 effects on respiratory function.

Consistent with preclinical findings,\(^{1-15}\) ABP-700 did not suppress the physiologic response of the adrenal axis to ACTH stimulation in human volunteers. A significant increase of at least 200 nM at 60 or 120 min poststimulation occurred and was not different from subjects who received a placebo. Although not directly compared in this study, adrenal responsiveness after single-bolus exposure to ABP-700 is superior to the substantial adrenal suppression caused by bolus dosing of etomidate.\(^6\)

Noncompartmental pharmacokinetics were studied for both ABP-700 (arterial and venous) and its metabolite CPM acid (arterial). The results showed rapid elimination of ABP-700 across all dose regimens. The mean clearance values observed in this study were relatively high compared with hepatic blood flow. Clearance and volume of distribution estimated for the venous blood samples were all higher than those estimated for the arterial blood samples, reflecting the rapid metabolism of ABP-700 by esterases during the arterial to venous transport. ABP-700 plasma exposure increased dose proportionally as the dose increased from 0.03 to 1.00 mg/kg for both arterial and venous blood samples. Dose-proportional arterial plasma exposures of CPM acid also were observed.

### Table 6. Estimated Model Parameters and Population Variances in the Final BIS Pharmacodynamic Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated Value</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_0)</td>
<td>90</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(E_{\text{max}})</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(C_{\text{e}50,\text{TYP}})</td>
<td>1,200</td>
<td>1,060</td>
<td>1,350</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>7.24</td>
<td>6.83</td>
<td>7.66</td>
</tr>
<tr>
<td>(k_{\text{e0, BIS, TYP}})</td>
<td>0.156</td>
<td>0.132</td>
<td>0.179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variance, (\omega^2)</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\eta_1)</td>
<td>0.139</td>
</tr>
<tr>
<td>(\eta_2)</td>
<td>0.742</td>
</tr>
</tbody>
</table>

| BiS observations | 6.35 |

\(E_0\) is the baseline pharmacodynamic measure when no drug is present; \(E_{\text{max}}\) is the maximum possible drug effect; \(C_{\text{e}50,\text{TYP}}\) is the typical population model parameter for the effect-site concentration of ABP-700 associated with 50% of the maximum effect; \(\gamma\) is the steepness of the concentration versus response relation; \(k_{\text{e0, BIS, TYP}}\) is the typical population model parameter for the first-order rate constant between plasma and effect-site compartment; and \(\eta_1\) and \(\eta_2\) represent population variances. BiS = Bispectral Index; CV = coefficient of variation; TYP = population typical value.

Clinical observations related to IMM, ventilation, and vital signs were dose-dependent and consistent with the mechanism of action of ABP-700 and its structurally related analog, etomidate.\(^{5,16}\) From a dosage of 0.175 mg/kg of ABP-700 upwards, IMM were observed in most of the volunteers. These IMMs varied from few muscle movements of a more twitching character to more extensive muscle movements that appeared to be of an intermittent myoclonic nature. In various volunteers, these muscle twitches were induced mostly by the IMM, resulting in a brief and self-limiting upper airway obstruction. Per protocol, brief chin lift was applied in four volunteers after 20 s of airway obstruction to maintain a patent airway. Two of these volunteers had received 0.75 mg/kg ABP-700, and two had received 1.00 mg/kg. Tachypnea was observed in parallel with the hypnotic-anesthetic effect in the two highest dosing groups, receiving 0.75 and 1.00 mg/kg AB-700 boluses. Self-limiting changes in SpO\(_2\) were only recorded occasionally. The notion that deep sedation/anesthesia is possible without any appreciable respiratory depression is obviously of potential clinical importance. Etomidate is associated with less respiratory depression than propofol but at deep sedation/anesthesia doses, both decrease medullary respiratory drive and right-shift the hypercarbic ventilator response.\(^{25,26}\) Although the stable respiratory rate and arterial carbon dioxide levels seen with ABP-700 are suggestive of preservation of respiratory drive, this MTD dose study was not intended to thoroughly evaluate ABP-700 effects on respiratory function.

Consistent with preclinical findings,\(^{1-15}\) ABP-700 did not suppress the physiologic response of the adrenal axis to ACTH stimulation in human volunteers. A significant increase of at least 200 nM at 60 or 120 min poststimulation occurred and was not different from subjects who received a placebo. Although not directly compared in this study, adrenal responsiveness after single-bolus exposure to ABP-700 is superior to the substantial adrenal suppression caused by bolus dosing of etomidate.\(^6\)

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A three-compartment pharmacokinetic model was developed to describe the time course of arterial drug concentration. The final model accurately predicts the arterial concentrations of ABP-700 after a single-bolus injection in the central compartment. Venous samples were not used for model estimation. For soft drugs, it is well known that venous samples are potentially very misleading in describing the clinical behavior of a drug through modeling.77 The

Fig. 5. Modified Observers Assessment of Alertness and Sedation (MOAA/S) scores by subject. The data are displayed by individual subject who received cyclopropyl-methoxycarbonylmetomidate (n = 50) and per cohort (10 cohorts in total). Data for placebo were omitted because no subject was scored less than 5.
DEFFTYP

b1

η

DEFF is also a fixed-effect parameter for the model; ke0, MOAA/S, TYP
etomidate can be attenuated by pretreatment with low doses
with the addition of fentanyl. It is well known IMM due to
decrease in BIS was seen. Less extensive IMMs were observed
as measured by MOAA/S. Nevertheless, a more pronounced
alter the onset, duration, and recovery profile of ABP-700
0.25 mg/kg ABP-700 and 0.35 mg/kg ABP-700 did not
accurate size descriptors than weight, and more covariates.
gations, hereby also exploring other than linear models, more
be developed, adding data from continuous-infusion investi-
gations of commonly used drugs during procedural care, such as opi-
oids and benzodiazepines.11,12 Although speculative, given
the chemical derivation of ABP-700 as an etomidate analog,
the origin of IMM seen with ABP-700 may be mechanisti-
cally similar to that seen with etomidate.
Consistent with known effects, some respiratory and
hemodynamic changes were associated with fentanyl admin-
istration before ABP-700. This study was not designed to
assess these changes, so it is not possible to comment on their
clinical significance. Because ABP-700 is not expected to
have any analgesic properties, its use in procedural sedation
or anesthesia will require concomitant dosing of opioids.
In general, there were no substantial differences in both
noncompartmental and compartmental pharmacokinetic
parameters for ABP-700 and CPM acid after a bolus dose of
0.25 and 0.35 mg/kg of ABP-700 without and with 1
μg/kg fentanyl pretreatment, respectively. However, these
comparisons on pharmacokinetics of ABP-700 or CPM acid
between the subjects that have been administered ABP-700
alone or coadministered with fentanyl might be biased and
were performed for exploratory purposes. The influence of
fentanyl on the pharmacokinetics of ABP-700 and CPM
acid should be studied in greater detail within a properly
designed drug–drug interaction study.
As always, studies of this type have limitations. One is
that the clinical hypnotic–anesthetic drug effect of ABP-
700 was assessed by the MOAA/S scale. A problem with
using the MOAA/S scale is that the volunteer is stimulated,
which might result in an arousal poststimulus and biasing
the hypnotic–anesthetic continuum. Furthermore, clinical
observations are made by clinicians and are therefore prone
to subjectivity. As there were three attending anesthesiolo-
gists involved in this study, some variability in MOAA/S
assessments is possible.
Another limitation of this study is that BIS monitor-
ning is not validated for monitoring the depth of anesthe-
sia achieved with ABP-700. However, BIS is an established
form of monitoring for other GABA-acting drugs,29 and the
BIS pattern follows the MOAA/S pattern closely. Therefore,
it can be assumed that the BIS data are valid for ABP-700.
In addition, as this is a safety and tolerability Phase 1 study,
findings should not be extrapolated to any clinical practice
guidelines yet.
We can conclude that ABP-700 was safe and well toler-
ated after single-bolus injections of up to a maximum tol-
erated bolus dose of 1.0 mg/kg. A bolus dose of 0.25 and
0.35 mg/kg was found to have a sufficiently favorable clinical
effect versus side-effect profile to be explored in future stud-
ies. These dosages of ABP-700 showed dose responsive hyp-
notic–anesthetic characteristics and a safety and tolerability
profile that warrants further investigation and development.

### Acknowledgments

The authors acknowledge the support of Rob Spanjersberg,
C.N., C.R.C., Clinical Research Coordinator, and Anne-Sophia

![Fig. 6. Population predictions of Modified Observers Assessment of Alertness and Sedation (MOAA/S) scores versus cyclopropyl-methoxycarbonylmetomidate (ABP-700) effect-site concentrations. The vertical lines to the x-axis denote the effect-site concentration at a 50% probability for having an MOAA/S score of 5 and 0, respectively.](image)

### Table 7. Estimated Model Parameters and Population Variances in the Final MOAA/S Pharmacodynamic Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated Value</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFFTYP</td>
<td>5.25</td>
<td>4.41</td>
<td>6.23</td>
</tr>
<tr>
<td>ke0_MOAA/S,TYP</td>
<td>0.488</td>
<td>0.443</td>
<td>0.537</td>
</tr>
<tr>
<td>b0</td>
<td>−10.1</td>
<td>−11.7</td>
<td>−8.77</td>
</tr>
<tr>
<td>b1</td>
<td>0.713</td>
<td>0.459</td>
<td>1.02</td>
</tr>
<tr>
<td>b2</td>
<td>0.518</td>
<td>0.307</td>
<td>0.817</td>
</tr>
<tr>
<td>b3</td>
<td>0.407</td>
<td>0.222</td>
<td>0.670</td>
</tr>
<tr>
<td>b4</td>
<td>1.02</td>
<td>0.735</td>
<td>1.36</td>
</tr>
<tr>
<td>Variance, ω²</td>
<td>0.0472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV, %</td>
<td>22.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b1 is a fixed-effect parameter representing the logit of the probability for score 0, b2 through b4 represent the difference in logits between the scores; DEFF is also a fixed-effect parameter for the model; ke0_MOAA/S,TYP is the typical population model parameter for the first-order rate constant between plasma and effect-site compartment; and η1 represents the population variance.

CV = coefficient of variation; MOAA/S = Modified Observers Assessment of Alertness and Sedation; DEFFTYP = typical population parameter for a fixed-effect parameter for the model.
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Competing Interests
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