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Sponsors Executive Summary

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BRIEFING MATERIALS

FOR

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL REVIEW OF THE SEDASYS® SYSTEM

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Prepared by Ethicon Endo-Surgery, Inc.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAAHC	Accreditation Association for Ambulatory Health Care
ACLS	Advanced Cardiac Life Support
ANOVA	Analysis of Variance
ANSI/AAMI SP10	American National Standards Institute/Association for the Advancement of Medical Instrumentation
ARM	Automated Responsiveness Monitor
ASA	American Society of Anesthesiologists
ASA I-III	American Society of Anesthesiologists Classification of Physical Status
ASA Guidelines	Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists
ASGE	American Society for Gastrointestinal Endoscopy
ASTM	American Society for Testing and Materials
AUC_{Desat}	Area-Under-the-Curve of Oxygen Desaturation
BMU	Bedside Monitoring Unit
CFR	Code of Federal Regulations
CSC	Current Standard of Care (opioid + benzodiazepine)
CSSI	Clinician Satisfaction with Sedation Instrument
DAQ	Data Acquisition System
DiasBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EGD(s)	Esophagogastroduodenoscopy(ies)
ESC	Effect Site Concentration
FDA	Food and Drug Administration
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IV	Intravenous

JCAHO	Joint Commission on the Accreditation of Healthcare Organizations (The Joint Commission)
LD	Loading Dose
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MOAA/S	Modified Observers Assessment of Alertness/Sedation
MR	Maintenance Rate
NIBP	Non-Invasive Blood Pressure
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PP	Per Protocol
PRN	Pro Re Nata (As Needed)
PRU	Procedure Room Unit
PSSI	Patient Satisfaction with Sedation Instrument
PSU	Power Supply Unit
RR	Respiration Rate
SD(s)	Standard Deviation(s)
SDS	Sedation Delivery System or SEDASYS System
SpO_2	Arterial Oxygen Saturation as Measured by Pulse Oximeter
SysBP	Systolic Blood Pressure
2 L/min	2 Liters per Minute
US	United States
V_D	Volume of Distribution

1.0 EXECUTIVE SUMMARY

This briefing package has been prepared for a meeting with the Anesthesiology and Respiratory Therapy Devices Panel on May 28, 2009. During this meeting, the Panel will discuss the safety and effectiveness of the SEDASYS® System, a Computer-Assisted Personalized Sedation System, as submitted in Ethicon Endo-Surgery's Premarket Approval Application.

1.1 Indications for Use

The SEDASYS System is indicated for the intravenous administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal-to-moderate sedation, as defined by the American Society of Anesthesiologists Continuum of Depth of Sedation, in adult patients (American Society of Anesthesiologists physical status I and II) undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

1.2 Intended User

The SEDASYS System is intended to be used by the same physician/nurse teams who currently administer minimal-to-moderate sedation (sometimes referred to as "conscious sedation") with benzodiazepines and opioids. This type of sedation is administered to approximately 12.2 million patients each year undergoing colonoscopy and EGD procedures.[1-2] Importantly, the SEDASYS System is not intended to replace anesthesia professionals currently administering sedation for high-risk patients or those who require deep sedation/general anesthesia.

1.3 Brief Device Description

The SEDASYS System is an integrated drug delivery and monitoring system developed in collaboration with anesthesiologists, clinical pharmacologists, and anesthesia device experts. The SEDASYS System was designed to be compliant with relevant sections of the Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists[3] developed by the American Society of Anesthesiologists (ASA), as well as the dosing recommendations in FDA-approved propofol labeling.[4]

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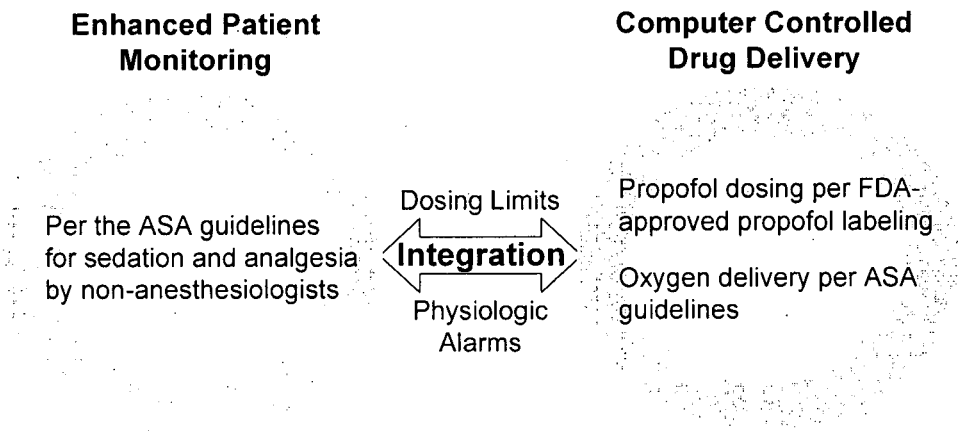
[1] Data obtained by MarketScan Research Database from Thomson Reuters 2006.

[2] Lawrence B. Cohen, M.D., Julie S. Wecsler, B.A., John N. Gaetano, B.A., Ariel A. Benson, B.A., Kenneth M. Miller, M.D., Valerie Durkalski, Ph.D., M.P.H., and James Aisenberg, M.D. 2006. Endoscopic Sedation in the United States: Results from a Nationwide Survey. *American Journal of Gastroenterology* 101:967–974.

[3] American Society of Anesthesiologists. 2002. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 96(4):1004-17.

[4] APP Pharmaceuticals, LLC. February 2008. DIPRIVAN (propofol) 1% Injectable Emulsion for I.V. Labeling.

Figure 1
Integration of Patient Monitoring With Drug Delivery



The SEDASYS System monitors the physiologic parameters recommended in the ASA practice guidelines. Patient monitors include a: 1) pulse oximeter, 2) capnometer, 3) electrocardiogram (EGD), 4) non-invasive blood pressure, and 5) novel automated responsiveness monitor. Inclusion of the capnometer, ECG, and automated responsiveness monitor exceeds what is typically used during the current standard of care.

The SEDASYS System uses a novel drug delivery algorithm to drive a peristaltic infusion pump. The drug delivery algorithm has been designed in accordance with the dosing guidelines for sedation in propofol labeling. The SEDASYS System contains an automated supplemental oxygen delivery system, conforming to the ASA guidelines for oxygen delivery during sedation. The incorporation of mandatory oxygen delivery also exceeds what is commonly done during the current standard of care.

Patient monitoring and drug delivery are integrated through four interlocking elements:

- Dosing restrictions
- Automated oxygen delivery
- Integrated patient alarms
- Subsystem status advisories

Dosing restrictions, based on FDA-approved propofol labeling, are designed to minimize over-sedation by limiting infusion rates and enforcing titration to clinical effect through lockout timers. Automated oxygen delivery is designed to minimize hypoxia. Integrated patient alarms are designed to alert the clinical team to any compromise in patient status and reduce, or stop, propofol delivery if appropriate. Subsystem status advisories are designed to ensure the patient monitors, oxygen manifold, and infusion pump are working as intended.

Details on the device design are found in Section 3.0, *Device Description.*

1.4 Summary of Clinical Studies

Ethicon Endo-Surgery conducted 14 clinical studies using the SEDASYS system. Four proof-of-concept studies focused on the dosing of propofol for sedation, both alone and in combination with fentanyl. Three studies assessed current sedation practice for colonoscopy and EGD procedures. Four studies evaluated the clinical functionality of key sub systems: oxygen delivery, automated responsiveness monitor, capnometry, and pulse oximetry. Two studies evaluated the feasibility of the SEDASYS System to enable physician/nurse teams to safely and effectively administer minimal-to-moderate sedation. Finally, a large pivotal study tested the hypothesis that the SEDASYS System was a safe and effective alternative to current benzodiazepine-based sedation.

1.4.1 Pivotal Study Design

The pivotal study was a multi-center, non-blinded, randomized (1:1), comparative study of the SEDASYS System (also referred to as the SDS) versus benzodiazepine-based sedation (referred to as Current Standard of Care [CSC]) versus benzodiazepine-based sedation in subjects undergoing colonoscopy or EGD procedures. A total of 1000 subjects (721 colonoscopy and 279 EGD) were enrolled across eight centers. The study, at the recommendation of FDA, intentionally enrolled more subjects undergoing colonoscopy because colonoscopies are typically longer than EGD procedures, potentially presenting a greater sedation challenge.

The primary endpoint of the study was area-under-the-curve of oxygen desaturation (AUC_{Desat}) ($SpO_2 < 90\%$ saturation for >15 seconds).

There were four secondary endpoints:

- Clinician satisfaction with sedation (CSSI questionnaire on a 0-100 scale)
- Patient satisfaction with sedation (PSSI questionnaire on a 0-100 scale)
- Recovery time
- Duration of deep sedation/general anesthesia

1.4.2 Pivotal Study Results

Tables 1 and 2 display the results for the primary and secondary endpoints for colonoscopy and EGD procedures, respectively.

Table 1
Primary and Secondary Endpoints for Colonoscopy[a]

	SDS (N = 358)	CSC (N = 363)	p-value[b]
Primary Endpoint			
AUC_{Desat} (seconds·%)	18 ± 125	99 ± 510	0.004
Secondary Endpoints			
CSSI	92 ± 10	76 ± 17	< 0.001
PSSI	93 ± 12	91 ± 12	0.052
Recovery Time (minutes)	2.7 ± 2.4	6.3 ± 6.8	< 0.001
Duration of Deep Sedation/General Anesthesia (minutes)	0.1 ± 1.2	0.1 ± 1.2	0.573

[a] Plus-minus values are means ± SD.
[b] Values were analyzed using an analysis of variance, except Recovery Time which used a Cox. Proportional Hazards Regression Analysis.

Table 2
Primary and Secondary Endpoints for EGD[a]

	SDS (N = 138)	CSC (N = 141)	p-value[b]
Primary Endpoint			
AUC_{Desat} (seconds·%)	39 ± 182	60 ± 180	0.315
Secondary Endpoints			
CSSI	92 ± 11	77 ± 16	< 0.001
PSSI	91 ± 13	88 ± 13	0.067
Recovery Time (minutes)	3.5 ± 2.5	7.0 ± 7.4	< 0.001
Duration of Deep Sedation/General Anesthesia (minutes)	0.0 ± 0.4	0.1 ± 0.9	0.731

[a] Plus-minus values are means ± SD.
[b] Values were analyzed using an analysis of variance, except Recovery Time which used a Cox Proportional Hazards Regression Analysis.

For colonoscopy procedures, 21 (5.9%) subjects in the SDS group experienced at least one adverse event, as reported by the investigator. The most frequently reported adverse events in the SDS group were nausea (1.4%) and abdominal pain (1.1%). In the CSC group, 29 (8.0%) subjects had at least one adverse event, as reported by the investigator. The most frequently reported adverse event in the CSC group was oxygen desaturation (4.7%). There was one subject in the CSC group that had a serious adverse event.

For EGD procedures, 8 (5.8%) subjects in the SDS group experienced at least one adverse event, as reported by the investigator. There were no reported adverse events in the SDS group with a frequency ≥ 1.0%. In the CSC group, 15 (10.6%) subjects had at least one adverse event, as reported by the investigator. The most frequently reported adverse events in the CSC group were oxygen desaturation (7.1%), pharyngolaryngeal pain (2.1%), and nausea (1.4%).

1.4.3 Pivotal Study Discussion

The pivotal study provided considerable scientific evidence demonstrating physician/nurse teams can safely and effectively administer minimal-to-moderate sedation with propofol to subjects undergoing colonoscopy and EGD procedures. The SEDASYS System was tested in a well-controlled investigation by physician/nurse teams under expected conditions of use, with both clinically and statistically significant results.

The primary endpoint was a reduction in the area-under-the-curve of oxygen desaturation (AUC_{Desat}). The SEDASYS System achieved its primary endpoint in colonoscopy. In the design of this pivotal study, patients undergoing colonoscopy procedures were judged to be at greater risk of oxygen desaturation, when compared to patients undergoing EGD procedures, a judgment confirmed by the pivotal study results. The SEDASYS System did not achieve its primary endpoint in EGD. This result was not unexpected given the diminished base size versus colonoscopy (279 vs. 721).

The CSSI secondary endpoint demonstrated that clinicians were more satisfied with sedation provided with the SEDASYS System than with current standard of care for the colonoscopy and EGD groups, a result that was clinically and statistically significant.

The PSSI secondary endpoint demonstrated that patients were highly satisfied with their sedation for both the colonoscopy and EGD procedures, regardless of whether it was provided with the SEDASYS System or the current standard of care.

The recovery time secondary endpoint demonstrated faster recovery from sedation with the SEDASYS System for both the colonoscopy and EGD groups. The faster recovery was clinically and statistically significant.

The incidence of deep sedation/general anesthesia was very low in both the colonoscopy and EGD studies. Deep sedation/general anesthesia occurred with approximately equal frequency with the SEDASYS System and the current standard of care.

Fewer patients experienced adverse events during colonoscopy and EGD when sedation was provided with the SEDASYS System when compared with the current standard of care group.

In summary, the pivotal study demonstrated that the SEDASYS System provides a safe and effective alternative to benzodiazepine-based sedation for both colonoscopy and EGD procedures. While the primary endpoint for EGD was not statistically significant, the data gathered from this study, when taken in totality, indicates that Ethicon Endo-Surgery clearly met its regulatory burden of providing 'reasonable assurance' of safety and effectiveness. Across all primary and secondary measures, the SEDASYS System performed equal or better than the current standard of care control group.

Details of the pivotal clinical study are found in Section 4.5, *Pivotal Study (CI-06-0004)*.

1.5 Post-approval Risk Minimization Plan

Upon FDA approval, Ethicon Endo-Surgery is planning to implement various programs to further minimize risk and maximize patient safety. The plan is comprehensive and includes a controlled launch, facility and user requirements, device training, and a post-approval study.

1.5.1 Controlled Launch

Consistent with the methodical development of the SEDASYS System, Ethicon Endo-Surgery will conduct a progressive, phased-launch plan. Initially, the SEDASYS System will be placed at no more than 20 facilities. These facilities will be large, established endoscopy centers that typically conduct in excess of 5000 procedures annually. After review of the feedback from these sites, the device will be made available to additional facilities.

1.5.2 Facility and User Requirements

The SEDASYS System will only be placed in accredited facilities (e.g., those certified by The Joint Commission [TJC], formerly known as JCAHO). This accreditation will be reinforced with requirements that prospective users be trained in minimal-to-moderate sedation, including airway management, before being allowed to use the device. Facilities will be required to verify and sign documentation acknowledging the above requirements have been met.

1.5.3 Device Training Program

Ethicon Endo-Surgery will implement a three-step device training program prospective users must complete in order to utilize the SEDASYS System. The curriculum was developed with input from anesthesiologists, gastroenterologists, registered nurses, and education specialists.

The first step consists of an on-line program designed to teach prospective users about every aspect of the SEDASYS System. Prospective users must successfully complete all the learning modules and pass a final test before they will be allowed to progress to the second step of the training program.

In the second step, an Ethicon Endo-Surgery clinical education specialist will conduct training to reinforce and enhance the knowledge that prospective users have in operating the device. At the conclusion of this training, all prospective users will document their participation in the training and verify that they are ready to use the SEDASYS System.

After prospective users have participated in the on-site instructor-led training, they will proceed with the third step of the device training program. During this final step, physicians and nurses will conduct colonoscopy and EGD procedures under the observation of an Ethicon Endo-Surgery clinical education specialist.

1.5.4 Post-approval Vigilance

Ethicon Endo-Surgery is committed to patient safety. Customer complaints will be tracked and investigated, and as appropriate, corrective action will be taken. If there is a question of patient safety, a health hazard analysis will be conducted.

1.5.5 Post-approval Study

Ethicon Endo-Surgery will conduct a post-approval study to further evaluate the safety of the SEDASYS System under real-world use conditions.

Specific details of this post-approval risk minimization plan are found in Section 5.0, *Post-approval Risk Minimization Plan.*

1.6 Conclusion

The SEDASYS System was designed with patient safety in mind from the earliest stages of development and will continue through the post-approval period. Anesthesiologists, gastroenterologists, nurses, and human factors engineers played key roles in the design of the device and training programs. The inclusion of capnometry, automated responsiveness monitoring, ECG and mandatory oxygen delivery represents an enhancement in safety over what is used today in the current practice of sedation.

The pivotal study provided substantial evidence demonstrating that trained physician/nurse teams can safely and effectively administer minimal-to-moderate propofol sedation with the SEDASYS System to patients undergoing colonoscopy and EGD procedures. Relative to the current standard of care, benefits included improved safety evidenced by lower area-under-the-curve of oxygen desaturation and fewer adverse events. Clinicians were more satisfied with the sedation administered and patients recovered faster. Patients were predominantly minimally-to-moderately sedated throughout their procedures and were satisfied with this level of sedation.

Ethicon Endo-Surgery has designed a risk minimization plan to help ensure the safe and effective use of the SEDASYS System post approval. Mitigations include a controlled launch, facility and user requirements that emphasize only properly trained physicians and nurses operate the SEDASYS System, a comprehensive device training program, and conduct of a post-approval study.

The SEDASYS System provides physician/nurse teams a safe and effective means of administering minimal-to-moderate propofol sedation for patients undergoing colonoscopy and EGD procedures.

2.0 CURRENT STATE OF SEDATION IN ENDOSCOPY

Gastroenterologists today provide benzodiazepine-based sedation in nearly 12.2 million procedures annually.[5-6] For these procedures, minimal-to-moderate sedation (also known as conscious sedation) is the targeted level of sedation. Deeper levels of sedation increase the likelihood of over-sedation related adverse events. Gastroenterologists must have the skills to manage these adverse events. The American Society for Gastrointestinal Endoscopy guidance[7] states, "endoscopy teams must be able to recognize the various levels of sedation and analgesia and rescue a patient who exhibits loss of responsiveness, airway protection, spontaneous respiration, or cardiovascular function." The low rate of adverse events associated with endoscopic sedation today demonstrates that gastroenterologists have the necessary skills.

Cardiopulmonary adverse events occur in approximately 0.05% of upper endoscopy procedures and in approximately 0.1% of colonoscopy procedures.[5] Though over-sedation accounts for a fraction of these events, quantifiable risks are associated with benzodiazepine-based sedation. These risks can be associated with the unpredictable response of a patient to benzodiazepines and opioids. Benzodiazepines can result in prolonged sedation[8], resulting in a prolonged recovery time. Also, not all endoscopists may appreciate the profound synergy of benzodiazepines administered in combination with opioids, which may result in cardiorespiratory depression.[9]

The American Society of Anesthesiologists (ASA) has published guidelines for sedation and analgesia by non-anesthesiologists to address the risks of over-sedation.[9] The ASA recommendation includes more monitoring than what is provided today in most endoscopy procedures. A survey of endoscopists, by Cohen et al[10], shows that pulse oximetry is used at 98.6% of endoscopic facilities while capnometry, recommended for use by the ASA, is used at only 3.1%.

The ASA Guidelines also recommend that supplemental oxygen be administered during sedation. In the Cohen survey, approximately 70% of respondents administered oxygen.

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[5] Data obtained by MarketScan Research Database from Thomson Reuters 2006.

[6] Lawrence B. Cohen, M.D., Julie S. Wecsler, B.A., John N. Gaetano, B.A., Ariel A. Benson, B.A., Kenneth M. Miller, M.D., Valerie Durkalski, Ph.D., M.P.H., and James Aisenberg, M.D. 2006. Endoscopic Sedation in the United States: Results from a Nationwide Survey. *American Journal of Gastroenterology* 101:967–974.

[7] American Society For Gastrointestinal Endoscopy. 2003. Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. *Gastrointestinal Endoscopy* Volume 58, No. 3.

[8] Vicari JJ. 2002. Sedation and analgesia. *Gastrointest Endosc Clin N Am* 12:297-311.

[9] American Society of Anesthesiologists. 2002. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 96(4):1004-17.

[10] Cohen LB, Delegge MH, Aisenberg J, *et al.* 2007. AGA Institute review of endoscopic sedation. *Gastroenterology* 133:675-701.

Therefore, opportunities to increase patient safety exist through:

- Providing monitoring as called for in ASA guidelines, including routine use of capnometry and monitoring the level of sedation
- Delivering supplemental oxygen to patients as called for in the ASA guidelines
- Adhering to dosing guidelines of the sedatives and analgesics

The sedative of choice for anesthesiologists is propofol. It has a rapid onset of action and short half-life, leading to faster induction of sedation and accelerated patient recovery, while still providing an excellent hypnotic state.[11] Endoscopic sedation studies comparing propofol with midazolam alone[12] or in combination with meperidine[13] or fentanyl[14] have found that propofol resulted in expedited procedures, greater patient comfort and satisfaction, quicker recovery, and less nausea and vomiting. Recently, other studies have shown improved quality of EGD procedures[15] and potential improvement in performance quality indicators for colonoscopy.[16]

There is a perception that propofol sedation equates to deep sedation or general anesthesia. As with any sedative, when propofol is titrated at lower doses, minimal-to-moderate sedation can be achieved.

Consistent with today's sedation practices, there are a number of high-risk patients who require administration of sedation by an anesthesiologist. These patients include those with:

- ASA physical status IV and V;
- Morbid obesity;
- Sleep apnea;
- Difficult airway; and
- A requirement for deep sedation or general anesthesia.

These patients will continue to require an anesthesiologist to ensure patient safety.

The SEDASYS System is intended to provide an alternative to benzodiazepine-based sedation by providing a means for physician/nurse teams to safely and effectively administer propofol to low-risk patients undergoing colonoscopy and EGD procedures.

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[11] Singh H, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev 2008:CD006268.

[12] Carlsson U, Grattidge P. 1995. Sedation for upper gastrointestinal endoscopy: a comparative study of propofol and midazolam. *Endoscopy* 27:240-3.

[13] Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. 2000. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 95:1476-9.

[14] Ulmer BJ, Hansen JJ, Overley CA, et al. 2003. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 1:425-32.

[15] Meining A, Semmler V, Kassem AM, *et al.* 2007. The effect of sedation on the quality of upper gastrointestinal endoscopy: an investigator-blinded, randomized study comparing propofol with midazolam. *Endoscopy* 39:345-9.

[16] Lee A. 2008. Propofol vs. meperidine/midazolam sedation for screening colonoscopy: improved quality indicators [abstract T1520]. *Gastrointest Endosc* 67:AB237.

3.0 DEVICE DESCRIPTION

3.1 Device Overview

The SEDASYS System is an integrated monitoring and drug delivery system intended to provide a safe means for a physician/nurse team to administer minimal-to-moderate sedation with propofol to patients undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

The SEDASYS System monitors the physiologic parameters recommended by the American Society of Anesthesiologists (ASA) for sedation by non-anesthesiologists.[17] These are arterial oxygen saturation, heart rate, respiration rate, blood pressure, and patient responsiveness. The monitors included in the SEDASYS System are:

- Pulse oximeter,
- Capnometer,
- Electrocardiogram (ECG),
- Non-invasive blood pressure (NIBP), and
- A novel automated responsiveness monitor.

The SEDASYS System uses a novel drug delivery algorithm (see Section 3.4.1, *Drug Delivery Algorithms Design*) to control a peristaltic infusion pump, enabling the physician/nurse team to achieve and maintain minimal-to-moderate sedation as defined by the ASA Continuum of Sedation. The drug delivery algorithm was designed to be compliant with the dosing guidelines for sedation specified in FDA-approved propofol labeling.[18] Additionally, the SEDASYS System contains an automated supplemental oxygen delivery system, which is consistent with the recommendations of the American Society of Anesthesiologists for procedural sedation.

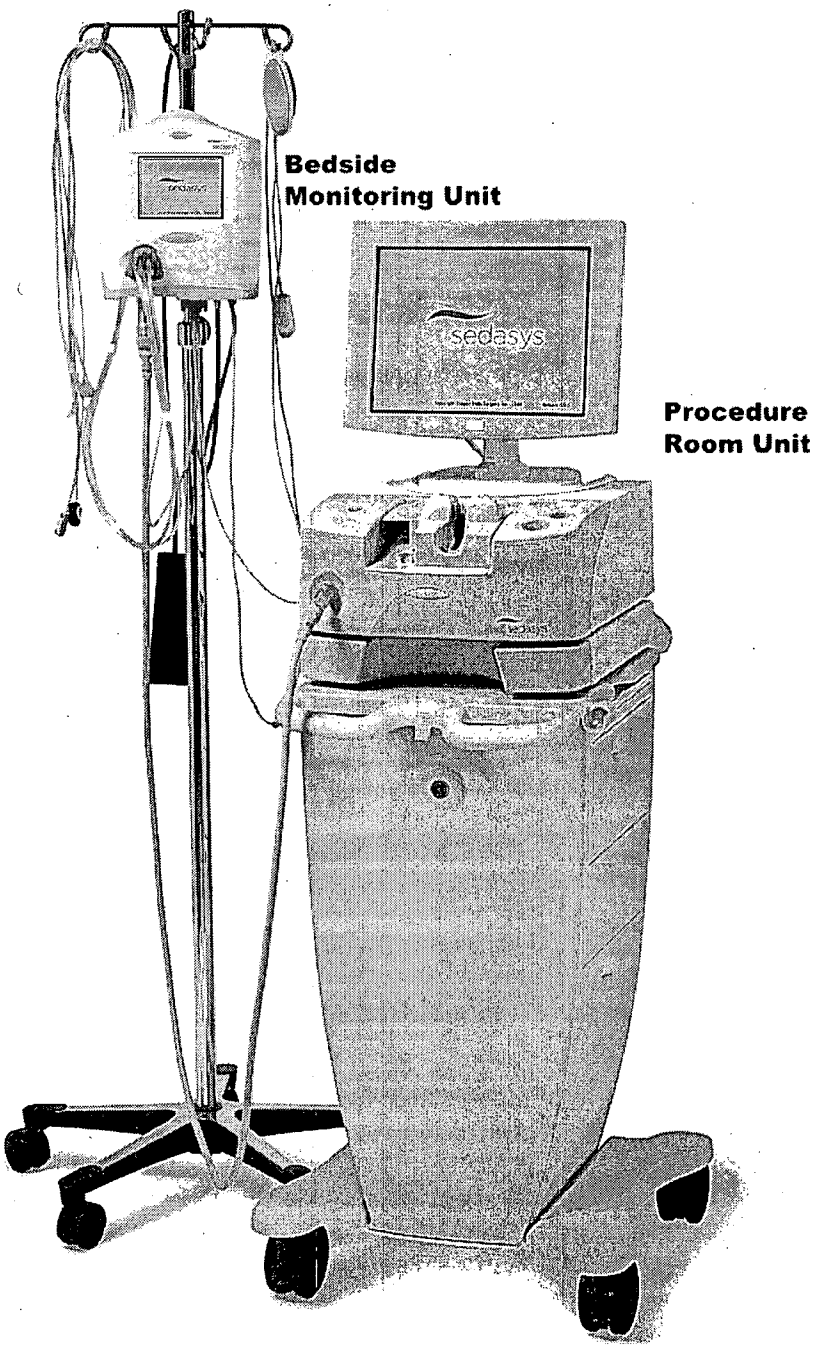
The SEDASYS System integrates patient monitoring and drug delivery to maximize patient safety and has four interlocking elements, each one by itself providing a level of safety (see Section 3.4.2, *Built-in System Safeguards*). These four elements are:

- Dosing restrictions
- Automated oxygen delivery
- Integrated patient alarms
- Subsystem status advisories

[17] American Society of Anesthesiologists. 2002. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 96(4):1004-17.
[18] APP Pharmaceuticals, LLC. February 2008. DIPRIVAN (propofol) 1% Injectable Emulsion for I.V. Labeling.

The SEDASYS System (Figure 2) was designed as two separate units: a Bedside Monitoring Unit and a Procedure Room Unit. The Bedside Monitoring Unit is attached to the patient pre-procedure, and remains attached until the patient is ready for discharge. It contains the pulse oximeter, ECG, NIBP, and automated responsiveness monitor. When not connected to the Procedure Room Unit, the Bedside Monitoring Unit displays the patient's arterial oxygen saturation, heart rate, and blood pressure. The Bedside Monitoring Unit enhances safety by providing continuous uninterrupted patient monitoring from prior to the procedure to the moment of discharge from the post procedure recovery room. As a practical matter, it facilitates patient throughput by eliminating the need to attach and then unattach the patient from the monitors as the patient moves to and from the procedure room.

Figure 2
SEDASYS System



The Procedure Room Unit remains in the procedure room. When the patient is wheeled into the procedure room, the Bedside Monitoring Unit is connected to the Procedure Room Unit through an umbilical cable. The Procedure Room Unit adds capnometry, propofol delivery, oxygen delivery, and the integration of patient monitoring to drug delivery. During the procedure the Procedure Room Unit is the primary interface between the physician/nurse team and the SEDASYS System. It vigilantly monitors the patient and displays all monitored physiologic data. It also provides the interface used to titrate propofol to achieve minimal-to-moderate sedation. By providing additional patient monitoring, delivering oxygen, and built-in safeguards, the Procedure Room Unit enhances patient safety during the administration of propofol sedation.

For additional information on the Bedside Monitoring Unit and the Procedure Room Unit see Exhibit B, *Additional Device Descriptions*, and the Clinical User Guide/Operator's Manual (provided on CD as Exhibit E).

3.2 The Automated Responsiveness Monitor

The automated responsiveness monitor assesses the patient's responsiveness to mild verbal and tactile stimulus. It consists of sequence of verbal requests, combined with vibrations of a handset. It starts with a pleasant request '*please squeeze the handset*' and a mild vibration of the handset. If the patient does not respond, by squeezing the handset, the verbal request becomes more urgent and louder '*squeeze the handset now*' and the vibration of the handset becomes more vigorous. If the patient does not respond to the requests within 14 seconds he, or she, is deemed non-responsive. In this manner, the automated responsiveness monitor provides an automatic assessment of drug effect.

The ASA has established a continuum of sedation that identifies the progressive loss of responsiveness with increasing level of sedation (Table 3).

Table 3
Definition of General Anesthesia and Levels of Sedation/Analgesia

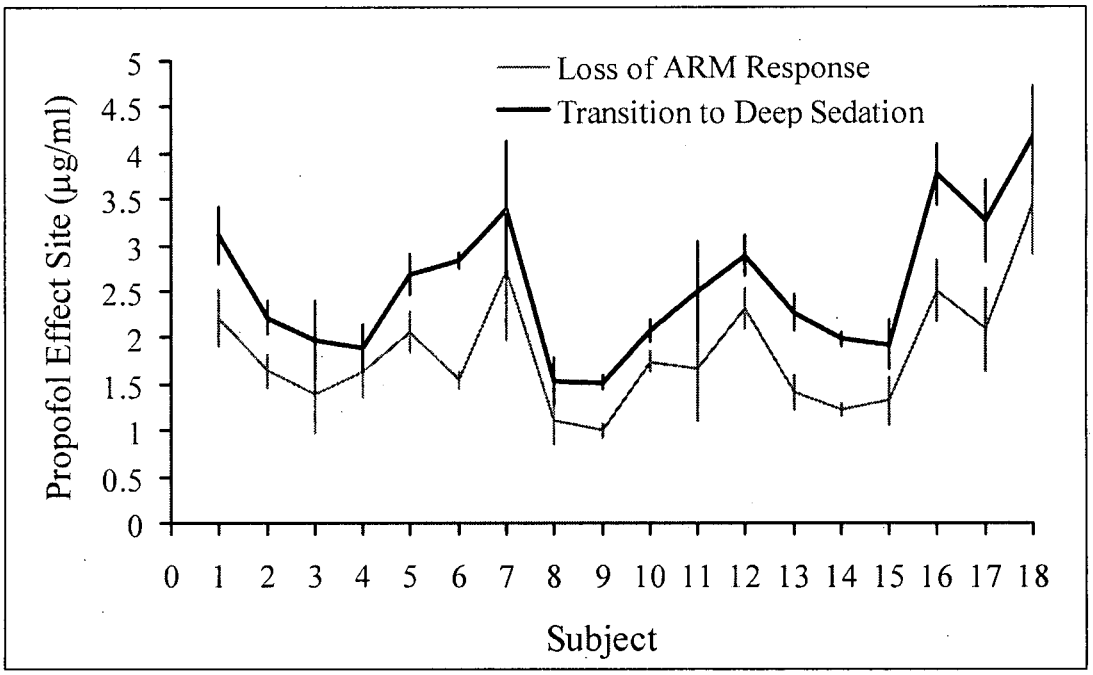
	Minimal Sedation ("Anxiolysis")	Moderate Sedation/ Analgesia ("Conscious Sedation")	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable,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

Developed by the American Society of Anesthesiologists, approved by ASA House of Delegates on October 13, 1999, and amended on October 27, 2004.

The automated responsiveness monitor provides both audible and tactile stimulation to the patient. A patient responding to it is minimally or moderately sedated. However, these stimuli are both fairly mild – a request to squeeze the hand, and a vibration of the handset. Lack of response to the automated responsiveness monitor does not mean the patient is in deep sedation. Instead, it occurs in moderate sedation, near the transition to deep sedation.

Figure 3 presents data from a clinical study evaluating the automated responsive monitor. In the study, 18 volunteers were administered propofol until they transitioned into deep sedation. Level of sedation was assessed with the Observers Assessment of Alertness/Sedation scale. Deep sedation was defined as loss of response to shaking. Responsiveness was assessed using the automated responsiveness monitor. Each subject was sedated 5 times, at different propofol infusion rates (0.1 μg/ml/min through 0.9 μg/ml/min). The data presented are the mean +/- standard deviation predicted propofol effect site concentration at which each patient lost response to the automated responsiveness monitor (the red line) and transitioned into deep sedation (the black line).

Figure 3
Transition to Deep Sedation In Relationship to the Automated Responsiveness Monitor



In each of the 18 volunteers, the predicted propofol effect site concentration at the loss of response to the automated responsiveness monitor was about 0.5 µg/ml lower than the propofol effect site concentration associated with loss of response to shaking, which is at the transition between moderate and deep sedation. Thus, the automated responsiveness monitor provided a clear indication of patient sensitivity, permitting individualization of propofol dosage across a nearly three-fold range of propofol concentrations. Additionally, as the loss of response reliably occurs before the patient loses responsiveness to shaking it provides a feedback mechanism by which the SEDASYS System can actively avoid placing patients into deep sedation.

3.3 User Interface

The SEDASYS System contains a simple and intuitive user interface designed to minimize user errors. It was designed in collaboration with physicians, nurses, and human factors experts. It incorporates key design principals:

- Multiple user actions are required to make infusion rate changes.
- Data is entered with up- and down-arrow buttons; eliminating errors associated with numeric keypads.
- Options, that may compromise safety at specific points in the procedure, are disabled and grayed out.

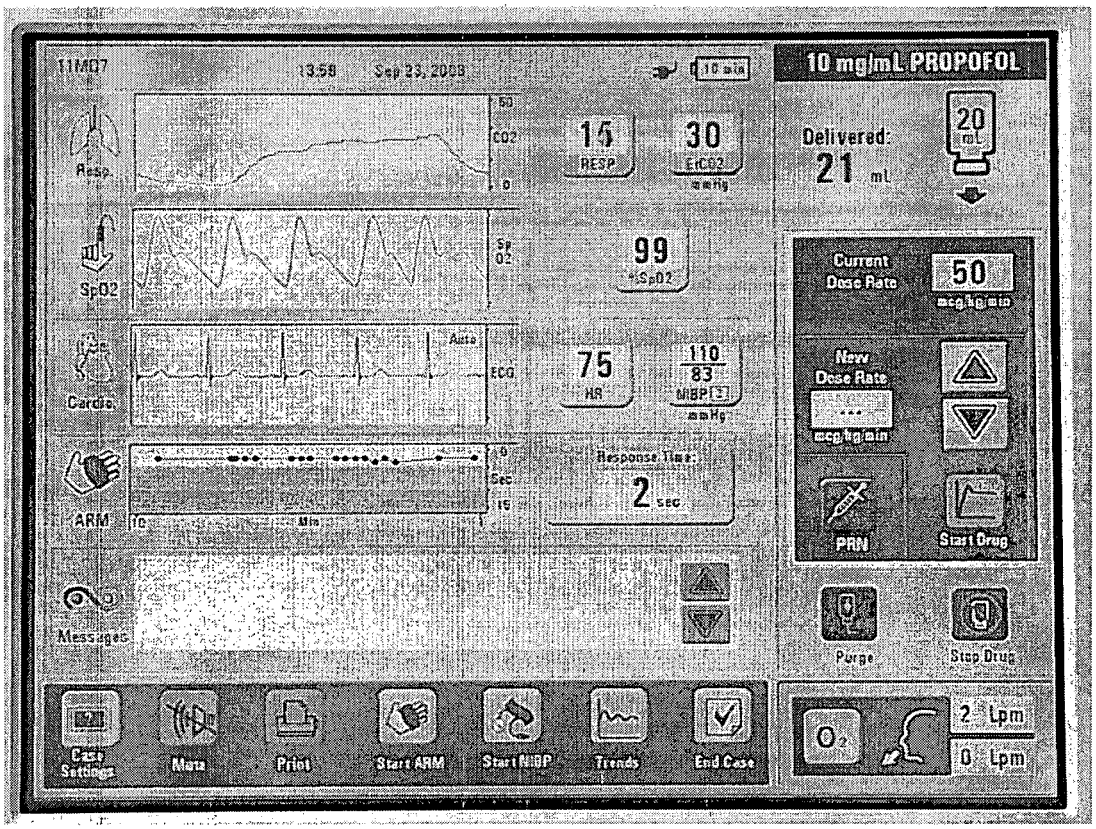
- Animations are limited to critical events; minimizing unnecessary distractions and retaining the impact of those events.

The Procedure Room Unit's main monitoring screen (Figure 4) displays the patient's:

- Respiration rate, $EtCO_2$ and capnogram
- Arterial oxygen saturation and plethysmogram
- Heart rate, systolic & diastolic pressure and electrocardiogram
- Patient's response time, both the current time as well as the history,

It also provides the physician/nurse team an interface to control the administration of propofol.

Figure 4
Procedure Room Unit's Main Monitoring Screen



3.4 Drug Delivery Algorithms and System Safeguards

3.4.1 Drug Delivery Algorithms Design

The drug delivery algorithms in the SEDASYS System were developed by Ethicon Endo-Surgery, in collaboration with experts in the pharmacokinetics and pharmacodynamics of anesthetic drugs (see Exhibit D, *Ethicon Endo-Surgery Anesthesia Advisory Panel Members*), to meet three needs:

- Rapidly achieve the desired clinical effect without overshoot.
- Comply with the dosing recommendations for sedation in the propofol package insert.
- Enable precise titration of minimal-to-moderate sedation.

The base algorithm utilizes loading doses and maintenance infusion rates to achieve and maintain a targeted level of sedation. A PRN function, that administers a fixed dose of propofol with a slow infusion, enables treatment of transient discomfort. The rationale for the drug delivery algorithms is located in Exhibit B, *Additional Device Descriptions*.

3.4.1.1 Base Algorithm

Pharmacokinetic principles dictate that to rapidly achieve a desired drug effect, the volume of distribution should first be loaded with drug. This loading dose (LD) is equal to the target concentration (the concentration at which the desired effect is achieved) multiplied by the volume of distribution (V_D).

$$LD = \text{Target Concentration} * V_D$$

The volume of distribution used in the calculation is the volume of distribution at the time of peak effect, as recommended by Shafer and Gregg.[19]

The same principle is used to subsequently increase the target concentration. For each desired change, the volume of distribution should be incrementally loaded to rapidly achieve the new effect. In the case of a change, the amount of the loading dose is not simply based on the target concentration, but rather on the difference between the new target concentration and the current concentration.

$$LD = (\text{Target Concentration}_N - \text{Concentration}_C) * V_D$$

The equation can be re-arranged to become the new target concentration multiplied by the volume of distribution minus the previous loading dose delivered.

$$LD = \text{Target Concentration}_N * V_D - \text{Concentration}_C * V_D$$

[19] Shafer SL, Gregg KM. 1992. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. *J Pharmacokinet Biopharm* 20:147-169.

For multiple changes in desired effect, the previous loading dose becomes the sum of the previous loading doses.

$$LD = \text{Target Concentration}_N * V_D - \text{Sum of Previous LD's}$$

The algorithm is also designed in accordance with FDA-approved propofol labeling. The labeling provides guidelines for the loading dose to initiate sedation and the range of maintenance rates required to maintain sedation. Specifically, the guidelines recommend maintenance rates between 25 and 75 μg/kg/min:

> *Maintenance of Sedation: "In most patients, the rates of Diprivan injectable emulsion administration will be in the range of 25-75 μg/kg/min."*

For the loading dose, propofol labeling only mentions 0.5 mg/kg as a suggested initiation dose.

> *Initiation of Sedation: "With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered ... titrated to clinical responses."*

This implies that most patients require an initiation dose UP TO 0.5 mg/kg. The base algorithm associates the 0.5 mg/kg loading dose with the high end of the recommended maintenance rate: 75 μg/kg/min. It then linearly interpolates to calculate an appropriately sized loading dose (LD) for any initial maintenance rate (MR) selected by the user.

$$LD = 0.5 * (MR / 75)$$

Furthermore, using the same linear interpolation, loading doses are calculated for subsequent maintenance rate changes during the procedure. Again, applying the pharmacokinetic principles discussed previously, the loading dose for a change in maintenance rate is the loading dose associated with the new maintenance rate minus the sum of all previous loading doses delivered.

$$LD = 0.5 * (MR / 75) - \text{Cumulative LD}$$

Propofol labeling recommends against rapid initiation of sedation to avoid cardiorespiratory compromise. It suggests that the dose should be delivered over 3 to 5 minutes.

> *Initiation of Sedation: "When Diprivan Injectable Emulsion is administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels."*

The SEDASYS System delivers the loading dose over 3 minutes at a constant infusion rate. It does this not only for the initiation dose, but for all subsequent incremental loading doses. These subsequent loading doses are delivered in addition to the previous maintenance rate (PrevMR).

$$\text{Pump Rate} = (1000 * LD / 3) + \text{PrevMR},$$

where: 1000 is the conversion from mg to μg, and

3 is the duration (in minutes) of LD.

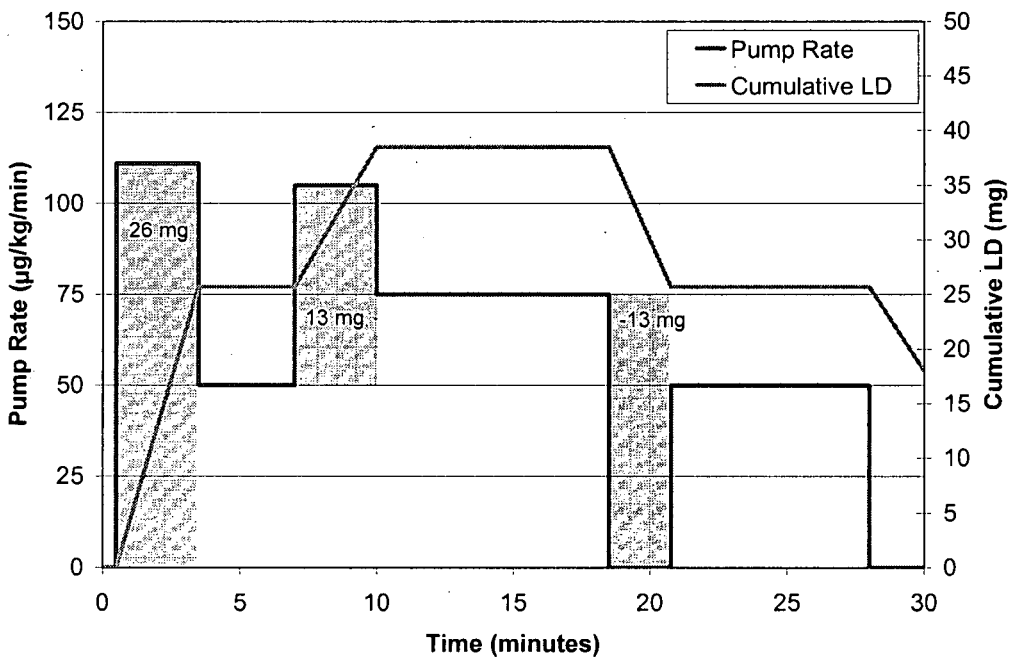
For example, the current maintenance rate is 50 μg/kg/min and the user increases the rate to 70 μg/kg/min. The base algorithm will calculate the required loading dose, the constant rate required to deliver the dose over 3 minutes, and then add 50 to that rate. This is the rate at which the pump is driven for 3 minutes.

If the clinician decreases the maintenance rate, the base algorithm will calculate a negative value for the loading dose. Obviously, the system cannot withdraw propofol from the patient. Instead, it relies on the short half-life of propofol to "effectively" decrease the cumulative loading dose by elimination and redistribution. The algorithm calculates a period of time (Time_zero) required for the redistributed/eliminated propofol to "effectively" be equal to the negative loading dose. It then turns the infusion to zero for that period of time.

$$\text{Time_zero} = 1000 * \text{LD} / \text{PrevMR}$$

Figure 5 is an illustrative example of the operation of the drug delivery algorithm during a typical colonoscopy procedure.

Figure 5
Operation of Drug Delivery Algorithm During Typical Colonoscopy Procedure



In this example,

- The clinician selects an initial maintenance rate of 50 μg/kg/min.
- The base algorithm calculates an initial loading dose of 0.33 mg/kg (or 26 mg – patient weighs 78 kg).

- The SEDASYS System delivers the 26 mg over 3 minutes at an infusion rate of 111 μg/kg/min
  - Notice that the algorithm tracks the cumulative loading dose during the delivery of the loading dose, rather than simply summing the loading doses after completion. This function is a key aspect of drug delivery algorithms and is leveraged by the built-in system safeguards described later.
- After completing delivery of the loading dose, the SEDASYS System immediately begins delivery of the maintenance rate (50 μg/kg/min).
- Assessing that the patient in this scenario is under-sedated, the clinician increases the maintenance rate to 75 μg/kg/min at 7 minutes.
- The base algorithm calculates a loading dose of 0.17 mg/kg (or 13 mg).
- The SEDASYS System delivers the 13 mg over 3 minutes at a rate of 105 μg/kg/min.
  - The actual rate to deliver this size loading dose is 55 μg/kg/min, but a loading dose is always delivered in addition to the previous maintenance rate which, in this example, is 50 μg/kg/min. So their sum is 105.
- Immediately after completing delivery of the loading dose, the SEDASYS System begins delivery of the new maintenance rate (75 μg/kg/min).
  - Notice that at the end of the second loading dose, the cumulative loading dose equals 38.5 mg, which is the sum of the two individual loading doses. This is the loading dose required to initiate sedation at a maintenance rate of 75 μg/kg/min.
- At 18.5 minutes the clinician, after having reached the cecum during a colonoscopy, decides to decrease the maintenance rate from 75 to 50 μg/kg/min.
- The base drug delivery algorithm calculates a –0.17 mg/kg loading dose (or –13 mg).
- Using the Time_Zero calculation, the SEDASYS System shuts the infusion rate off for 2.26 minutes.
- Immediately following completion of the negative loading dose, the system starts delivering the new maintenance rate (50 μg/kg/min).
  - Notice that the cumulative loading at 5 minutes is the same as the cumulative loading dose at 25 minutes – both are for the same maintenance rate. This is a critical aspect of the drug delivery algorithms: any given maintenance rate is associated with its own unique loading dose.
- At 28 minutes, the clinician has completed the colonoscopy, sets the maintenance rate to zero, and removes the scope.

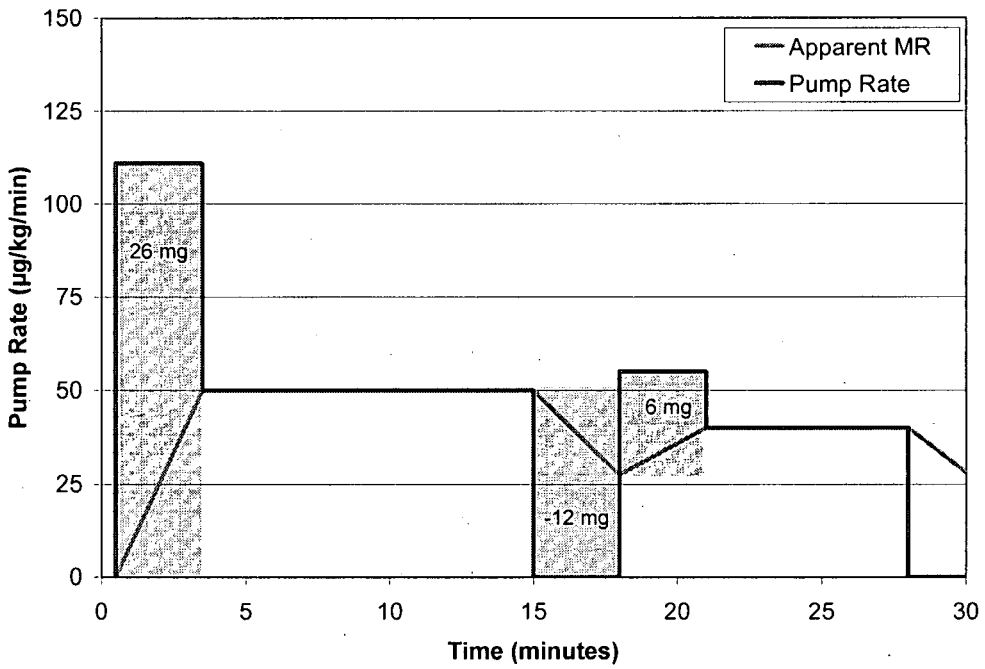
A significant feature of drug delivery algorithms is the concept of an apparent maintenance rate. As mentioned in the above example, every maintenance rate is associated with one, and only one, loading dose. The apparent maintenance rate is the maintenance rate associated with the cumulative loading dose at any point in time. During a loading dose, while the cumulative loading dose is being increased/decreased (depending on if the clinician increased or decreased the maintenance rate), the apparent maintenance rate is being calculated at every interval. To calculate the apparent maintenance rate, the basic loading dose equation is rewritten, solving for maintenance rate as a function of loading dose.

$$\text{Apparent MR} = 75 * (\text{Cumulative LD} / 0.5)$$

The apparent maintenance rate is used by the drug delivery algorithms to determine the correct loading dose for maintenance rate changes following interrupted infusions. In addition, a key feature of the built in system safeguards utilize the apparent maintenance rate.

Figure 6 is an illustrative example of how the drug delivery algorithms utilize the apparent maintenance rate.

Figure 6
Example of Apparent Maintenance Rate in the Drug Delivery Algorithms



In this example,

- The clinician selects an initial maintenance rate of 50 μg/kg/min.
- The base algorithm calculates an initial loading dose of 0.33 mg/kg (or 26 mg – patient weighs 78 kg).
- The SEDASYS System delivers the 26 mg over 3 minutes at an infusion rate of 111 μg/kg/min.
  - Notice that the drug delivery algorithms track the apparent maintenance rate during the delivery of the loading dose. This function is leveraged by the built-in system safeguards.
- After completing delivery of the loading dose, the SEDASYS System immediately begins delivery of the maintenance rate (50 μg/kg/min).
- At 15 minutes, the clinician stops propofol delivery after reaching the cecum.
- After a few minutes, the patient starts to exhibit agitation. At 18 minutes, the clinician selects a maintenance rate of 40 μg/kg/min to restart propofol infusion.
- At this time, the apparent maintenance rate is 28 μg/kg/min. Since 40 is greater than the apparent maintenance rate, the drug delivery algorithm will treat this as a maintenance rate increase from 28 to 40 μg/kg/min.
  - If the new maintenance rate was less than the apparent maintenance rate, the algorithm would have treated it as a maintenance rate decrease and calculated the appropriate Time_zero.
- The SEDASYS System calculates a loading dose of 6 mg, and delivers it over 3 minutes at a rate of 55 μg/kg/min.
- After completing delivery of the loading dose, the system immediately begins delivery of the new maintenance rate (40 μg/kg/min).
- At 28 minutes, the clinician has completed the colonoscopy, sets the maintenance rate to zero, and removes the scope.

In summary, the base drug delivery algorithm is a method of delivering propofol based on both sound pharmacokinetic principles and propofol labeling guidelines. It uses standard concepts of loading doses and maintenance rates to rapidly achieve and maintain a desired sedation effect.

3.4.1.2 PRN

The PRN feature allows the clinician to treat transient episodes of discomfort with a transient increase in the sedation effect.

The PRN dose is 0.25 mg/kg (e.g., 2 mls of propofol for an 80 kg patient) and it is delivered slowly, at a pump rate of 450 mL/hour. For lighter patients, the PRN dose will be delivered in ~10 seconds. For heavier patients the dose will be delivered in ~30 seconds.

The PRN dose was chosen to rapidly achieve a slight increase in sedation, while precluding the overshoot that can easily occur with larger doses.

3.4.2 Built-in System Safeguards

The SEDASYS System integrates patient monitoring and drug delivery to maximize patient safety and has four interlocking elements, each one by itself providing a level of safety. These four elements are:

- Dosing restrictions
- Automated oxygen delivery
- Integrated patient alarms
- Subsystem status advisories

The dosing restrictions are designed to minimize over-sedation by limiting the infusion rates to those of the FDA approved propofol labeling and enforcing titration to clinical effect through lockout timers. The automated oxygen delivery system is designed to minimize the occurrence of hypoxia should over-sedation occur. The integrated patient alarms are designed to alert the clinical team of patient status and reduce, or stop, propofol delivery if appropriate. The subsystem status advisories are designed to ensure that the patient monitors, oxygen manifold and infusion pump are working as intended, enabling the other three elements to minimize the risk of injury due to over-sedation.

3.4.2.1 Propofol Dosing Limits

The dosing limits are consistent with FDA-approved propofol labeling and ensure clinicians titrate to clinical effect. These limits include:

- 75 μg/kg/min maximum initial maintenance rate
- 3 minute increase lockout following a maintenance rate increase (or initiation)
- Maintenance rate increase limits tied to automated responsiveness monitor (ARM) response time
- Automatic reduction of maintenance rate when ARM response is lost during loading dose
- Automatic reduction of maintenance rate for sustained loss of ARM response
- 90 second PRN lockout following a PRN dose

Initial Maintenance Rate

Propofol labeling states that most patients require an infusion rate of 25 to 75 μg/kg/min to adequately maintain sedation. It also states that each patient is different, and dosing should be individualized and titrated to clinical effect. Since "most patients" will require less than 75 μg/kg/min to achieve adequate sedation, the SEDASYS System places an upper limit on the initial maintenance rate the clinician can enter to initiate sedation. This automatically places an upper limit on the loading dose used to initiate sedation, since the loading dose is calculated by the drug delivery algorithm from the maintenance rate.

Maintenance Rate Increase Lockout
The dosing guidelines in the propofol label are recommendations for "most patients". The labeling states that, due to patient variability, dosing should be individualized and titrated to clinical effect. If the patient requires more propofol to be adequately sedated, the clinician should increase the maintenance rate.

The drug delivery algorithms deliver the loading dose over 3 minutes, per the propofol labeling. The full effect of the loading dose is not observed until the end of the 3 minute loading infusion. Therefore, the SEDASYS System prevents the clinician from increasing the maintenance rate during an ongoing loading dose. This 3-minute lockout enforces titration to clinical effect.

Maintenance Rate Increase Limits Tied to Automated Responsiveness Monitor
The SEDASYS System uses the automated responsiveness monitor to aid in titration in accordance with the labeling guidelines to avoid accidental over-sedation. The system limits the maintenance rate increase based on the patient's time to respond to the automated responsiveness monitor.

- If the patient responds in less than 5 seconds, he/she is responding to the mildest automated responsiveness monitor stimulus. This indicates a very lightly sedated patient and the SEDASYS System limits maintenance rate increases to $\leq$ 50 μg/kg/min.
- If the patient responds in 5 to 14 seconds, he/she is responding to either the moderate or vigorous automated responsiveness monitor stimulus. This indicates a more sedated patient and the SEDASYS System limits maintenance rate increases to $\leq$ 25 μg/kg/min.
- If the patient is non-responsive to automated responsiveness monitor, the SEDASYS System limits maintenance rate increases to $\leq$ 10 μg/kg/min. Loss of response occurs in moderate sedation. By limiting increases in propofol infusion rate to 10 μg/kg/min following the loss of response, the SEDASYS System helps prevent the patient from crossing the threshold into deep sedation.

Maintenance Rate Reduced If Response Lost During Loading Dose
If the patient loses response to automated responsiveness monitor during a loading dose, the SEDASYS System will terminate the loading dose and reduce the maintenance rate to the Apparent Maintenance Rate as calculated by the drug delivery algorithms at the time the patient lost response.

Sustained Non-Responsiveness to Automated Responsiveness Monitor
With constant infusion rates, there is a slow accumulation of propofol in the plasma. Over time, the accumulation of propofol can cause transition to deeper sedation than intended. Therefore, the SEDASYS System automatically reduces the maintenance rate by 5% if the patient is not responsive for a sustained period of time (6 minutes).

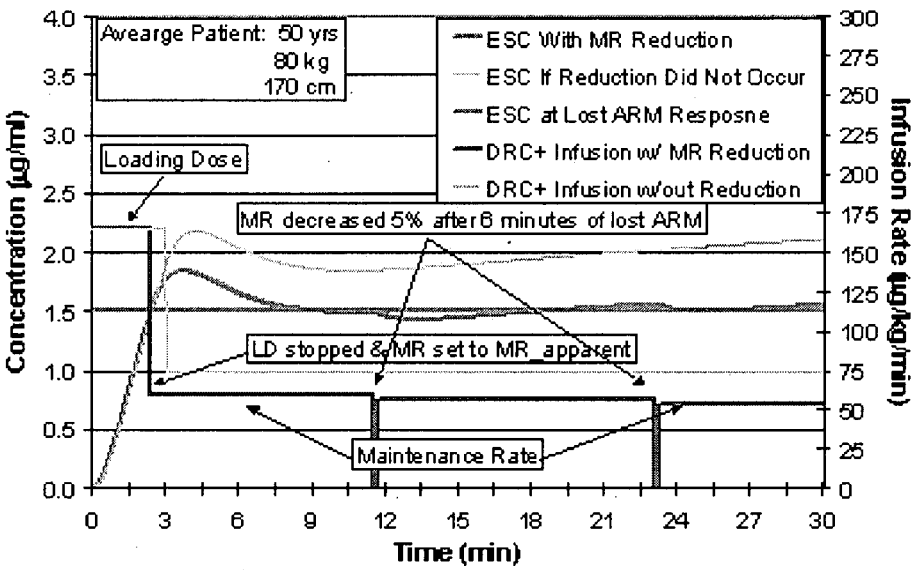
Figure 7 is a hypothetical example that illustrates the effectiveness of these last two dosing limits of the SEDASYS System. In this example, the clinician selects an initial maintenance

rate (MR) of 75 µg/kg/min. The light blue line represents the dosing from the base drug delivery algorithm absent the built-in safeguards. Specifically, the drug delivery algorithm calculates a loading dose of 40 mg, and delivers it over 3 minutes. The infusion rate is then dropped to 75 µg/kg/min. The pink line represents the patient's effect site propofol concentration for this infusion rate profile (effect site propofol concentration is being used to represent level of sedation in this example).

In this hypothetical example the patient loses response at an effect site propofol concentration of 1.5 µg/ml (shown as the green line in the figure). The selected maintenance rate would have significantly over-sedated (30% by effect site propofol concentration) the patient for the duration of the procedure, placing the patient at a greater risk for hypoventilation and hypoxia.

The dark blue line represents the modified dosing from the drug delivery algorithm combined with the safeguards built into the SEDASYS System. The red line represents the patient's resulting effect site propofol concentration. When the patient lost response to automated responsiveness monitor, 32 mg of the loading dose had been delivered. The SEDASYS System terminates the loading dose because of the loss of response, and sets the maintenance rate to 60 µg/kg/min, (the Apparent MR for a 32 mg loading dose). By itself, this significantly reduces the patient's sedation level as represented by the effect site propofol concentration.

Figure 7
Loss of ARM Response Impact on Maintenance Rate



Then, both at ~12 and ~23 minutes into drug delivery, the SEDASYS System reduced the maintenance rate by 5%, following 6 minute periods of sustained non-responsiveness. This maintained the patient's effect site propofol concentration very near 1.5 μg/ml. By extension, the patient's level of sedation would have been maintained at the level required to remain comfortable during the procedure.

PRN Lockout
A PRN is delivered in ~10 to 30 seconds depending on the patient's weight. The full effect of the PRN is not observed for approximately 90 seconds after it is administered. Therefore, the SEDASYS System prevents the clinician from delivering a PRN within 90 seconds of administering a previous PRN. This 90-second lockout enforces titration to clinical effect.

In summary, each one of these Propofol Dosing Limits provides a level of safety. When working in combination, as designed, they provide a significant level of safety by minimizing the risk of over-sedation.

3.4.2.2 Automated Oxygen Delivery

There are four elements of the automated oxygen delivery system:

- Oxygen delivery is mandatory – propofol cannot be delivered unless the SEDASYS System is delivering oxygen to the patient.
- Oxygen is delivered to both the patient's nose and mouth.
- Oxygen is delivered at a lower rate during exhalation and a higher rate during inhalation (nasal breathing only) to minimize dilution of CO_2 sample.
- Oxygen delivery rate is automatically increased as the patient's saturation decreases.

Mandatory Oxygen Delivery
Oxygen delivery is mandatory because the ASA guidelines for sedation by non-anesthesiologists recommend it for propofol sedation.[20] In order to ensure that users of the SEDASYS System follow the recommendations of the ASA, oxygen delivery was integrated into the system.

Oxygen Delivered to Nose and Mouth
The traditional method of delivering supplemental oxygen via a nasal cannula to patients undergoing procedural sedation is relatively ineffective in patients who are orally breathing; a likely occurrence during EGD procedures. To better oxygenate oral breathing patients, the SEDASYS System's novel oral/nasal cannula delivers oxygen to both the patient's nose and mouth. By delivering oxygen to both the nose and mouth, the SEDASYS System effectively delivers oxygen to patients regardless of whether they are breathing through their nose or mouth.

[20] American Society of Anesthesiologists. 2002. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 96(4):1004-17.

Oxygen Delivery Gated to Inhalation
At high oxygen delivery rates, CO_2 sampling via an oral/nasal cannula can become diluted, decreasing the sensitivity of the capnogram and the accuracy of calculated respiration rates. To minimize dilution of CO_2 from the oxygen delivery system, transducers detect exhalation and control oxygen flow based on breathing cycle. In the nasal breathing mode, oxygen flow switches between two rates in synchrony with patient inhalation (high O_2 rate) and exhalation (low O_2 rate to facilitate CO_2 sampling). In oral breathing mode, oxygen flows at a continuous rate because the change in pressure between inhalation and exhalation is too low to accurately discriminate the transition between inhalation and exhalation.

The SEDASYS System's default baseline oxygen delivery rate is 2 L/min. In the oral breathing mode, this means patients will receive 2 L/min continuously. In the nasal breathing mode, the patient will receive 2 L/min during inhalation and 0 L/min during exhalation. This baseline oxygen delivery rate can be increased (up to 8 L/min) by the clinical team. Oxygen delivery cannot be decreased below 2 L/min.

Oxygen Delivery Increase in Response to Decreased Saturation
The last element of the oxygen delivery system is the automatic increases of oxygen delivery in response to decreasing oxygen saturation. If a patient's oxygen saturation decreases to 96% or less, the SEDASYS System will automatically increase the rate of oxygen delivery. In the oral breathing mode, the increased rate is 5 L/min (surpassing the increase to 4 L/min typically seen in endoscopy today). In the nasal breathing mode, the increased rate is 8 L/min (inhale) and 2 L/min (exhale). A higher rate can be delivered during inhale in the nasal breathing mode since there is no dilution of the CO_2 sampling. If a patient's oxygen saturation decreases to 88% or less, the oral breathing mode oxygen delivery rate is increased to 7 L/min and the nasal breathing mode inhale rate is increased to 12 L/min. The nasal breathing mode exhale oxygen delivery rate remains at 2 L/min.

3.4.2.3 Alarms Based on Patient Physiology

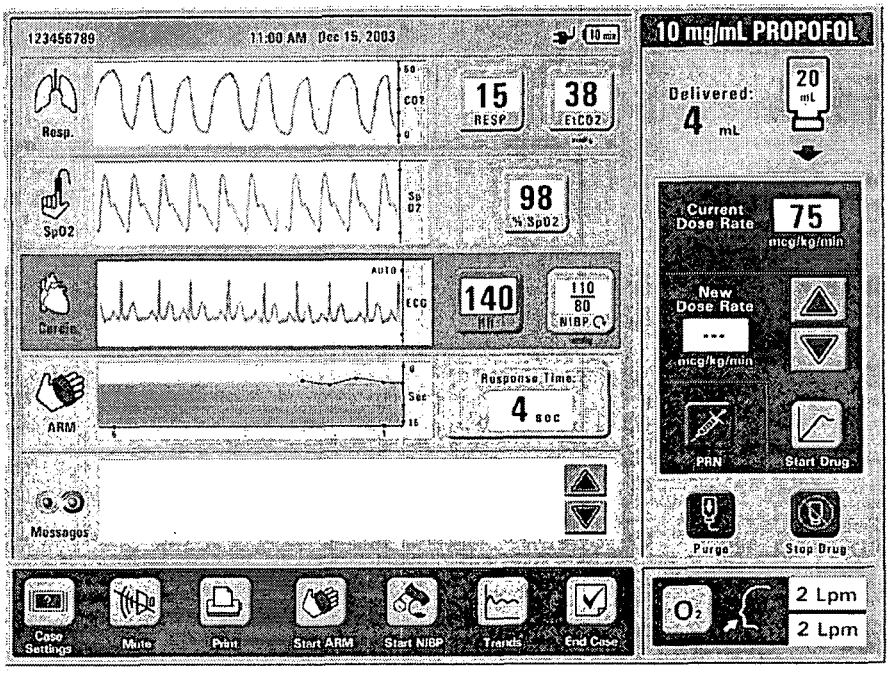
Interconnected with the dosing limits are alarms that are based on patient physiology. Should adverse physiology develop, despite the dosing restrictions, the SEDASYS System will alert the user through visual and audible means and stop or reduce the propofol infusion automatically if conditions warrant.

Red Alarms
Red Alarms (or Warning Alarms) are designed to alert the clinician to compromised cardiorespiratory conditions, such as hypoxia, apnea, tachycardia, or hypertension. During a Red Alarm, the following changes occur to the SEDASYS System:

- The background field and display button for alarming parameter on the Procedure Room Unit main monitoring screen change to red.
- The Procedure Room Unit sounds a distinct audible alarm.
- The light bar on top of the Bedside Monitoring Unit flashes.

Figure 8 illustrates the changes made to the Procedure Room Unit's main monitoring screen in response to a Red Alarm (in this case, heart rate >120).

Figure 8
PRU Main Monitoring Screen During Red Alarm That Does Not Stop Propofol Delivery



When the Red Alarm condition clears, the audible alarm ceases, the light bar on the Bedside Monitoring Unit stops flashing, and the Procedure Room Unit's main monitoring screen returns to normal.

Red Alarms That Stop Propofol Delivery

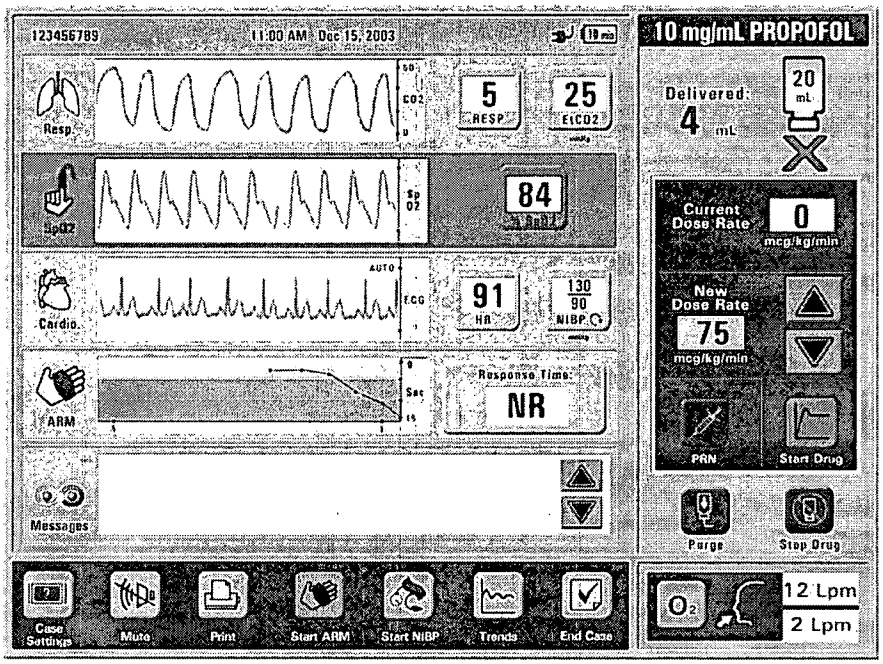
There are certain physiologic conditions that have a high correlation to over-sedation; specifically, hypoxia and prolonged apnea. In responses to a Red Alarm for these conditions, the SEDASYS System stops the infusion of propofol.

The following additional actions occur:

- A flashing red "X" is placed under the vial icon on the Procedure Room Unit main monitoring screen indicating that the infusion has been stopped.
- **Start Drug** and **Up** or **Down Arrow** buttons are grayed out and inactive.
- The SEDASYS System suspends the ARM queries, replacing them with an audible command to "Take A Deep Breath" that repeats every 10 seconds during the alarm.

Figure 9 illustrates the changes made to the Procedure Room Unit's main monitoring screen in response to a Red Alarm (in this case, $SpO_2 < 85\%$) that stops propofol delivery.

Figure 9
PRU Main Monitoring Screen During Red Alarm
That Stops Propofol Delivery



After the Red Alarm clears, the red "X" remains below the vial icon, as a reminder that the SEDASYS System stopped the propofol infusion. The physician/nurse team must manually re-start the propofol infusion.

Yellow Alarms

In order to provide additional safety, the SEDASYS System includes alarms that trigger prior conditions requiring a Red Alarm. The purpose of these Yellow Alarms (or Caution Alarms) is to prevent or guard against adverse conditions necessitating a Red Alarm. These alarms are only designed for events with a high correlation with over-sedation: hypoxia and apnea.

In response to these alarms, the SEDASYS System automatically reduces the maintenance rate and alerts the clinician of the patient's condition. The first step in reducing the rate is stopping the infusion (similar to when the clinician decreases the maintenance rate and the drug delivery algorithm stops the propofol infusion for the Negative Loading Dose). When the Yellow Alarm condition clears, the SEDASYS System reinitiates the infusion at a reduced dose rate; the apparent maintenance rate calculated by the drug delivery algorithms at the time the Yellow Alarm cleared.

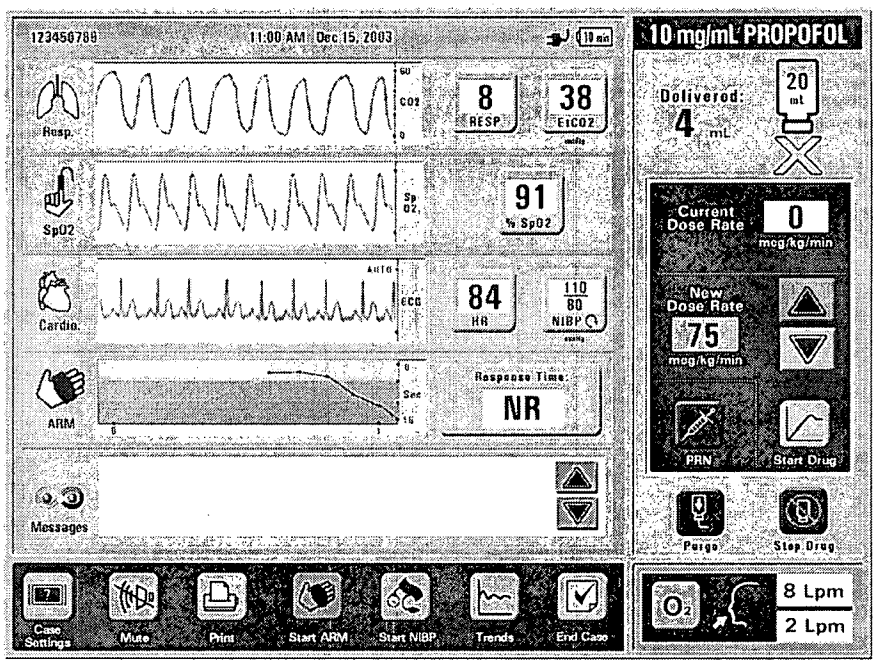
Because Yellow Alarms aim to prevent adverse physiology, the default thresholds are more conservative than typical patient monitors. For example, most stand-alone pulse oximeters are set to alarm at $SpO_2 < 90\%$; signaling an adverse condition. The SEDASYS System Yellow Alarm default threshold is 92% to prevent the saturation from falling below 90%.

During a Yellow Alarm, the following changes occur to the SEDASYS System:

- The background field and display button for the alarming parameter change to yellow.
- The digital value of alarming parameter flashes.
- A flashing yellow "X" appears under the vial icon, which indicates that propofol infusion has been temporarily stopped.
- The Procedure Room Unit sounds a distinct audible alarm.
- The light bar on top of the Bedside Monitoring Unit flashes.

Figure 10 illustrates the changes made to the Procedure Room Unit's main monitoring screen in response to a Yellow Alarm (in this case, $SpO_2 < 92\%$).

Figure 10
PRU Main Monitoring Screen During Yellow Alarm



When the Yellow Alarm condition clears, the audible alarm signal ceases, the light bar on the Bedside Monitoring Unit stops flashing, the Procedure Room Unit's main monitoring screen returns to normal, and the regular ARM queries are re-instated.

Alarm Thresholds

Table 4 lists the Red Alarm thresholds for each monitored parameter. These values were determined by comparison to marketed patient monitors.[21-22]

Table 4
Red Alarm Thresholds for Each Monitored Parameter

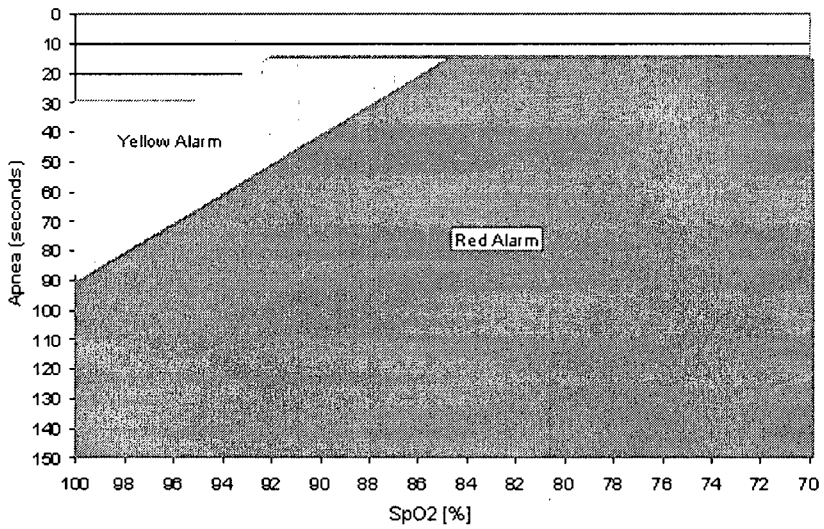
	Factory Default		Available Range	
	Minimum	**Maximum**	**Minimum** (in increments of 5)	**Maximum** (in increments of 5)
SpO2[a]	85%		75–91%	
Apnea (low respiration rate)[b]	90 seconds[c]		60–120 seconds[c]	
Heart Rate (HR)	50 beats/min	120 beats/min	35–60 beats/min	110–150 beats/min
Diastolic NIBP	35 mmHg	110 mmHg	20–40 mmHg in	105–130 mmHg
Systolic NIBP	80 mmHg	200 mmHg	65–85 mmHg in	180–220 mmHg
EtCO2		50 mmHg		50–70 mmHg
Respiration Rate (RR)		30 breaths/min		25–40 breaths/min

[a] The Yellow Alarm limit for SpO_2 is 92%. The limit is not adjustable.
[b] The Yellow Alarm limit for apnea is a function of the patient's SpO_2 (see Figure 11).
[c] At 100% SpO_2.

[21] PROPAQ Directions for Use, Welch Allyn Inc., Skaneateles Falls, NY.
[22] Dash 300/4000 Patient Monitor Operator's Manual, GE Medical Systems, Waukesha, WI.

The low respiration rate (RR)/apnea alarm thresholds are a function of the patient's SpO_2. At high saturation levels, the patient can withstand longer periods of apnea. At decreased saturation levels, apnea is less well tolerated. Although there is a large range in the Red Alarm threshold (as high as 90 seconds and as low as 15 seconds), the SEDASYS System will have stopped delivering propofol within 15 to 30 seconds of apnea (depending on the patient's SpO_2). The presence of a Red Alarm means that the clinician must restart propofol infusion. If the patient's saturation remains high during a period of apnea, the SEDASYS System restarts propofol infusion. If the patient's saturation is low or falls during the period of apnea, the clinician must restart it. Figure 11 is an illustration of the low respiration rate/apnea alarm thresholds.

Figure 11
Low Respiration Rate/Apnea Alarm Thresholds



Advisories Based on Subsystem Status

Advisories based on subsystem status fall into three categories:

- Correctable Advisories
- Failure Advisories
- Synchronization Advisories

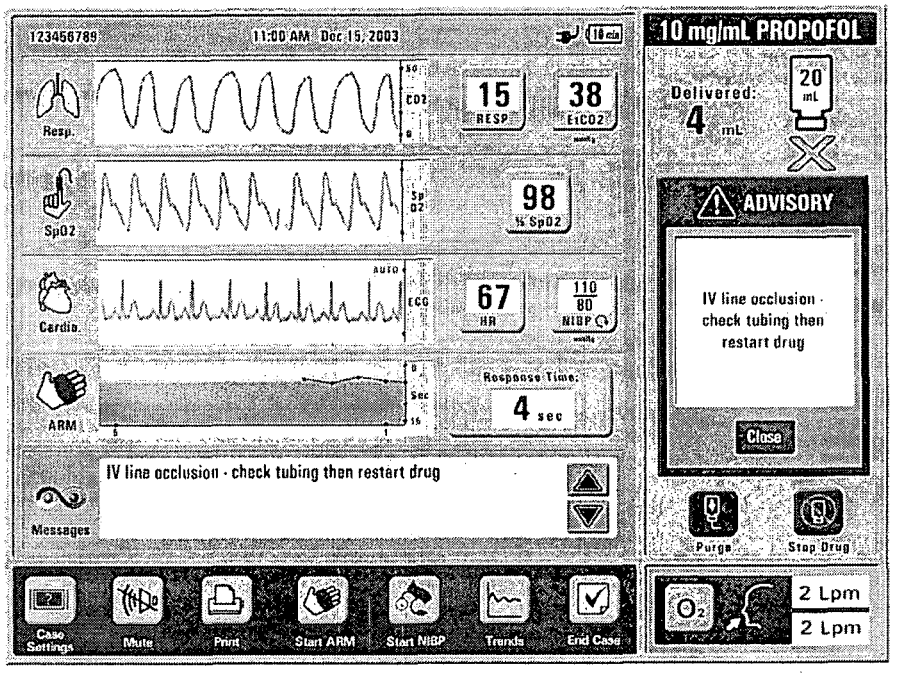
Correctable Advisories

A Correctable Advisory is a hardware problem, of identifiable cause, that can be corrected by the clinician. The individual subsystems within the SEDASYS System (e.g., pulse oximeter module, infusion pump, etc.) can each detect various hardware problems that can adversely affect their performance. The SEDASYS System alerts the clinician of a Correctable Advisory through both visual and audible signals.

In addition to the above, the SEDASYS System has specific responses depending on which subsystem is affected:

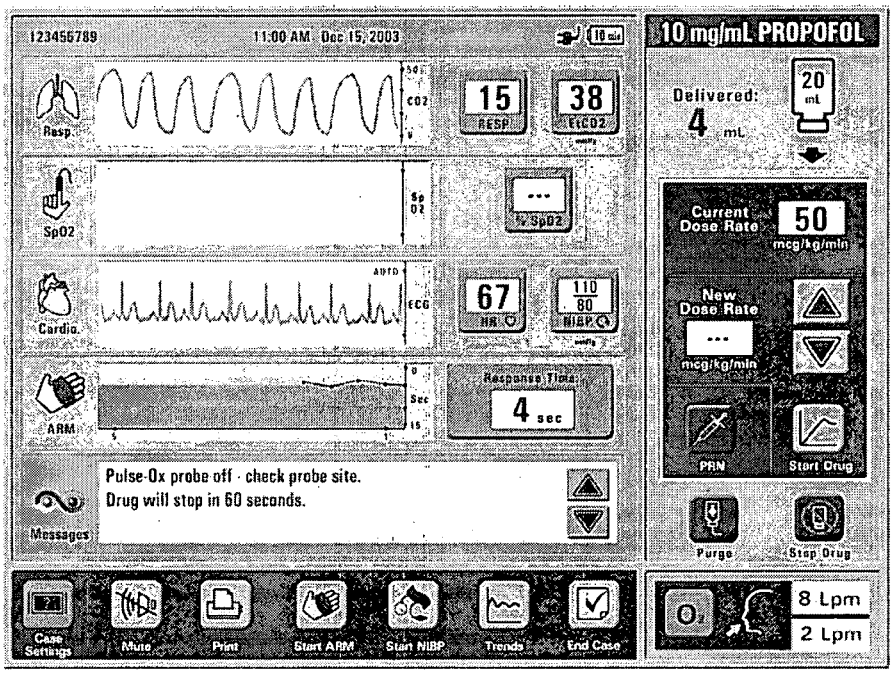
- An IV Pump Correctable Advisory immediately stops the delivery of propofol (Figure 12). IV pump advisories include downstream occlusions, air-in-line, and empty vial. The clinician must correct the problem and then restart propofol delivery.

Figure 12
PRU Main Monitoring Screen During IV Pump Correctable Advisory

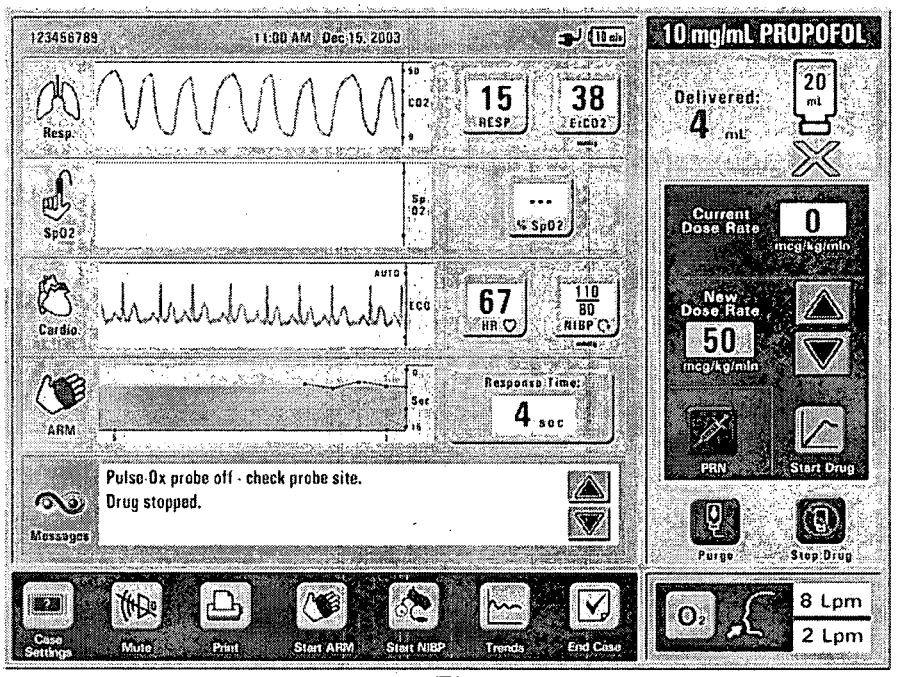


- Correctable Advisories for the pulse oximeter, capnometer, automated responsiveness monitor (ARM), or oxygen delivery subsystems stop propofol delivery after 60 seconds if the problem is not corrected (Figure 13). Examples of these advisories are: probe-off (pulse oximeter), occlusion (capnometer), missing handset (ARM), and hypoxic gas (oxygen delivery). If propofol delivery is stopped by the SEDASYS System, it must be manually restarted after the problem is corrected.

Figure 13
PRU Main Monitoring Screen During Pulse Oximeter Correctable Advisory: (A) First 60 Seconds and (B) After 60 Seconds



(A)



(B)

- A non-invasive blood pressure or electrocardiogram correctable advisory does not affect propofol delivery. The ECG supplies a redundant heart rate (the heart rate from the pulse oximeter is the primary value used for alarms) and Red Alarms associated with both heart rate and blood pressure do not stop propofol delivery. Examples of these advisories are: lead-off (ECG) and occlusion (NIBP).

Failure Advisories

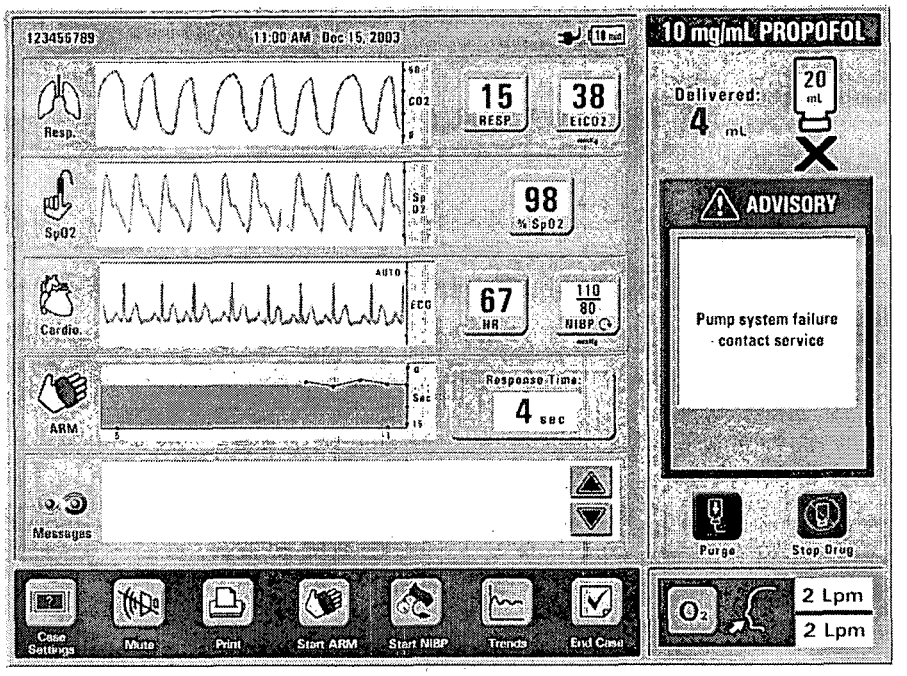
A Failure Advisory is a hardware or software problem, of identifiable cause, that ***cannot be corrected*** by the clinician. The SEDASYS System identifies the problem and alerts the clinician of a Failure Advisory through both visual and audible signals. These include:

- Problem description appears in the Procedure Room Unit main monitoring screen (either in the Messages field or an Advisory pop-up screen).
- Alarm sounds at a tone specific to a Failure Advisory.
- Light bar on top of the Bedside Monitoring Unit flashes.

The SEDASYS System also responds differently to a Failure Advisory, depending on which subsystem has failed:

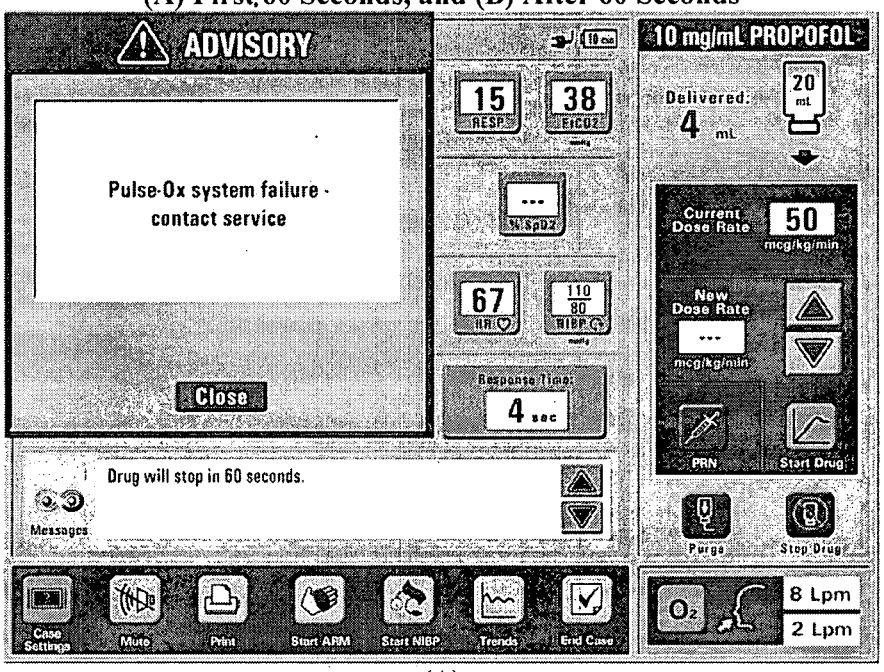
- A failure of the IV pump immediately terminates the delivery of propofol (Figure 14).

Figure 14
PRU Main Monitoring Screen Following IV Pump Failure Advisory

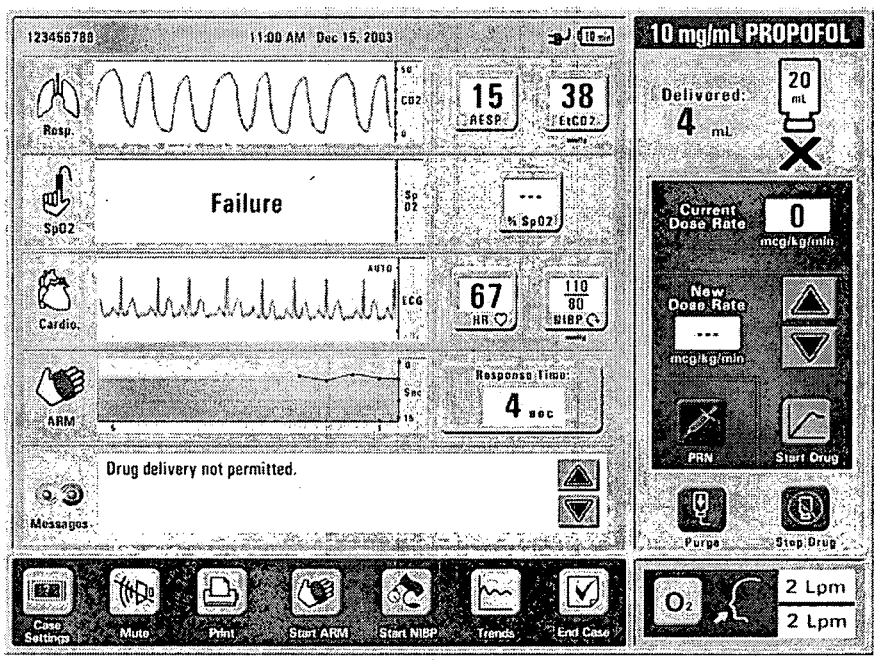


- A failure of the pulse oximeter or capnometer results in the termination of drug delivery after 60 seconds (Figure 15).

Figure 15
PRU Main Monitoring Screen Following Pulse Oximeter Failure: (A) First 60 Seconds, and (B) After 60 Seconds



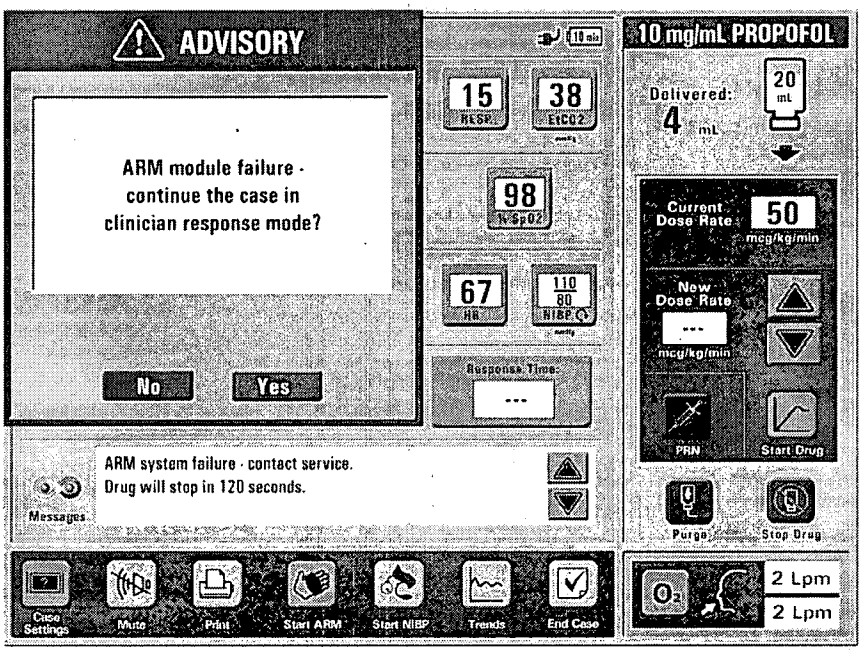
(A)



(B)

- Failure of the ARM module terminates drug delivery after 120 seconds, but only if the clinician decides not to continue the case in the Clinician-Response mode (Figure 16).

Figure 16
PRU Main Monitoring Screen Following ARM Failure



- A failure of the NIBP or ECG modules during a case does not affect drug delivery. A pop-up screen displaying the failure appears, and lasts for 120 seconds. If the ECG failed, "Failure" is displayed in the ECG waveform box. If NIBP failed, "---" is displayed in the NIBP button.

Synchronization Advisories

A Synchronization Advisory is a system problem of identifiable cause that can be corrected by the SEDASYS System, such as synchronization problems between the host controller and a subsystem. The SEDASYS System identifies the problem and alerts the clinician of a Synchronization Advisory through visual signals:

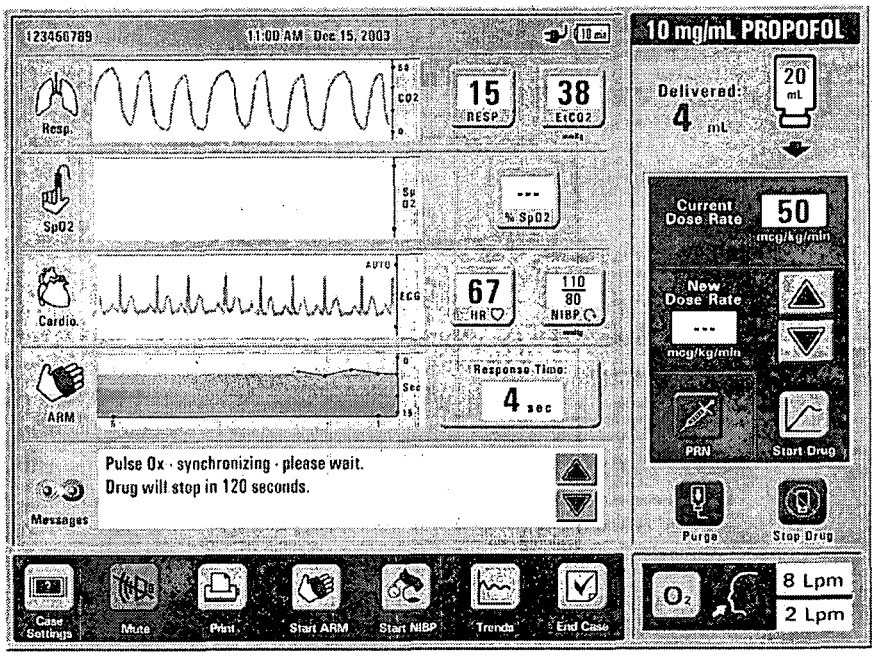
- Problem description appears in the Messages field of the Procedure Room Unit main monitoring screen.

If the SEDASYS System cannot correct the problem causing the Synchronization Advisory within 60 seconds, it will trigger a Failure Advisory.

In addition to the above, the SEDASYS System has specific responses depending on which subsystem is affected.

- Synchronization Advisories for the pulse oximeter or capnometer subsystems will warn the user that propofol infusion will be terminated in 120 seconds if the problem cannot be corrected (Figure 17). The SEDASYS System will try to correct the problem for 60 seconds. If the problem could not be corrected, it will declare a Failure Advisory and infusion will be stopped 60 seconds later.

Figure 17
PRU Main Monitoring Screen During Pulse Oximeter Synchronization Advisory



- Synchronization Advisories for the ECG or NIBP subsystems will simply warn the user of the problem. If the problem cannot be corrected within 60 seconds, the SEDASYS System will declare a Failure Advisory. There is no impact to propofol infusion.

3.5 Summary of Device Description

The SEDASYS System is an integrated system designed to enable a physician/nurse team to safely and effectively administer propofol sedation. Each element of the system – enhanced patient monitoring, drug delivery algorithms, dosing restrictions, automated oxygen delivery, and patient alarms integrating monitoring and drug infusion, as well as propofol itself – were carefully designed to work together to reduce the risk of injury resulting from over-sedation.

4.0 SEDASYS SYSTEM CLINICAL PROGRAM

4.1 Clinical Experience

To date, the SEDASYS System clinical program includes 14 clinical studies. These clinical studies are described in Table 5.

Table 5
Clinical Studies Conducted

Protocol # / Country / Year Completed	Objective	Study Design	# Subjects	Outcome
Proof-of-Concept/Drug Dosing Studies				
CI-01-0001 • United States • July 2001	Feasibility of early prototype device to safely deliver propofol sedation in subjects undergoing a colonoscopy	• Non-comparative, single center study • Colonoscopy procedure • Device operated by an anesthesiologist	10 subjects	Propofol infusion rates were ~165 µg/kg/min and subjects reached deep sedation
CI-01-0002 • United States • March 2002	Feasibility of early prototype device to safely deliver propofol sedation in subjects undergoing an EGD	• Non-comparative, single center study • EGD procedure • Device operated by an anesthesiologist	10 subjects	Propofol alone not sufficient to sedate patients undergoing EGD
CI-02-0003 • United States • June 2002	Feasibility of adding an opioid pre-medication (fentanyl) to maintain the average propofol maintenance rate below 100 µg/kg/min	• Non-comparative, single center study • Colonoscopy procedure • Device operated by an anesthesiologist	8 subjects	Small dose (~ 1 µg/kg) of fentanyl reduced propofol dose needed to maintain sedation
CI-02-0005 • United States • January 2004	Determine appropriate fentanyl dose (1.0, 1.5, or 2.0 µg/kg) to maintain propofol infusion within approved rates for sedation	• Non-comparative, single center study • Colonoscopy or EGD procedure • Device operated by an anesthesiologist	32 subjects (26 colon-oscopy; 6 EGD)	Recommended fentanyl dose: 50 to 100 µg for healthy adults; 25 to 50 µg for frail or elderly
Current Clinical Practice Studies				
CI-02-0004 • United States • April 2003	Evaluate sedation risks in subjects undergoing an upper and/or lower endoscopy under benzodiazepine sedation and propofol sedation	• Comparative, multi-center study • Upper and/or lower endoscopy • Benzodiazepine sedation by endoscopist/nurse team • Propofol sedation by anesthesia professionals	300 subjects enrolled (150 benzodiaze-pine; 150 propofol)	Area-under-the-curve of oxygen desaturation provides a more sensitive measure of risk of sedation

Protocol # / Country / Year Completed	Objective	Study Design	# Subjects	Outcome
Lextant Study • United States • March 2005	Quantitative analysis of tasks performed by nurses during endoscopy	• Observational, non-comparative, multi-center study • Colonoscopy or EGD procedure • SEDASYS System not used in this study	100 subjects	The nurse's tasks are interruptible
United BioSource Corporation Study • United States • May 2006	Develop and validate tools to assess physician and patient satisfaction with sedation	• Prospective, multi-center, psychometric validation study • SEDASYS System not used in this study	180 subjects and 22 physicians	Validated tools: Patient Satisfaction with Sedation Instrument (PSSI) and Clinician Satisfaction with Sedation Instrument (CSSI)
Clinical Functionality Studies				
CI-03-0001 • United States • December 2004	Compare the relative effectiveness of the SEDASYS System oral/nasal cannula to deliver oxygen, compared to the Oridion oral/nasal cannula (Oridion Capnography Inc, Needham, MA) and a conventional nasal cannula	• Open, randomized, comparative, single-center study • No procedures were performed	13 subjects enrolled	Delivery of supplemental oxygen by all three devices resulted in an increase in PaO_2 over baseline
CI-03-0004 • United States • August 2005	Determine where the loss of response to the automated responsiveness monitor (ARM) component of the SEDASYS System occurs along the continuum of sedation/anesthesia	• Open, comparative, single center study • No procedures were performed; only sedation provided	27 subjects enrolled	Loss of responsiveness to the automated responsiveness monitor component of the SEDASYS System precedes, or occurs concurrently with, the transition to deep
CI-03-0005 • United States • December 2004	To evaluate the accuracy of the SEDASYS System capnometer for monitoring respiration rate	• Open, single center study • No procedures were performed	50 subjects enrolled	The capnometry component of the SEDASYS System accurately measures respiration rate and apnea

Protocol # / Country / Year Completed	Objective	Study Design	# Subjects	Outcome
Clinical Accuracy Validation • United States • December 2004	To clinically validate the Dolphin ONE model 210 reusable sensors and Dolphin ONE model 520 adult disposable sensors used in conjunction with the SEDASYS System's Bedside Monitoring Unit	• Open, single center study	11 subjects enrolled	Demonstrated an accuracy of 1.78% average root mean square during the study, in a range from 70–100% SpO_2
Feasibility Studies				
CI-04-0005 • United States • March 2006	Determine the feasibility of the SEDASYS System to enable a physician/nurse care team, to safely and effectively administer minimal-to-moderate sedation with propofol in subjects undergoing a colonoscopy or EGD	• Open, comparative, single center study • Colonoscopy or EGD procedure	48 subjects enrolled (24 colon-oscopy; 24 EGD)	Established the feasibility of the SEDASYS System to enable physician/nurse teams to safely and effectively administer minimal-to-moderate sedation with propofol for patient undergoing colonoscopy or EGD
CI-05-0002 • Gent, Belgium • January 2006	Determine the feasibility of the SEDASYS System to enable a physician/nurse care team, to safely and effectively administer minimal-to-moderate sedation with propofol in subjects undergoing a colonoscopy or EGD	• Open, comparative, single center study • Colonoscopy or EGD procedure	48 subjects enrolled (24 colon-oscopy; 24 EGD	Established the feasibility of the SEDASYS System to enable physician/nurse teams to safely and effectively administer minimal-to-moderate sedation with propofol for patient undergoing colonoscopy or EGD
Pivotal Study				
CI-06-0004 • United States • October 2007	Provide substantial scientifically valid evidence that physician/nurse teams can safely and effectively administer propofol for minimal-to-moderate sedation to subjects undergoing colonoscopy or EGD procedures	• Comparative, multi-center study • SEDASYS System vs. benzodiazepine-based sedation • Colonoscopy or EGD procedure	1000 subjects (721 colon-oscopy; 279 EGD)	The SEDASYS System enables physician/nurse teams to safely and effectively administer minimal-to-moderate sedation with propofol for patient undergoing colonoscopy or EGD

4.2 Proof-of-Concept/Drug Dosing Studies (CI-01-0001, CI-01-0002, CI-02-0003 and CI-02-0005)

The first two proof-of-concept studies (CI-01-0001 and CI-01-0002) demonstrated that sedation, with propofol as the sole agent, was either insufficient to keep subjects calm and cooperative or required deep sedation to keep subjects comfortable during colonoscopy or EGD procedures. In these studies, average infusion rates of propofol ranged between 140 and 200 μg/kg/min. The third study (CI-02-0003) demonstrated that combining small doses of fentanyl reduced the average propofol infusion rates to ~100 μg/kg/min and fewer subjects reached deep sedation.

A fourth proof-of-concept study (CI-02-0005) was conducted to determine the appropriate single dose of fentanyl to be used with the SEDASYS System during colonoscopy and EGD procedures. A total of 32 subjects were enrolled in the study, and as with the three previous studies, an anesthesiologist administered sedation.

With the addition of fentanyl, the average propofol infusion rate ranged between 68 and 85 μg/kg/min. The dosing guidelines in FDA-approved propofol labeling states that most patients will be adequately sedated with infusion rates of 25 to 75 μg/kg/min.

Data from this study (CI-02-0005) supported the use of a single dose of fentanyl administered 3 minutes prior to the start of the propofol infusion with the SEDASYS System. The recommended fentanyl dose is 50 to 100 μg for healthy adults and 25 to 50 μg for the frail, elderly, or debilitated.

4.3 Sedation Risk Study (CI-02-0004)

Numerous published studies have looked at parameters to assess risk in endoscopic sedation including, but not limited to:

- The level of sedation,
- Incidence of apnea, and
- Hypoxia.

Incidence of hypoxia is the most widely used measure, as it is the direct mechanism of injury due to over-sedation.

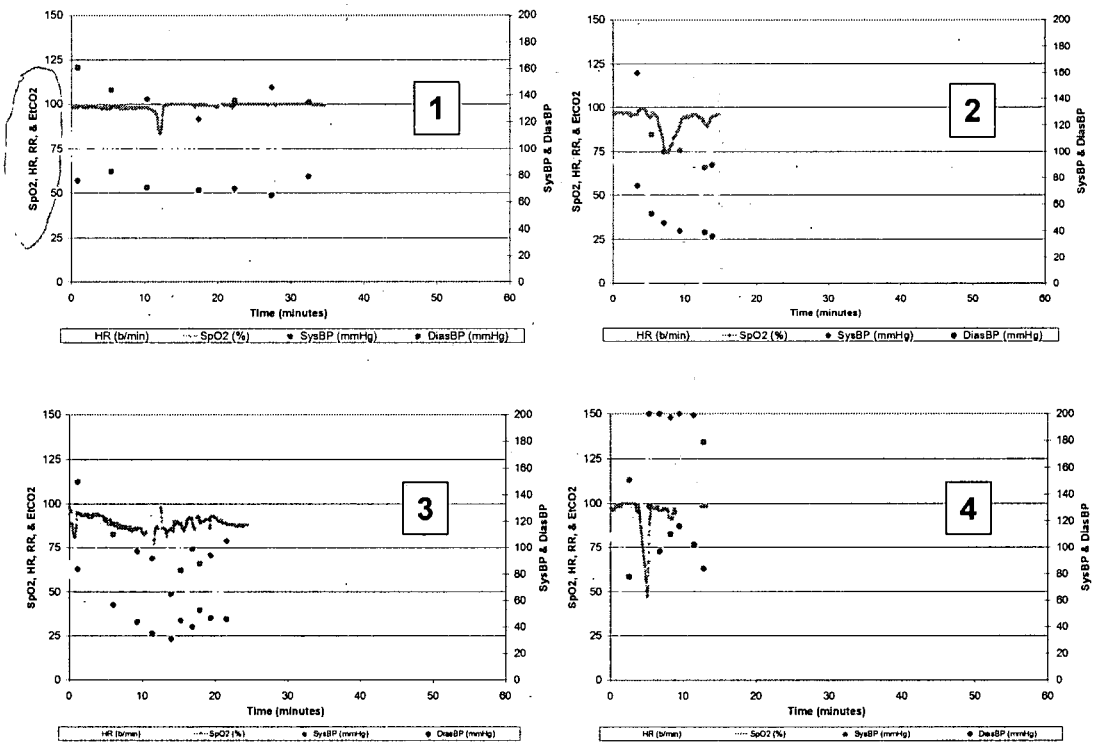
To better characterize the risks in endoscopic sedation, a 300 subject clinical study was conducted. This was a multi-center center study with one center sedating 150 subjects undergoing colonoscopy and EGD procedures with benzodiazepines and opioids administered by an endoscopist/nurse team. The second site sedated 150 subjects undergoing colonoscopy and EGD procedures with propofol administered by an anesthesia professional (certified registered nurse anesthetist or anesthesiologist).

In both treatment groups, patients experienced oxygen desaturation which is defined as saturation less than 90% for greater than 15 seconds. Duration of a desaturation ranged from

15 seconds to almost 10 minutes and the lowest saturation reached ranged from 89% to 47%. Many subjects had multiple desaturation events.

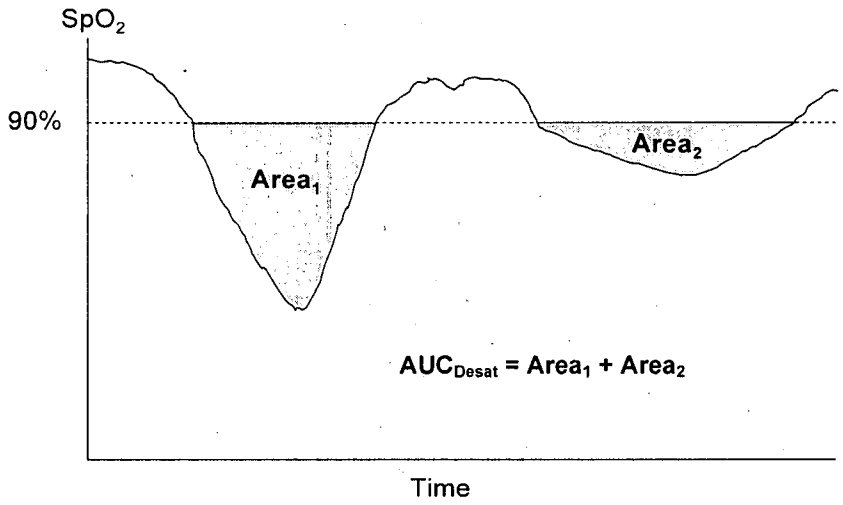
Figure 18 illustrates Subject 4 with a minimum desaturation of 47% is at a much greater risk than Subject 1 whose minimum value is 83%. Similarly, Subject 3 with a desaturation lasting ~7 minutes is at a greater risk than Subject 1 whose desaturation event lasted less than a minute. Yet, looking at incidence alone, each of these subjects would be considered to be exposed to the same risk.

Figure 18
Risk Study (CI-02-0004) Oxygen Desaturation



The incidence of hypoxia is clearly not a complete measure of risk. That is, incidence alone does not capture the severity of the event. A more complete measure of risk would integrate the incidence, duration, and depth of desaturation into a single 'composite' endpoint. Area-under-the-curve of oxygen desaturation is such a measure. Figure 19 graphically depicts area-under-the-curve of oxygen desaturation.

Figure 19
Area-Under-The-Curve of Oxygen Desaturation



4.4 Feasibility Studies (CI-04-0005 and CI-05-0002)

4.4.1 Objective

The studies were designed to evaluate the feasibility of the SEDASYS System to enable a physician/nurse care team to safely and effectively administer minimal-to-moderate sedation with propofol in subjects undergoing a colonoscopy or EGD procedure.

4.4.2 Study Design

The studies were open, single-center studies conducted in the United States (CI-04-0005) and Belgium (CI-05-0002). Each study was conducted in two stages:

- **Stage 1**

  An anesthesiologist operated the SEDASYS System to administer propofol sedation to each subject. The anesthesiologist assessed the subject's level of sedation throughout the procedure and was responsible for the subject's safety.

- **Stage 2**

  The physician/nurse care team operated the SEDASYS System to administer propofol sedation to each subject. An anesthesiologist was present to assess subject's level of sedation throughout the procedure and ensure subject's safety.

In both stages, subjects were administered a single intravenous bolus of fentanyl 25 – 100 µg, depending on age and physical status. To minimize the risk of ventilatory depression, a 3-minute interval occurred prior to initiation of propofol infusion at 75 µg/kg/min.

4.4.3 Results

Ninety-six subjects (ASA I-III) were enrolled in the studies (48 subjects in each study), with 24 subjects (12 colonoscopy and 12 EGD) participating in each stage (Stages 1 and 2) of each study (CI-04-0005 and CI-05-0002). The demographics of the subjects enrolled into the studies were similar across stages and studies as shown in Table 6.

Table 6
Feasibility Studies Demographics[a]

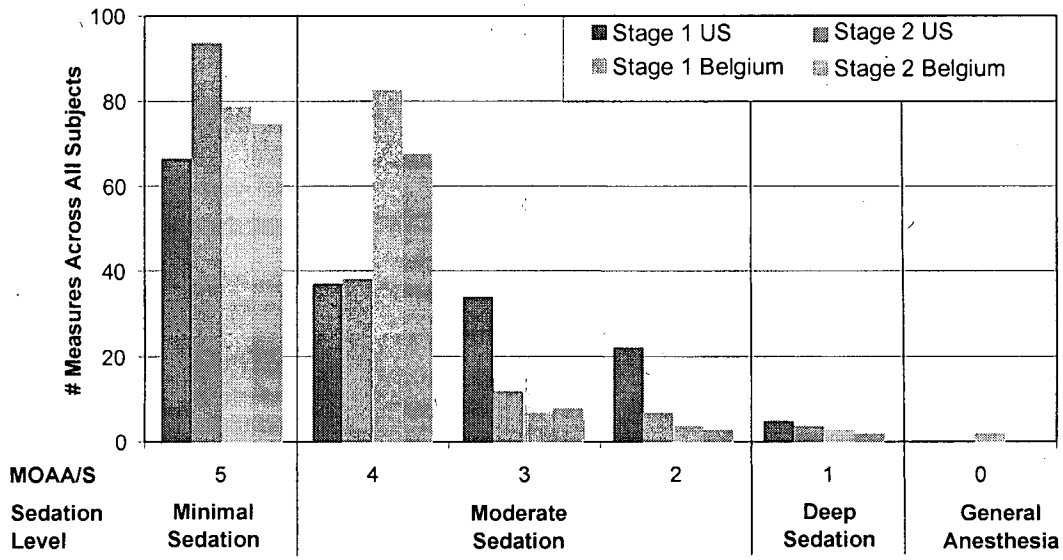
Demographics	US Stage 1 (N = 24)	US Stage 2 (N = 24)	Belgium Stage 1 (N = 24)	Belgium Stage 2 (N = 24)
Age (years)	51 ± 11	54 ± 10	54 ± 12	53 ± 14
Gender n (%)				
Male	10 (42%)	11 (46%)	9 (38%)	12 (50%)
Female	14 (58%)	13 (54%)	15 (63%)	12 (50%)
Race n (%)				
Caucasian, not of Hispanic origin	23 (96%)	21 (88%)	24 (100%)	24 (100%)
American Indian or Alaskan Native	0	0	0	0
Asian/Pacific Islander	0	1 (4%)	0	0
Black, Not of Hispanic origin	1 (4%)	2 (8%)	0	0
Hispanic	0	0	0	0
Other	0	0	0	0
Body Mass Index (kg/m^2)	29 ± 5	28 ± 5	26 ± 6	26 ± 6
ASA Classification n (%)				
Class I	2 (8%)	2 (8%)	10 (42%)	11 (46%)
Class II	13 (54%)	15 (63%)	9 (38%)	9 (38%)
Class III	9 (38%)	7 (29%)	5 (21%)	4 (17%)

[a] Plus-minus values are means ± SD.

Level of Sedation

Figure 20 illustrates the majority of subjects experienced minimal-to-moderate sedation throughout the procedure as measured by the MOAA/S scale. Less than 3% of all measures were MOAA/S of 1 or 0.

Figure 20
MOAA/S Correlation to Continuum



Propofol Dosing

As shown in Table 7, propofol administration was consistent with FDA-approved propofol labeling (25 – 75 μg/kg/min) during colonoscopy procedures.

Table 7
Propofol Dosing – Colonoscopy Procedure

Propofol Maintenance Rate (μg/kg/min)	US	Belgium
Stage 1	38 ± 8	58 ± 9
Stage 2	55 ± 9	68 ± 14

As shown in Table 8, propofol administration was consistent with FDA-approved propofol labeling (25 – 75 μg/kg/min) during EGD procedures.

Table 8
Propofol Dosing – EGD Procedure

Propofol Maintenance Rate (μg/kg/min)	US	Belgium
Stage 1	64 ± 9	65 ± 13
Stage 2	51 ± 18	65 ± 6

Clinician Satisfaction
As shown in Table 9, users (physician/nurse teams) were very satisfied with the sedation administered and mean Clinician Satisfaction with Sedation Instrument scores were similar across stages and countries in both studies.

Table 9
Clinician Satisfaction

CSSI	US	Belgium
Stage 1	95 ± 8	89 ± 14
Stage 2	99 ± 2	86 ± 8

Patient Satisfaction
As shown in Table 10, subjects were very satisfied with the sedation received and mean Patient Satisfaction with Sedation Instrument scores were similar across stages and countries in both studies.

Table 10
Patient Satisfaction

PSSI	US	Belgium
Stage 1	94 ± 8	93 ± 11
Stage 2	95 ± 8	90 ± 10

Serious Adverse Events
In the US study (CI-04-0005), one subject that had undergone an EGD in Stage 1 experienced a serious adverse event two days after the procedure. That subject fell off of a ladder resulting in a fractured neck which required hospitalization. The event was deemed not related to the study procedure, study device, or study drug. No other serious adverse events were reported during the study.

In the Belgium study (CI-05-0002), there were no serious adverse events in either Stage 1 or Stage 2.

4.4.4 Conclusions: Feasibility Studies

The two studies demonstrated the feasibility of the SEDASYS System to enable physician/nurse teams to safely and effectively administer minimal-to-moderate sedation with propofol:

- The SEDASYS System facilitated administration of minimal-to-moderate sedation;
- Propofol dosing was consistent with propofol labeling;
- Endoscopists were satisfied with the sedation administered;
- Patients were satisfied with the sedation received; and
- Data were comparable across different users and practice settings.

4.5 Pivotal Study (CI-06-0004)

4.5.1 Study Objective

The objective of this study was to demonstrate that the SEDASYS System enabled physician/nurse teams to safely and effectively administer propofol for minimal-to-moderate sedation in subjects undergoing colonoscopy and EGD procedures.

4.5.2 Inclusion/Exclusion Criteria

Subjects were to be male or female (not pregnant and not lactating); aged 18 years or older; had English as their primary language; undergoing a routine EGD or colonoscopy; had taken nothing by mouth (except for water and the preparation necessary to vacate the bowel for colonoscopy) for a minimum of 6 hours prior to the study procedure; and were ASA physical status I, II or III (Table 11). No subjects were to have been diagnosed with sleep apnea or gastroparesis; have baseline oxygen saturation less than 90%; or a body mass index greater than or equal to 35 kg/m^2.

Table 11
ASA Classification of Physical Status

American Society of Anesthesiologists Classification of Physical Status	
I	Healthy patient
II	Mild systemic disease – no functional limitations
III	Severe systemic disease – definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient not expected to survive 24 hours with or without operation
Adapted from: Kost M. *Manual of Conscious Sedation.* 1998. W.B. Saunders and Company, Philadelphia. pp 57-58.	

4.5.3 Investigational Plan

This was a non-blinded, multi-center, randomized, comparative study of the SEDASYS System (SDS) versus the current standard of care (CSC) for sedation in subjects with ASA physical status I, II, or III during routine colonoscopy or EGD procedures. One thousand subjects from eight sites were screened and randomized equally to either the SDS or CSC group. In order to concentrate on more challenging procedures with longer duration, 721 subjects undergoing colonoscopies were enrolled and 279 subjects undergoing EGDs were enrolled.

This study consisted of five phases: screening, pre-procedure, procedure, recovery, and a 24 – 48 hour follow-up phase.

Following screening, subjects entered the pre-procedure phase where they were randomized to a group and prepared for the procedure. The randomization schedule was blocked by center and procedure to allot approximately equal number of subjects in each treatment at each site. Subjects then continued to the procedure phase where they underwent sedation for their endoscopic procedure.

For the SDS group, a single dose of fentanyl was administered via IV bolus in the amount of 50 – 100 μg for healthy subjects aged 64 years or younger; or 25 – 50 μg for subjects who were frail, debilitated, or aged 65 years or older. No additional fentanyl dosing was allowed beyond the initial dose. Three minutes after the administration of fentanyl, the physician was to determine and initiate the propofol maintenance rate of between 5 μg/kg/min and 75 μg/kg/min. Throughout the procedure, the propofol maintenance rate was titrated by the clinician to achieve a desired clinical effect.

For the CSC group, opioids and benzodiazepines were administered per each site's standard operating procedure. Supplemental oxygen was administered at 2 liters per minute and was manually increased, if clinically indicated.

Oxygen saturation was measured every second from the time of the first dose of medication until two consecutive MOAA/S scores of 5 were achieved or 15 minutes following "scope-out", whichever came first (for MOAA/S definition, see Table 11). The MOAA/S was performed every 2 minutes from the time the first dose of medication was administered and continued until two consecutive scores of 5, following "scope-out", were achieved. All rescue interventions, including use of reversal medications, were documented during the study. All adverse events reported or observed during the study were collected through study exit.

The recovery phase began at the time of "scope-out" and ended when the subject was discharged from the study center. For this study, "time of recovery" was defined as the point in which the first of two consecutive MOAA/S scores of 5 was achieved. A psychomotor test was administered at the time of recovery, and 30 minutes after time of recovery. The physician completed the Clinician Satisfaction with Sedation Instrument questionnaire during the recovery phase. Subjects were discharged from center per the center's procedures.

Each subject was contacted by telephone 24 – 48 hours post-discharge to complete the Patient Satisfaction with Sedation Instrument questionnaire. Upon completion of the Patient Satisfaction with Sedation Instrument questionnaire or three documented failed attempts, the subject was considered "exited from the study."

A Data Monitoring Committee was established by Applied Clinical Intelligence, LLC to review safety data throughout the study.

4.5.4 Primary and Secondary Endpoints

Details of the Statistical Analyses are provided in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study*.

4.5.4.1 Primary Endpoint

The primary endpoint for both colonoscopy and EGD procedures was area-under-the-curve of oxygen saturation (AUC_{Desat}); oxygen desaturation defined as $SpO_2 < 90\%$ for > 15 seconds. AUC_{Desat} is a measure of risk that integrates the incidence, duration, and depth of desaturation into a single endpoint.

A Data Acquisition System recorded each subject's oxygen saturation every second during the procedure. AUC_{Desat} was calculated as the difference between the threshold (90%) and the actual oxygen saturation summed every second (including the first 15 seconds) when oxygen saturation was below threshold (Figure 19 above). Each subject may have had multiple excursions below the 90% threshold that were greater than 15 seconds in length. The endpoint was total AUC_{Desat} (seconds·%) for all excursions throughout the entire procedure.

4.5.4.2 Secondary Endpoints

The secondary endpoints for both colonoscopy and EGD procedures were: 1) clinician satisfaction scores, 2) patient satisfaction scores, 3) recovery time, and 4) duration of deep sedation/general anesthesia.

Clinician Satisfaction Scores
Clinician satisfaction was measured using the Clinician Satisfaction with Sedation Index (Exhibit C, *Clinician and Patient Satisfaction With Sedation Instrument Questionnaires*). This validated measure contains 16 questions encompassing the ease of sedation administration, the adequacy of monitoring, and patient comfort. Each of the 16 questions is scored from 1 to 7, and the total raw score is linearly rescaled to range from 0 to 100. Therefore, the aggregate score ranges from 0 to 100, with 100 being extremely satisfied.

Patient Satisfaction Scores
Patient satisfaction was measured using the Patient Satisfaction with Sedation Index (Exhibit C, *Clinician and Patient Satisfaction With Sedation Instrument Questionnaires*). This validated measure contains 16 questions encompassing the discomfort during the procedure, recall, and return to normal activities. Each of the 16 questions is scored from 1 to 7, and the total raw score is linearly rescaled to range from 0 to 100. Therefore, the aggregate score ranges from 0 to 100, with 100 being extremely satisfied.

Recovery Time
Recovery time was defined as the time (to the nearest minute) from "scope-out" until the first of two consecutive MOAA/S scores of 5 was achieved. Table 12 presents the MOAA/S scale used in the study and its correlation to the ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists.[23]

Duration of Deep Sedation/General Anesthesia
The duration of deep sedation/general anesthesia was measured by the occurrence of all MOAA/S scores of 1 or 0 during a procedure.

[23] American Society of Anesthesiologists. 2002. Practice guidelines for sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 96(4):1004-17.

Table 12
MOAA/S and the ASA Continuum of Sedation/Anesthesia

MOAA/S	Level of Sedation	ASA Continuum
5	Responds readily to name spoken in normal tone	Minimal
4	Lethargic response to name spoken in normal tone	Moderate
3	Responds after name called loudly or repeatedly	Moderate
2	Purposeful response to mild prodding or shaking	Moderate
1	Responds to painful stimulus (trapezius squeeze)	Deep
0	No response to painful stimulus (trapezius squeeze)	General Anesthesia

4.5.5 Disposition of Subjects

Of the 1000 subjects randomized in this study, 496 subjects (50%) were randomized to the SDS group and 504 subjects (50%) were randomized to the CSC group.

Colonoscopy Procedure
Of the 721 subjects who underwent a colonoscopy, 358 (50%) subjects were randomized to the SDS group and 363 (50%) subjects were randomized to the CSC group (Table 13). A total of 354 (99%) subjects completed the study in the SDS group compared with 354 (98%) in the CSC group.

Four subjects in the SDS group did not complete the study for the following reasons:

- 1 subject was withdrawn due to a device failure;
- 1 subject withdrew consent; and
- 2 subjects were withdrawn for other reasons, specified as withdrawn due to a device failure; and withdrawn due to a high tolerance to propofol which resulted in an inability to complete the procedure while on study.

Nine subjects in the CSC group did not complete the study for the following reasons:

- 1 subject was withdrawn due to poor bowel preparation that prevented completion of the procedure;
- 4 subjects were withdrawn due to a device failure;
- 1 subject withdrew consent; and

- 3 subjects were withdrawn for other reasons, specified as withdrawn due to a device failure; a Data Acquisition System issue; and a history of sleep apnea discovered after randomization but prior to performing the procedure.

Table 13
Subject Disposition – Colonoscopy Procedure

Parameter n (%)	SDS (N = 358)	CSC (N = 363)	Total (N = 721)
Completed study	354 (99%)	354 (98%)	708 (98%)
Did not complete study	4 (1%)	9 (3%)	13 (2%)
Withdrawn for adverse event	0	0	0
Withdrew – noncompliance	0	0	0
Withdrawn for poor prep	0	1 (11%)	1 (8%)
Withdrawn for device failure	1 (25%)	4 (44%)	5 (38%)
Withdrawal of consent	1 (25%)	1 (11%)	2 (15%)
Death	0	0	0
Other, specified as:	2 (50%)	3 (33%)	5 (38%)
Device failure	1	1	2
Data Acquisition System issue	0	1	1
High tolerance to propofol	1	0	1
History of sleep apnea	0	1	1

EGD Procedure
Of the 279 subjects who underwent an EGD, 138 (49%) subjects were randomized to the SDS group and 141 (51%) subjects were randomized to the CSC group (Table 14). A total of 135 (98%) subjects completed the study in the SDS group compared with 139 (99%) in the CSC group.

Three subjects in the SDS group did not complete the study for the following reasons:

- 1 subject was withdrawn due to an exclusionary history of sleep apnea; and
- 2 subjects were withdrawn for other reasons specified as withdrawn due to Data Acquisition System issues.

Two subjects in the CSC group did not complete the study for the following reasons:

- 1 subject withdrew consent; and
- 1 subject was withdrawn for other, specified as withdrawn due to a Data Acquisition System issue.

Table 14
Subject Disposition – EGD Procedure

Parameter n (%)	**SDS** (N = 138)	**CSC** (N = 141)	**Total** (N = 279)
Completed study	135 (98%)	139 (99%)	274 (98%)
Did not complete study	3 (2%)	2 (1%)	5 (2%)
Withdrawn for adverse event	0	0	0
Withdrew – noncompliance	1 (33%)	0	0
Withdrawn for poor prep	0	0	0
Withdrawn for device failure	0	0	0
Withdrawal of consent	0	1 (50%)	1 (20%)
Death	0	0	0
Other, specified as:	2 (67%)	1 (50%)	3 (60%)
Data Acquisition System issue	2	1	3

4.5.6 Demographic Data

Colonoscopy Procedure

Table 15 summarizes the demographic information for the 721 subjects who underwent a colonoscopy.

Table 15
Demographic Data – Colonoscopy Procedure[a]

Parameter	SDS (N = 358)	CSC (N = 363)	p-value[b]
Age (years)	54 ± 12	55 ± 12	0.637
Gender n (%)			
Female	198 (55%)	168 (46%)	
Male	160 (45%)	195 (54%)	0.015
Race n (%)			
Caucasian, not of Hispanic origin	319 (89%)	316 (87%)	
American Indian or Alaskan Native	1 (0.3%)	3 (0.8%)	
Asian/Pacific Islander	5 (1%)	5 (1%)	
Black, Not of Hispanic origin	26 (7%)	31 (9%)	
Hispanic	5 (1%)	8 (2%)	
Other	2 (0.6%)	0	0.534
Body Mass Index (kg/m^2)	26 ± 4	27 ± 4	0.127
ASA Classification n (%)			
Class I	147 (41%)	152 (42%)	
Class II	200 (56%)	205 (57%)	
Class III	11 (3%)	6 (2%)	0.454

[a] Plus-minus values are means ± SD.
[b] p-value was based on analysis of variance with factors for treatment and the respective variable for continuous variables (age and body mass index) and based on a Chi-squared test for categorical variables (gender, race, and ASA classification).

EGD Procedure

Table 16 summarizes the demographic information for the 279 subjects who underwent an EGD.

Table 16
Demographic Data – EGD Procedure[a]

Parameter	SDS (N = 138)	CSC (N = 141)	p-value[b]
Age (years)	50 ± 14	49 ± 16	0.340
Gender n (%)			
Female	68 (49%)	80 (57%)	
Male	70 (51%)	61 (43%)	0.212
Race n (%)			
Caucasian, not of Hispanic origin	119 (86%)	114 (81%)	
American Indian or Alaskan Native	0	0	
Asian/Pacific Islander	0	3 (2%)	
Black, Not of Hispanic origin	14 (10%)	19 (14%)	
Hispanic	4 (3%)	2 (1%)	
Other	1 (0.7%)	3 (2%)	0.240
Body Mass Index (kg/m^2)	26 ± 4	26 ± 4	0.970
ASA Classification n (%)			
Class I	58 (42%)	53 (38%)	
Class II	73 (53%)	84 (60%)	
Class III	7 (5%)	4 (3%)	0.410

[a] Plus-minus values are means ± SD.
[b] p-value was based on analysis of variance with factors for treatment and the respective variable for continuous variables (age and body mass index) and based on a Chi-squared test for categorical variables (gender, race, and ASA classification).

4.5.7 Analysis Population

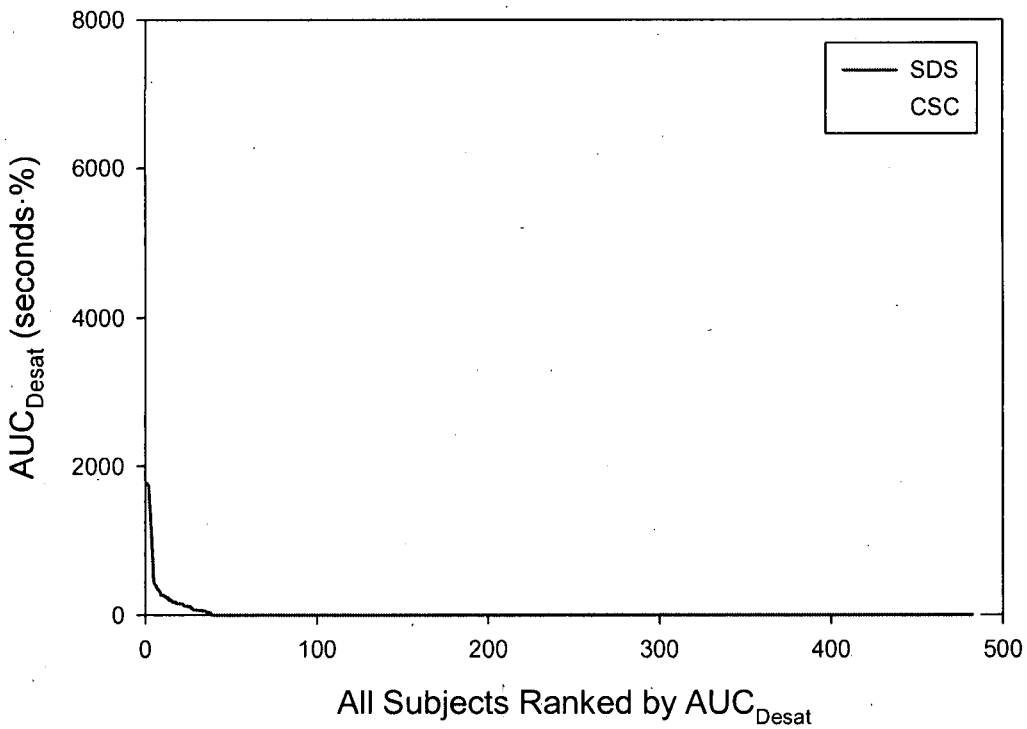
Analyses presented below were based upon the modified Intent-To-Treat (mITT) population. This population includes all randomized subjects with observed data available for each analysis (see Exhibit A, *Statistical Analysis of the Pivotal Clinical Study*).

Details of the mITT population are provided in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study*.

4.5.8 Primary Outcome: AUC_{Desat}

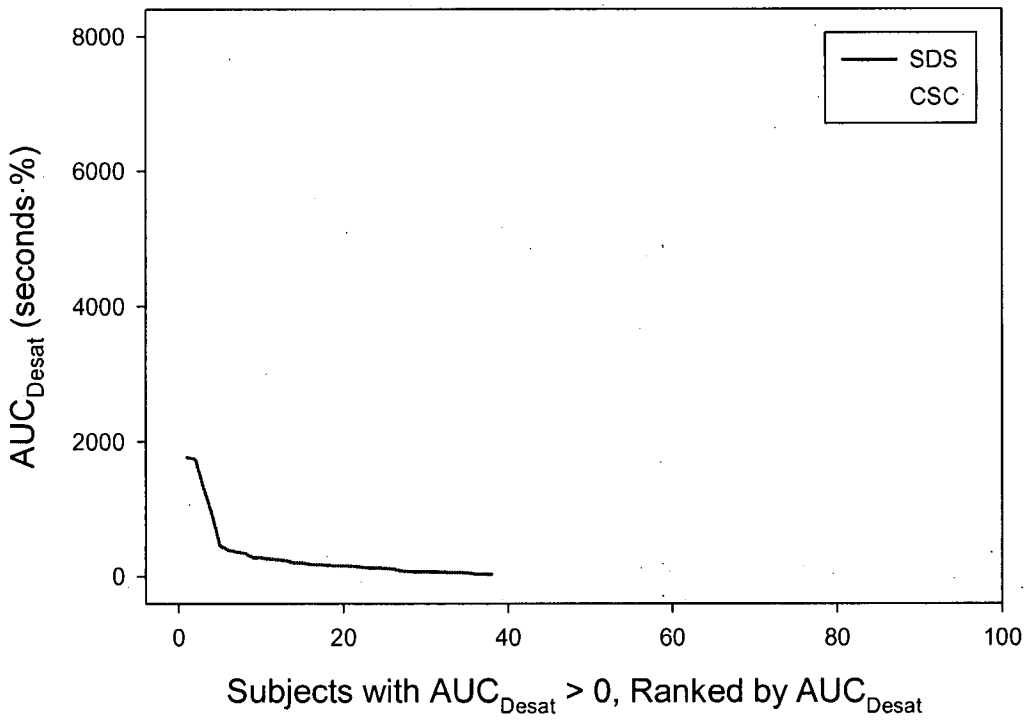
Figure 21 depicts the AUC_{Desat} data for all subjects in the study for each treatment group, for the combined EGD and colonoscopy procedures. The data demonstrate that for both treatment groups the majority of subjects did not experience an oxygen desaturation ($AUC_{Desat} = 0$).

Figure 21
AUC_{Desat} for All Subjects



To provide more granularity on the data Figure 22 shows the AUC_{Desat} data for all subjects in the study that experienced an oxygen desaturation. Eighty-three (17%) current standard of care subjects had at least one oxygen desaturation, compared to only 38 (8%) SEDASYS System subjects. Six current standard of care subjects had an AUC_{Desat} greater than 2000 seconds·%, while no SEDASYS System subject's AUC_{Desat} was greater than 2000.

Figure 22
AUC_{Desat} for All Subjects With An Oxygen Desaturation



4.5.8.1 Colonoscopy Procedures – Primary Analysis

The mean area-under-the-curve of oxygen desaturation for the SDS group was statistically significantly lower ($p = 0.004$) compared with the CSC group (Table 17). The maximum area-under-the-curve of oxygen saturation was four-fold greater in the CSC group (7040 seconds·%) compared with the SDS group (1741 seconds·%).

Table 17
Between Group Comparison of the Mean AUC_{Desat}
Colonoscopy Procedure[a]

	SDS	CSC	p-value[b]
AUC_{Desat} (seconds·%)	18 ± 125	99 ± 510	0.004

[a] Plus-minus values are means ± SD.
[b] The AUC_{Desat} values were analyzed using an analysis of variance with factors for group and study site; $\alpha = 0.05$ significance level.

Examination of the mean AUC_{Desat} values and corresponding 95% confidence intervals for each study site suggest that results are consistent between study sites.

Due to the possibility that the large number of $AUC_{Desat} = 0$ observations and the presence of a few large values of AUC_{Desat} lead to a non-normal distribution of data, two follow-up analyses were conducted.

First, a simulation was conducted to assess the extent to which the distribution of data may have lead to an inflation of type I error. The data generation scheme for the simulation was based upon data from the pivotal study. Specifically, data were generated under the null hypothesis of no treatment effect from a zero-inflated gamma regression model with fixed effects for study site. The parameters from this model were estimated from the pivotal study. Ten thousand datasets were generated and the difference between mean AUC_{Desat} values compared between the assigned treatment groups using analysis of variance (ANOVA). If the ANOVA procedure is appropriate for such highly skewed data, one would expect that p-values to be uniformly distributed with the proportion less than 0.05 equal to 5%. The proportion of p-values that were less than 0.05 was 0.046 for colonoscopy data and 0.047 for EGD data. The simulation study indicates that the ANOVA is not contra-indicated for the analysis of the AUC_{Desat} data.

Additionally, to verify the robustness of the analysis, the primary colonoscopy analysis was rerun using an ANOVA by Ranks. AUC_{Desat} values were ranked by study center and the resulting ranks were included as the dependent measure in an ANOVA with effects for treatment and center. Consistent with the planned primary analysis, the SDS group reported significantly lower mean ranked AUC_{Desat} ($p = 0.004$) when compared to the CSC group.

4.5.8.2 EGD Procedures – Primary Analysis

The mean area-under-the-curve of oxygen desaturation for the SDS group was lower compared with the CSC group (Table 18); however, the difference was not statistically significant ($p = 0.315$). The maximum area-under-the-curve of oxygen desaturation was greater in the SDS group (1771 seconds·%) compared with the CSC group (996 second·%).

Table 18
Between Group Comparison of the Mean AUC_{Desat}
EGD Procedure[a]

	SDS	CSC	p-value[b]
AUC_{Desat} (seconds·%)	39 ± 182	60 ± 180	0.315

[a] Plus-minus values are means ± SD.
[b] The AUC_{Desat} values were analyzed using an analysis of variance with factors for group and study site $\alpha = 0.05$ significance level.

Examination of the mean area-under-the-curve of oxygen desaturation values and corresponding 95% confidence intervals for each study site suggest that there are no significant differences between study sites.

4.5.8.3 Procedure Graphs for Largest AUC_{Desats}

The following graphs show the temporal relationships of the subject's cardiorespiratory status, depth of sedation, and sedative/analgesic dosing for the subjects from both treatment groups with the largest AUC_{Desat}.

Explanation of Graphs
There are two different procedure graphs for each subject:

- Physiology
- Drug delivery/depth of sedation

The physiology graphs are the same for the SEDASYS System and current standard of care subjects. They present the subject's:

- Oxygen saturation (SpO_2); RED line, scale on the left Y axis
- Respiratory rate (RR); BLUE line, scale on the left Y axis
- End-tidal CO_2 ($EtCO_2$); GREEN line, scale on the left Y axis
- Heart rate (HR); YELLOW line, scale on the far right Y axis
- Systolic pressure (SysBP); BLUE circles, scale on the near right Y axis
- Diastolic pressure (DiasBP); MAROON circles, scale on the near right Y axis

The drug delivery/depth of sedation graphs are similar for the SEDASYS System and current standard of care subjects. In addition to oxygen saturation (RED line), carried over from the physiology graph to provide a temporal reference frame, they present the subject's:

- Level of sedation (MOAA/S); BROWN circles, scale on the right Y axis

For SEDASYS System subjects the graphs contain:

- The propofol maintenance rate (MR); MAGENTA line, scale on the far right Y axis
- Time of a PRN dose; MAGENTA diamond on the X axis
- Time of a fentanyl dose; BRIGHT GREEN diamond on the X axis

For current standard of care subjects the graphs contain:

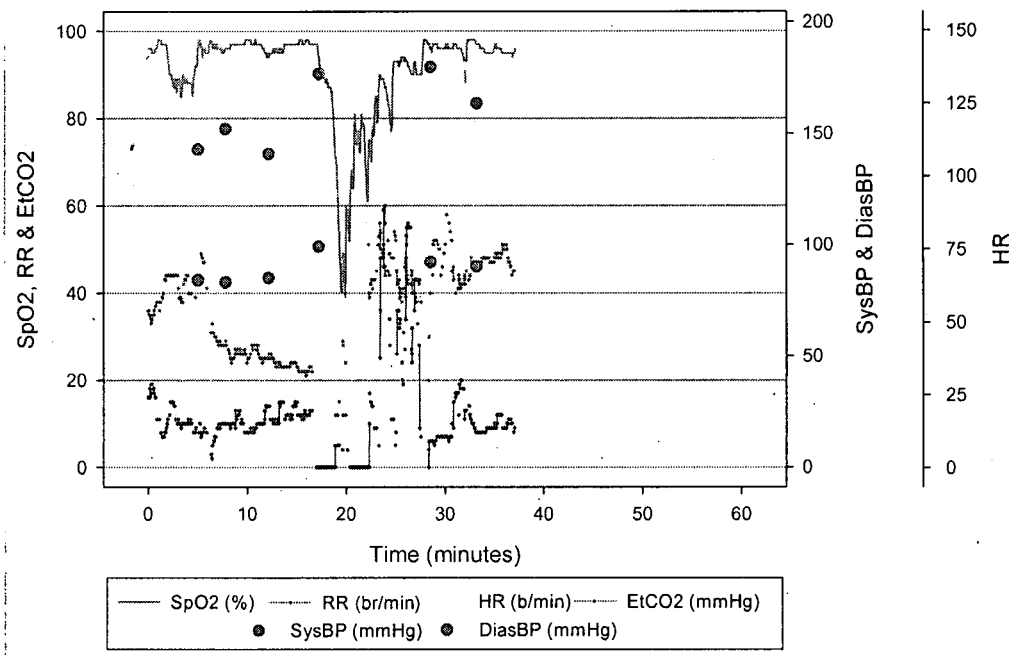
- Time of a midazolam dose; MAGENTA diamond on the x-axis
- Time of a fentanyl (or meperidine) dose; BRIGHT GREEN diamond on the x-axis

On all graphs, Time = 0 corresponds to the time of the administration of the first sedative/analgesic. Additionally, the time the endoscope was inserted (start of procedure)

and the time it was removed (end of procedure) are highlighted on the drug delivery/depth of sedation graph.

Current Standard of Care – [redacted]
[redacted] was a 70 year old, ASA II female with a BMI of 32 kg/m^2 scheduled for a colonoscopy. The subject has a history of hypertension since 2006 and was status post hysterectomy in 1996. Figure 23 presents the subject's cardiorespiratory status during the procedure and Figure 24 presents the sedatives/analgesic dosing and the subject's level of sedation.

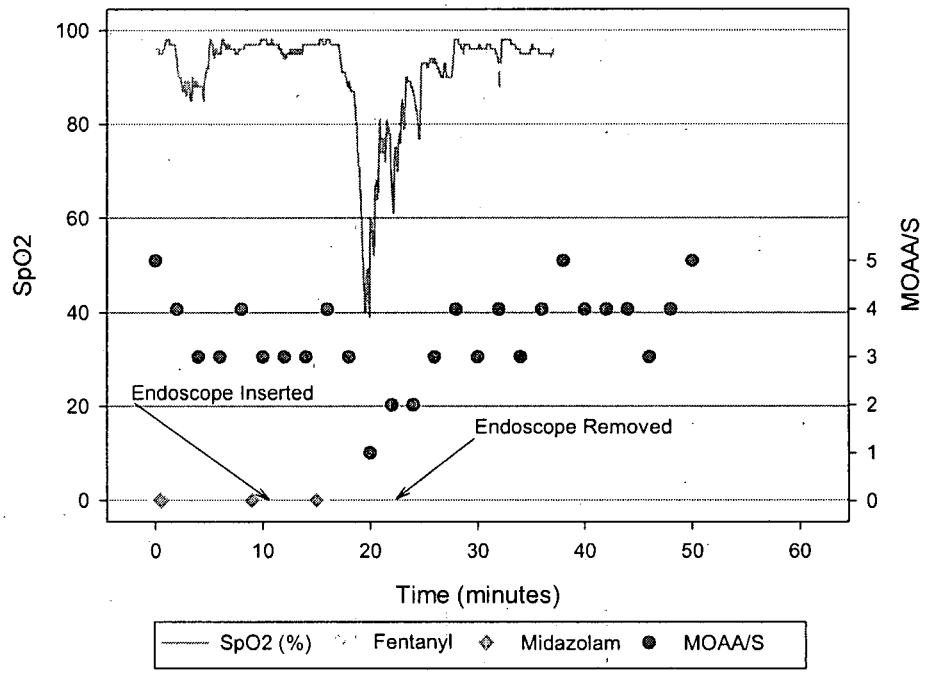
Figure 23
[redacted] – CSC Colonoscopy
Physiology



Sedation started with initial doses of midazolam (2 mg) and fentanyl (100 µg). Two minutes after initiation of sedation the subject experienced an oxygen desaturation event, reaching a minimum SpO_2 of 85% and lasting 133 seconds. In response to this event, the clinical team increased the subject's flow of oxygen from 2 to 4 L/min. During this time, the subject's MOAA/S decreased to 3 (moderate sedation).

Nine minutes after the initial dose of sedative, the subjects MOAA/S rose to 4 (moderate sedation) and the clinical team administered a second dose of midazolam (2 mg). The subjects MOAA/S fell to 3, and the procedure began with the insertion of the endoscope. Within 6 minutes, MOAA/S was back at 4 and the clinical team administered a third dose of midazolam (1 mg) and a second dose of fentanyl (100 mg). Within 4 minutes, the subject's MOAA/S fell to 1 (deep sedation).

Figure 24
[redacted] – CSC Colonoscopy
Drug Delivery/Depth of Sedation



The subject experienced two periods of prolonged apnea (> 2 minutes, each) and a significant oxygen desaturation event; reaching a minimum SpO_2 of 39% and lasting 335 seconds. In response to the event, the clinical team increased the subject's oxygen flow from 4 L/min to 8 L/min; where it remained for the duration of the procedure. The event was recorded by the investigator as an adverse event. The event resolved without sequelae and the subject had no additional adverse events.

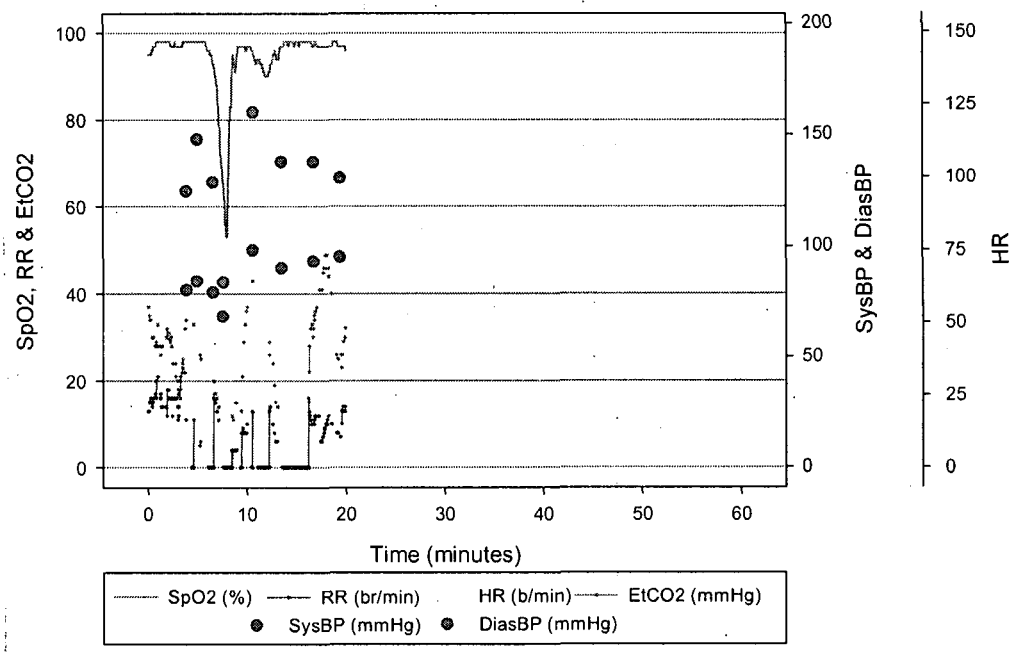
The procedure was completed towards the end of this desaturation event and the endoscope was removed; the procedure lasted 11.8 minutes. Following removal of the scope, the subject had a third oxygen desaturation event, reaching a minimum SpO_2 of 77% and lasting 76 seconds. For the next 15 minutes, the subject remained moderately sedated (MOAA/S 3 and 4) and remained in the procedure room. After 15 minutes, per study protocol, the subject was disconnected from the Procedure Room Unit (ending DAQ data recording) and moved to recovery. In recovery, the patient remained monitored by the Bedside Monitoring Unit and the study nurse continued assessing MOAA/S until the patient recovered from the effects of sedation; 28 minutes later.

All totaled, this subject had 3 oxygen desaturation events. In addition to the significant desaturation event where SpO_2 fell to 39%, the subject had another desaturation event where SpO_2 fell to 77%. The event with SpO_2 falling to 39% occurred when the subject was

receiving 4 L/min supplemental oxygen. The last event, with SpO_2 reaching 77%, occurred when the subject was receiving 8 L/min supplemental oxygen.

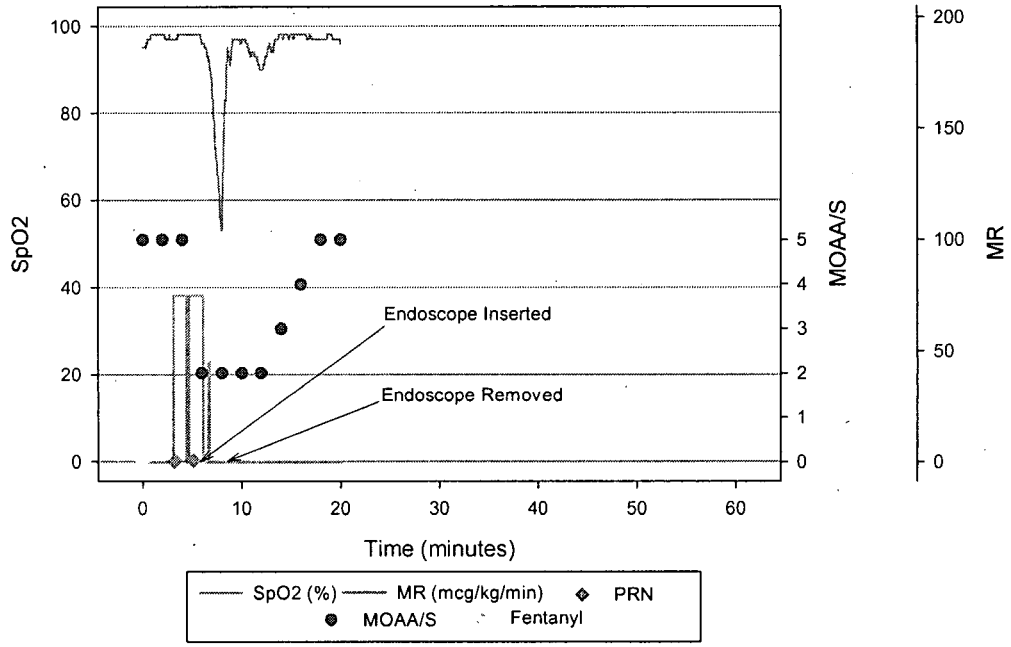
SEDASYS System – [redacted]
[redacted] was a 71 year old, ASA III male with a BMI of 29 kg/m^2 scheduled for an EGD. The subject has a history of asthma, hypertension, and coronary artery disease. Figure 25 presents the subject's cardiorespiratory status during the procedure and Figure 26 presents the sedatives/analgesic dosing and the subject's level of sedation.

Figure 25
[redacted] – SDS EGD
Physiology



One minute prior to initiating sedation, the patient received a single spray of benzocaine as a topical anesthetic. Sedation started with a single dose of fentanyl (50 µg). Three minutes later, the clinical team started propofol infusion with a maintenance rate of 75 µg/kg/min and administered a PRN dose (23.4 mg; 0.25 mg/kg for a 93.5 kg subject). A little over a minute later, the subject experienced a brief period of apnea. The SEDASYS System triggered a yellow alarm and stopped propofol delivery. When the alarm cleared, the system automatically resumed the maintenance rate at 75 µg/kg/min. At this point, the subject's MOAA/S was a 5 (minimal sedation).

Figure 26
[redacted] – SDS EGD
Drug Delivery/Depth of Sedation



A short time later, the clinical team inserted the endoscope, starting the procedure, and administered a second PRN dose. The subject became non-responsive to the ARM queries and his MOAA/S decreased to a 2 (moderate sedation). Then he experienced a 62 second period of apnea, and the SEDASYS System triggered a yellow alarm and stopped propofol delivery. When the alarm cleared, the system automatically resumed propofol delivery at a reduced rate of 45 μg/kg/min.

Almost immediately after this, while still at a MOAA/S of 2, the subject experienced an oxygen desaturation event, reaching a minimum SpO_2 of 53% and lasting 97 seconds. The SEDASYS System triggered a red alarm and stopped the delivery of propofol. This desaturation event was recorded by the investigator as an adverse event. In response to the event, the clinical team used a tongue depressor to restore the subject's respiration. The event resolved without sequelae and the subject had no additional adverse events.

Approximately the same time that the subject's saturation recovered, the procedure was completed and the endoscope removed; the procedure lasted 2.6 minutes. The subject recovered from the effects of sedation in 10 minutes. During the recovery period, the subject experienced a 101 second period of apnea, but did not have a desaturation event (SpO_2 decreased but did not fall below 90%). The last respiratory event seen on the procedure graphs was identified as artifact; likely caused by movement of the oral/nasal cannula. There were ~3 minutes of no apparent respiratory activity, with no accompanying decrease in oxygen saturation.

4.5.8.4 Primary Analysis Conclusions

The area-under-the-curve of oxygen desaturation results in this study were in favor of the SDS group, indicating that administration of propofol via the SEDASYS System reduced the risks associated with over-sedation compared to the current standard of care. For colonoscopy procedures, the results were statistically significantly in favor of the SEDASYS System, using both untransformed and ranked data. For EGD procedures, the results were directionally better. The lack of statistical significance is likely due to the smaller sample size for the EGD analysis.

Sensitivity analyses, examination of center effect and sub-population analyses are provided in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study.*

4.5.9 Secondary Analyses

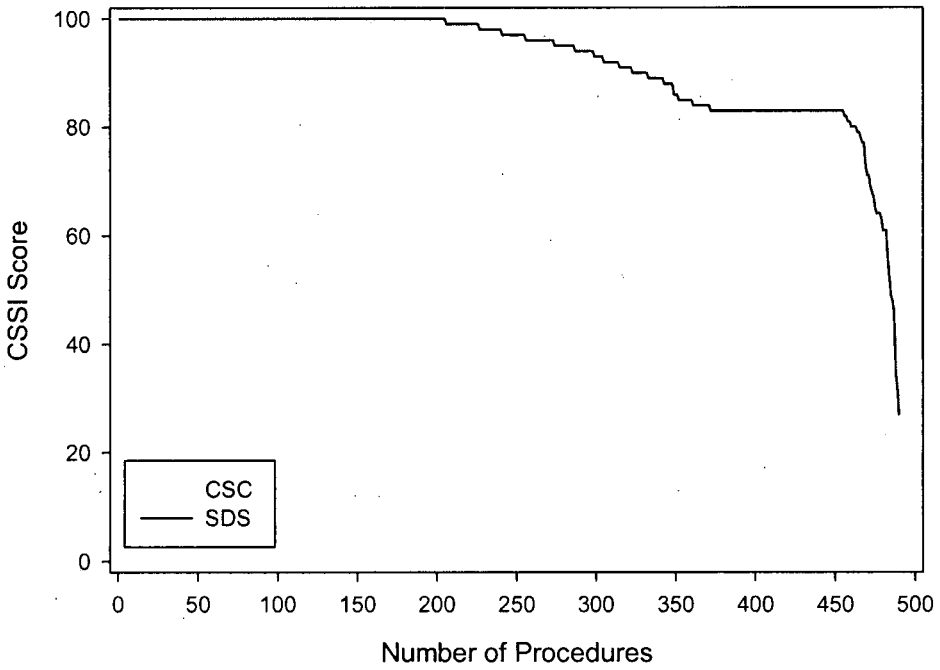
All planned secondary analyses were conducted using a Tukey multiplicity adjusted $\alpha = 0.0253$ significance level.[24] Results of additional descriptive and exploratory analyses are provided in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study.*

4.5.9.1 Clinician Satisfaction with Sedation Instrument

Figure 27 shows the endoscopist's satisfaction (CSSI scores) for all subjects in the study. In the SEDASYS System group, the CSSI score was 100 in 205 (42%) cases, compared to 36 (7%) cases in the current standard of care group. We recognize that CSSI is a subjective measure, and therefore can be influenced by bias. However, the fact that the minimum CSSI for both treatment groups is similar, suggests that the physicians did score the SEDASYS System poorly when they had difficulty sedating patients; just as they did with current standard of care.

[24] Dmitrienko, A., Molenberghs, G., Chuang-Stein, C., and Offen, W. 2005. Analysis of Clinical Trails Using SAS, A Practical Guide, Cary, NC: SAS Institute, Inc.

Figure 27
CSSI Scores for All Subjects
EGD and Colonoscopy



Colonoscopy Procedures

Between groups there was a statistically significant difference with respect to the mean Clinician Satisfaction with Sedation Instrument (CSSI) score. The SDS group had a statistically significantly greater ($p < 0.001$) mean CSSI score when compared to the CSC group (Table 19). The minimum CSSI scores were 27 and 25 in the SDS and CSC groups, respectively.

Table 19
Between Group Comparison of the CSSI
Colonoscopy Procedure[a]

Parameter	SDS	CSC	p-value[b]
CSSI	92 ± 10	76 ± 17	< 0.001

[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

EGD Procedures

Between groups there was a statistically significant difference with respect to the mean CSSI score. The SDS group had a statistically significantly greater ($p < 0.001$) mean CSSI score when compared to the CSC group (Table 20). The minimum CSSI scores were 35 and 43 in the SDS and CSC groups, respectively.

Table 20
Between Group Comparison of the CSSI
EGD Procedures[a]

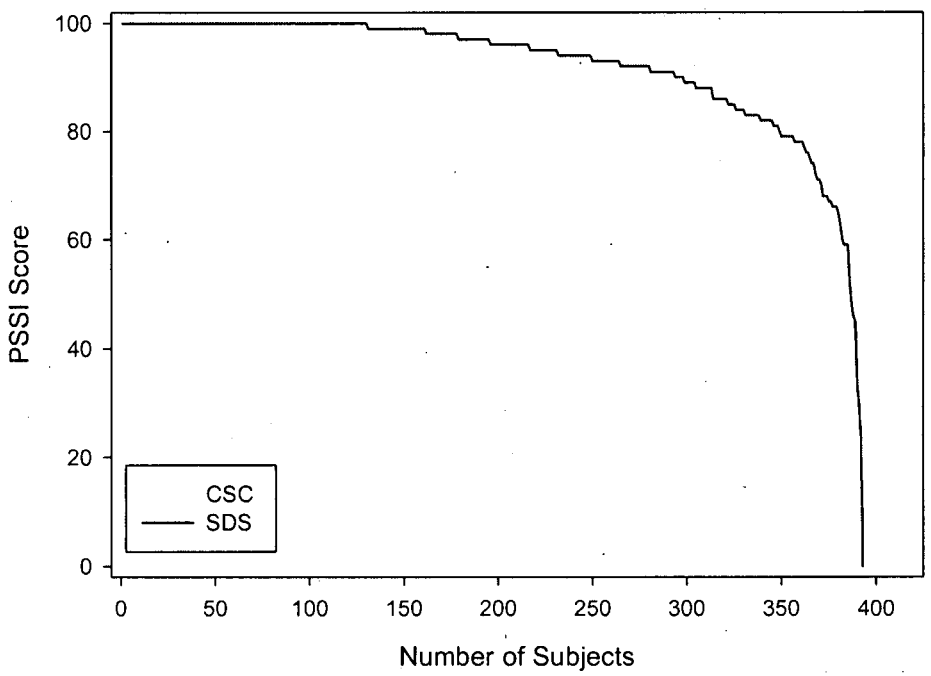
Parameter	SDS	CSC	p-value[b]
CSSI	92 ± 11	77 ± 16	< 0.001

[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

4.5.9.2 Patient Satisfaction with Sedation Instrument

Figure 28 shows the patient's satisfaction (PSSI scores) for all subjects in the study. These PSSI curves are quite similar, indicating that patients were similarly satisfied with the sedation they received, irrespective of the treatment group.

Figure 28
PSSI Scores for All Subjects
EGD and Colonoscopy



Colonoscopy Procedures
The between group comparison of the mean Patient Satisfaction with Sedation Instrument (PSSI) score demonstrated no statistical difference (p = 0.052) between the SDS group when compared to the CSC group (Table 21). While mean scores did not show statistical significance, the SDS score was higher than the CSC score for PSSI. The minimum PSSI scores were 0 and 35 in the SDS and CSC groups, respectively.

Table 21
Between Group Comparison of the PSSI
Colonoscopy Procedure[a]

Parameter	SDS	CSC	p-value[b]
PSSI	93 ± 12	91 ± 12	0.052

[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

EGD Procedures
The between group comparison of the mean PSSI score demonstrated no statistical difference (p = 0.067) between the SDS group when compared to the CSC group (Table 22). While mean scores did not show statistical significance, the SDS score was higher than the CSC score for PSSI. The minimum PSSI scores were 24 and 40 in the SDS and CSC groups, respectively.

Table 22
Between Group Comparison of the PSSI
EGD Procedures[a]

Parameter	SDS	CSC	p-value[b]
PSSI	91 ± 13	88 ± 13	0.067

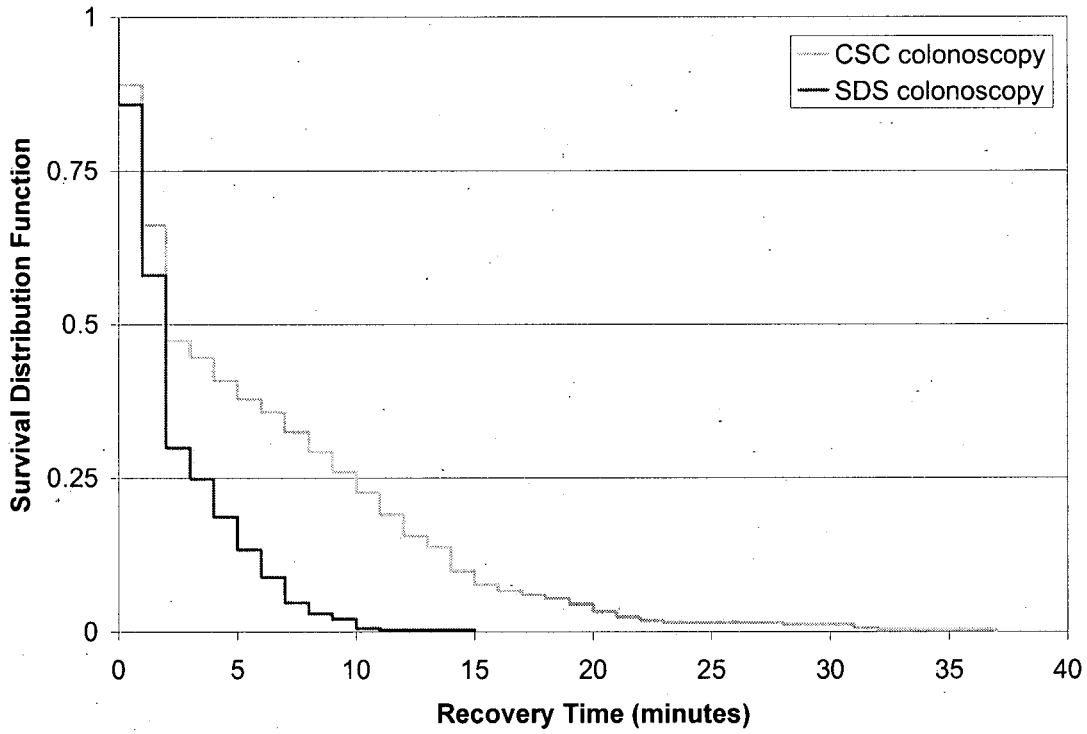
[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

4.5.9.3 Recovery Time

Colonoscopy Procedures
The between group comparison for time to recover from sedation demonstrated that the CSC group (6.3 ± 6.8 minutes) had a greater than two-fold longer time to recover, when compared to the SDS group (2.7 ± 2.4 minutes). The longest recovery time for a CSC subject was 37 minutes compared to only 15 minutes for a SDS subject.

Figure 29 (Kaplan-Meier curve) illustrates the statistically significantly shorter recovery time in the SDS group when compared to the CSC group (Cox Proportional Hazard Regression, $p < 0.001$). The median recovery time for the SDS group was 2.0 minutes (95% Confidence Interval was undefined) and median recovery time for the CSC group was 3.0 minutes (95% Confidence Interval = 2.0 to 4.0 minutes; $p < 0.001$). Ten minutes after conclusion of the procedure ("scope-out"), only 0.6% (95% Confidence Interval = 0.1% to 2.1%) of subjects in the SDS group had not fully recovered compared with 24.0% (95% Confidence Interval = 19.5% to 28.6%) of subjects in the CSC group.

Figure 29
Comparison of Kaplan-Meier Curves for Time to Recovery
Colonoscopy Procedure



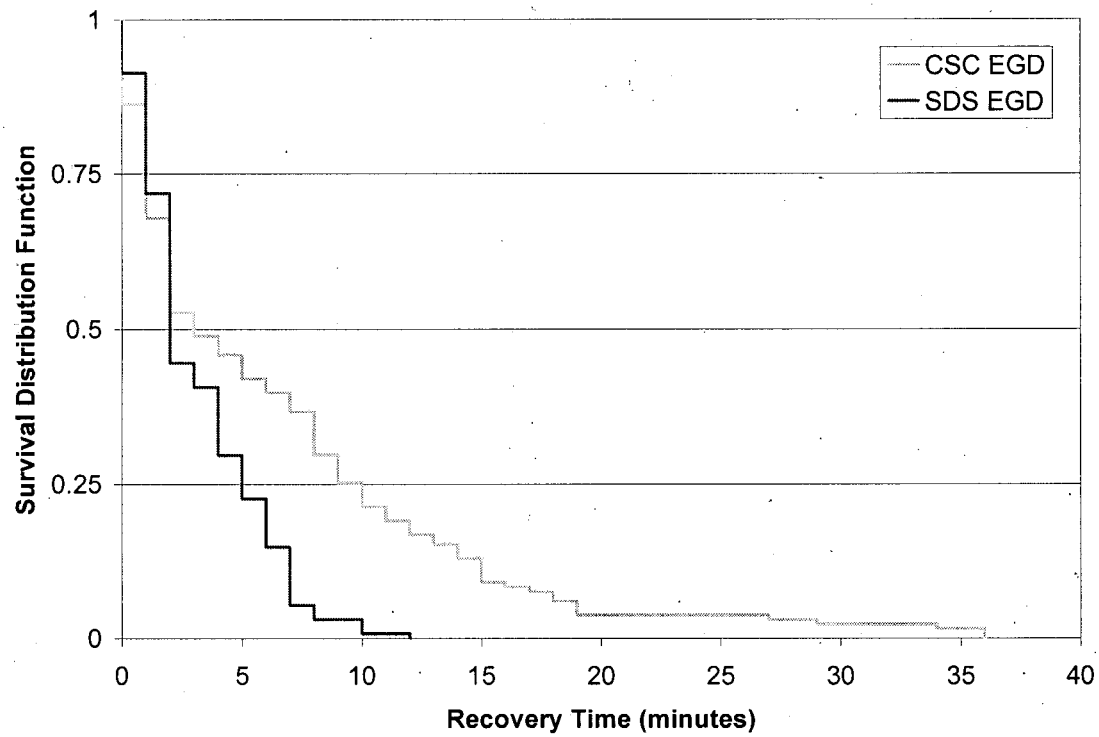
EGD Procedures

The between group comparison for time to recover from sedation demonstrated that the CSC group (7.0 ± 7.4 minutes) had a two-fold longer time to recover, when compared to the SDS group (3.5 ± 2.5 minutes). The longest recovery time for a CSC subject was 36 minutes compared to only 12 minutes for a SDS subject.

Figure 30 (Kaplan-Meier curve) illustrates the statistically significantly shorter recovery time in the SDS group when compared to the CSC group (Cox Proportional Hazard Regression, $p < 0.001$). The median recovery time for the SDS group was 2.0 minutes (95% Confidence Interval = 2.0 to 4.0 minutes) and median recovery time for the CSC group was

5.0 minutes (95% Confidence Interval = 2.0 to 7.0 minutes; $p < 0.001$). Ten minutes after conclusion of the procedure ("scope-out"), only 0.8% (95% Confidence Interval = 0.1% to 3.9%) of subjects in the SDS group had not fully recovered compared with 23.7% (95% Confidence Interval = 16.8% to 31.2%) of subjects in the CSC group.

Figure 30
Comparison of Kaplan-Meier Curves for Time to Recovery
EGD Procedure



4.5.9.4 Sedation Level

Colonoscopy Procedures
Prior to the start of the procedure, all investigators targeted minimal-to-moderate levels of sedation in both the SDS (100%; 358 of 358 subjects) and CSC (100%; 363 of 363 subjects) groups. The mean MOAA/S scores recorded during the colonoscopy procedure were 4.3 ± 0.6 and 4.2 ± 0.6 in the SDS and CSC groups, respectively. The mean MOAA/S scores were consistent with the targeted level of sedation determined by the investigators prior to the procedure.

The between group comparison of the mean duration of deep sedation/general anesthesia demonstrated no statistical difference ($p = 0.573$) between the SDS group when compared to

the CSC group (Table 23). In both groups, the mean duration of deep sedation/general anesthesia was 6 seconds.

In the SDS group, 10 (2.8%) subjects reached deep sedation or general anesthesia at some point during the procedure. In the CSC group, 4 (1.1%) subjects reached deep sedation or general anesthesia at some point during the procedure. The maximum duration a subject was in deep sedation/general anesthesia was 16 minutes and 22 minutes in the SDS and CSC groups, respectively.

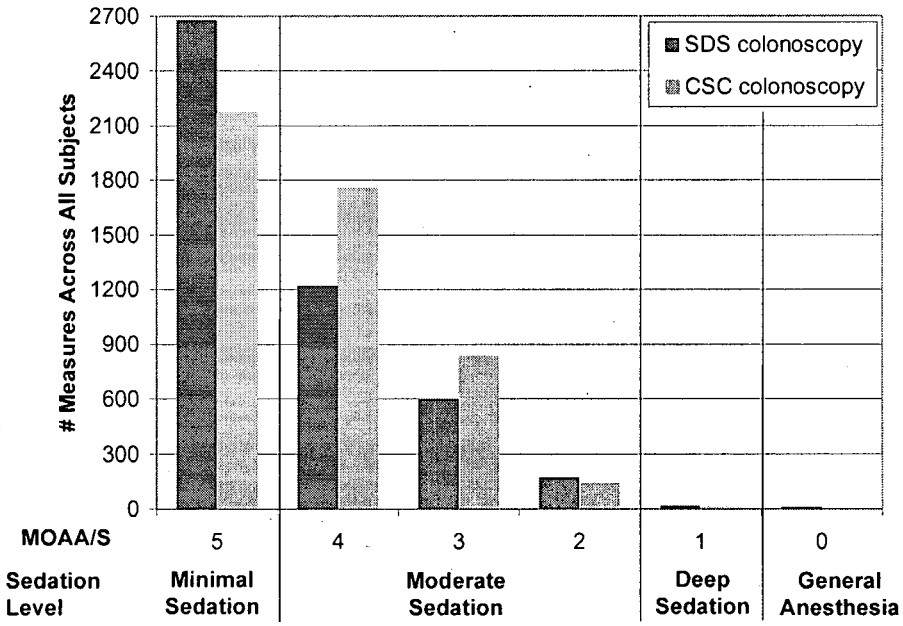
Table 23
Between Group Comparison of the Sedation Level
Colonoscopy Procedure[a]

	SDS	CSC	p-value[b]
Duration of Deep Sedation/General Anesthesia: MOAA/S = 0 or 1 (minutes)	0.1 ± 1.2	0.1 ± 1.2	0.573

[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

Figure 31 presents all 9621 MOAA/S measurements taken during colonoscopy procedures, from the start of the procedure (first sedative/analgesic administered) until recovery. In the SDS group, 57% of all MOAA/S measures were 5 compared to 44% in the CSC group. In the SDS group, 0.6% of all MOAA/S measures were either 1 or 0 compared to 0.4% in the CSC group.

Figure 31
MOAA/S Measures and the ASA Continuum
Colonoscopy Procedure



EGD Procedures

Prior to the start of the procedure, all investigators targeted minimal-to-moderate levels of sedation in both the SDS (100%; 138 of 138 subjects) and CSC (100%; 141 of 141 subjects) groups. The mean MOAA/S scores recorded during the EGD procedure were 4.5 ± 0.5 and 4.4 ± 0.6 in the SDS and CSC group, respectively. The mean MOAA/S scores were consistent with the targeted level of sedation determined by the investigators prior to the procedure.

The two groups were not clinically or statistically different ($p = 0.731$) with respect to the duration of deep sedation/general anesthesia, as measured by the occurrence of all MOAA/S scores of 1 or 0 during a procedure. The mean duration of deep sedation/general anesthesia was zero seconds in the SDS group and 6 seconds in the CSC group.

In the SDS group, 2 (1.4%) subjects reached deep sedation or general anesthesia at some point during the procedure. In the CSC group, 1 (0.7%) subject reached deep sedation or general anesthesia at some point during the procedure. The maximum duration a subject was in deep sedation/general anesthesia was 4 minutes and 10 minutes in the SDS and CSC groups, respectively.

Table 24 depicts the between group comparison for duration of deep sedation/general anesthesia for MOAA/S of 0 or 1.

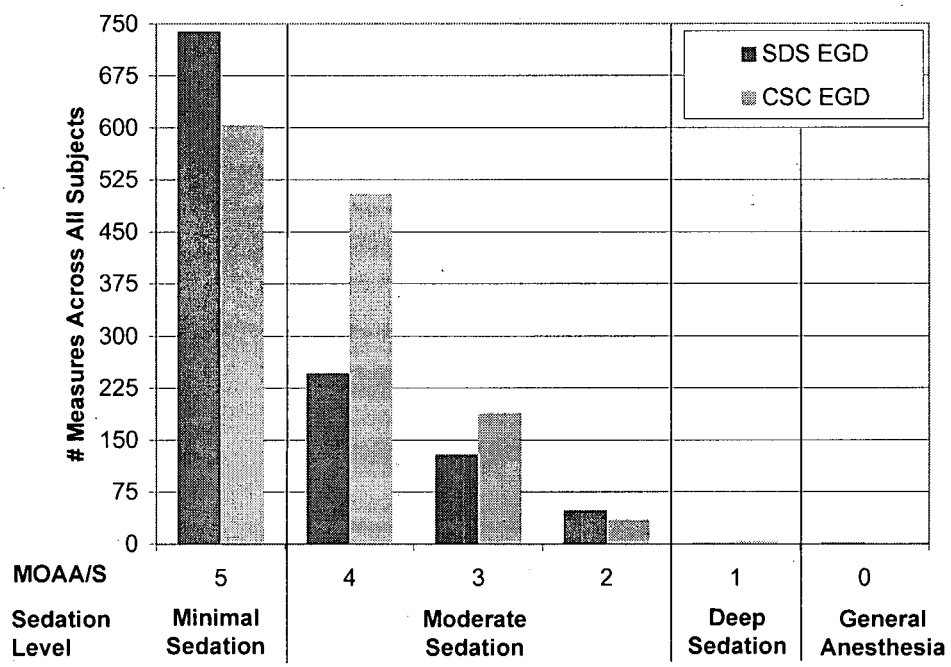
Table 24
Between Group Comparison of the Sedation Level
EGD Procedures[a]

Parameter	SDS	CSC	p-value[b]
Duration of Deep Sedation/General Anesthesia: MOAA/S = 0 or 1 (minutes)	0.0 ± 0.4	0.1 ± 0.9	0.731

[a] Plus-minus values are means ± SD.
[b] Tukey multiplicity adjusted α=0.0253 significance level. The values were analyzed using an analysis of variance with factor for group.

Figure 32 presents all 2501 MOAA/S measurements taken during EGD procedures, from the start of the procedure (first sedative/analgesic administered) until recovery. In the SDS group, 63% of all MOAA/S measures were 5 compared to 45% in the CSC group. In the SDS group, 0.3% of all MOAA/S measures were either 1 or 0 compared 0.4% in the CSC group.

Figure 32
MOAA/S Measures and the ASA Continuum
EGD Procedure



Level of Sedation Conclusions
The level of sedation data demonstrates a clear safety benefit of the SEDASYS System's dosing restrictions. These restrictions are in essence the first line of safety in the SEDASYS System. They minimize the potential for over-sedation; as documented by the less than 1% all sedation level measures in the pivotal clinical study that were deep sedation or general anesthesia.

4.5.9.5 Secondary Analyses Conclusions

Both clinician satisfaction and recovery time for the SDS group were shown to be statistically significantly better when compared with the CSC group, for both the colonoscopy and EGD procedures. In both groups, subjects were minimally-to-moderately sedated with only a few occurrences of deep sedation or general anesthesia.

4.5.10 Subjects Reaching Deep Sedation/General Anesthesia

There were a total of 17 (1.7%) subjects in the study who had at least one MOAA/S measure of 1 or 0, indicating deep sedation or general anesthesia, respectively. Of these, 12 were SDS subjects (2.4% of SDS subjects) and 5 were CSC subjects (1.0% of CSC subjects). Table 25 presents summary data for all 17 subjects.

There were no device or drug-related adverse events in the SDS subjects who reached deep sedation or general anesthesia. There were three drug-related adverse events in the CSC subjects. These events were attributed to "Oxygen Desaturation", and are reflected in the high mean AUC_{Desat} for these 5 subjects. There were a total of 14 oxygen desaturation events (SpO_2 < 90% for > 15 seconds) in the CSC subjects, and none in the SDS subjects.

Table 25
Summary Data for Subjects with MOAA/S = 1 or 0
Colonoscopy and EGD Procedures[a]

Parameter	SDS (n = 12)	CSC (n = 5)
Number of adverse events related to device or drug	0	3
Mean AUC_{Desat} (seconds·%)	0	2190 ± 2884
Total Number of Cardiorespiratory Events	**5**	**21**
Oxygen Desaturation	*0*	*14*
Apnea	*4*	*7*
Bradycardia	*1*	*0*
Hypotension	*0*	*0*
Mean Duration MOAA/S 0 or 1 (minutes)	3.8 ± 2.9	8.8 ± 7.9
Mean Time to Recovery (minutes)	3.4 ± 2.0	24 ± 9.7
Mean PSSI Score	92 ± 13	86 ± 18
Mean CSSI Score	91 ± 8	50 ± 13

[a] Plus-minus values are means ± SD.

Due to the rapid pharmacokinetics of propofol, the subjects in the SDS group had a mean duration of deep sedation/general anesthesia of 3.8 ± 2.9 minutes; while the CSC subjects were in deep sedation/general anesthesia twice as long, with a mean duration of 8.8 ± 7.9 minutes.

The rapid offset of propofol is also highlighted by the mean recovery time. For the SDS subjects, the mean recovery time was 3.4 minutes, similar to the mean recovery time for the SDS mITT population; while the mean recovery time for the CSC subjects was 24 minutes, more than three times longer than the CSC mITT population.

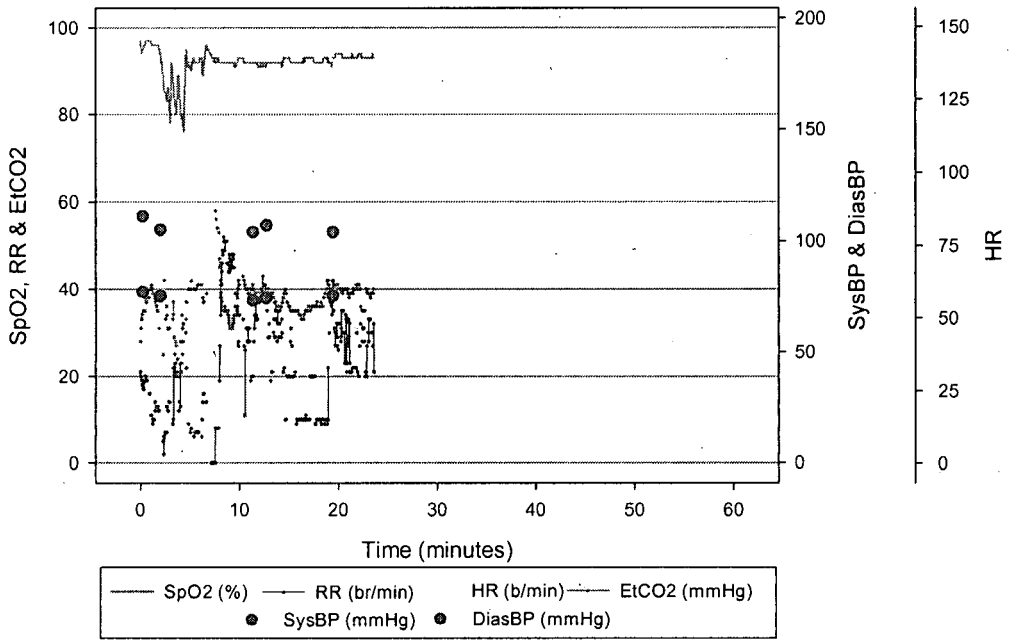
Interestingly, in the CSC group these patients and the physicians were noticeably less satisfied with the sedation compared to the CSC mITT population; while there is no difference in satisfaction in the SDS group.

4.5.10.1 Procedure Graphs for Subjects in General Anesthesia

The following graphs show the temporal relationships of the subject's cardiorespiratory status, depth of sedation, and sedative/analgesic dosing for one subject from each treatment group that reached general anesthesia at some point in their procedure.

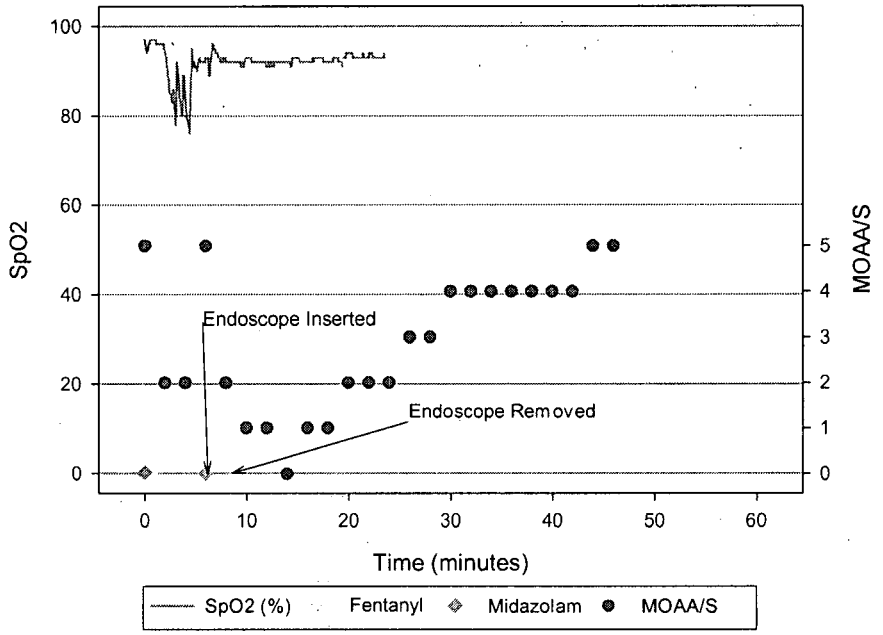
Current Standard of Care – [redacted]
[redacted] was a 60 year old, ASA II female with a BMI of 27 kg/m^2 scheduled for an EGD. The subject was status post cholecystectomy and hysterectomy. Figure 33 presents the subject's cardiorespiratory status during the procedure and Figure 34 presents the sedatives/analgesic dosing and the subject's level of sedation.

Figure 33
[redacted] – CSC EGD
Physiology



One minute prior to initiating sedation, the patient received a single spray of benzocaine as a topical anesthetic. Sedation was started with initial doses of midazolam (3 mg) and fentanyl (100 μg). Approximately 2 minutes later, the subject's MOAA/S was a 2 (moderate sedation) and she experienced an oxygen desaturation event, reaching a minimum SpO_2 of 78% and lasting 52 seconds. This event was recorded by the investigator as an adverse event. In response, the clinical team increased supplemental oxygen from 2 to 4 L/min, where it remained for the rest of the procedure. The event resolved without sequelae.

Figure 34
[redacted] – CSC EGD
Drug Delivery/Depth of Sedation



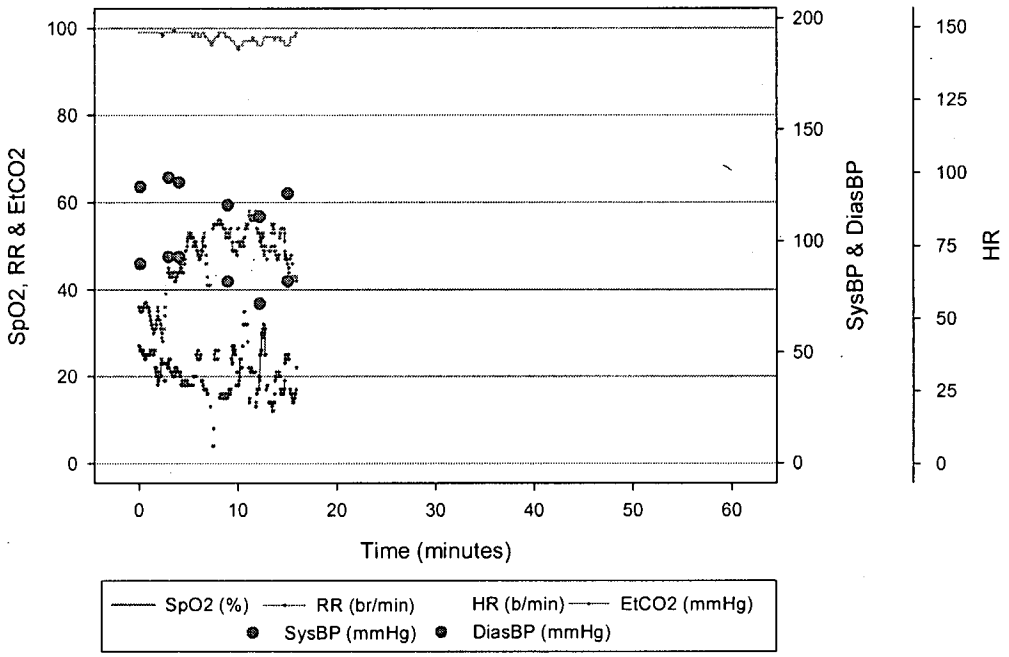
Immediately after this first event, the subject experienced a second oxygen desaturation event, reaching a minimum SpO_2 of 76% and lasting 78 seconds. From the graphs above, these two events could be viewed as one. However, by definition they are two separate events, as the subject's SpO_2 rose above 90% between to two events. Shortly after the subjects saturation recovered, the endoscope was inserted starting the procedure. This resulted in the subject's MOAA/S jumping from a 2 to a 5 (minimal sedation). In response, the clinical team administered a second dose of midazolam (2 mg).

Two minutes later, the procedure was complete and the endoscope removed. At this time, the subject's MOAA/S was again a 2, and the subject experienced a 52 second period of apnea. Two minutes after completion of the procedure, the subject's MOAA/S dropped to 1 (deep sedation). Four minutes later, the subject's MOAA/S dropped to 0 (general anesthesia). In total, the subject spent 10 minutes in either general anesthesia or deep sedation during recovery. In current practice, this is a time when a patient will likely be in a recovery area and be less closely monitored. The patient took 36 minutes to recover from the effects of sedation.

SEDASYS System – [redacted]

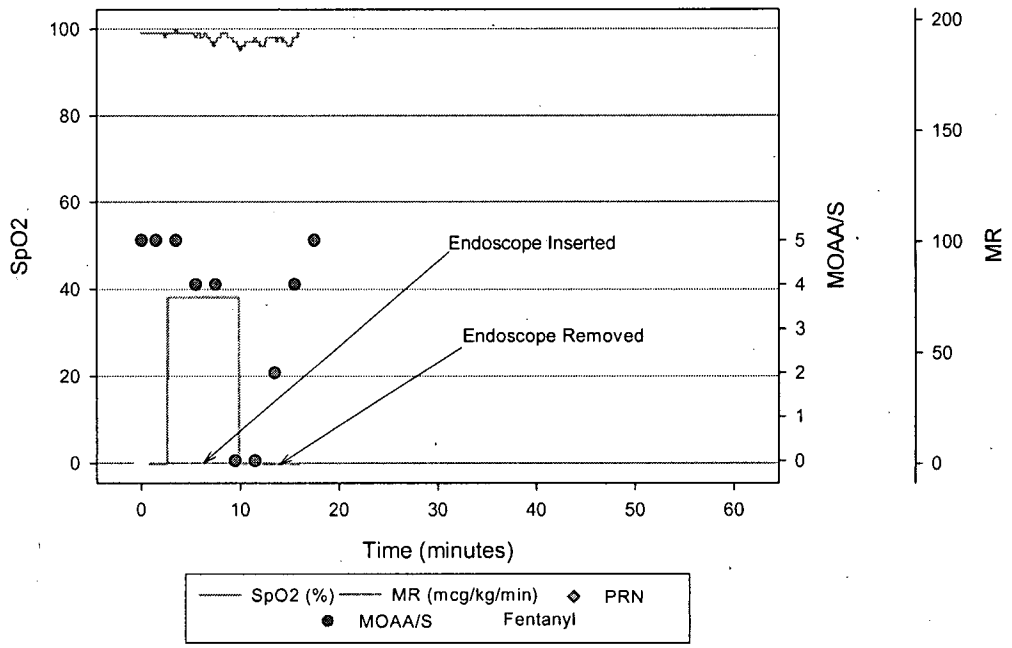
[redacted] was a 34 year old, ASA II male with a BMI of 24 kg/m^2 scheduled for an EGD. The subject was a cigarette smoker with a history of asthma and hypertension. Figure 35 presents the subject's cardiorespiratory status during the procedure and Figure 36 presents the sedatives/analgesic dosing and the subject's level of sedation.

Figure 35
[redacted] – SDS EGD
Physiology



Two minutes prior to initiating sedation, the subject received a single spray of benzocaine as a topical anesthetic. Sedation started with a single dose of fentanyl (100 µg). Three minutes after the fentanyl dose, the clinical team started propofol infusion with a maintenance rate of 75 µg/kg/min. The maintenance rate remained at 75 µg/kg/min for the next 7 minutes, until the clinical team stopped propofol delivery. There were no PRN doses administered to this subject.

Figure 36
[redacted] SDS EGD
Drug Delivery/Depth of Sedation



Approximately 3 minutes after starting propofol, the subject's MOAA/S had decreased to a 4 (moderate sedation) and the endoscope was inserted, starting the procedure. Four minutes later, the subject's MOAA/S decreased to a 0 (general anesthesia) where it remained for 4 minutes. The clinical team stopped the propofol delivery right after the subject reached general anesthesia. A little under 4 minutes after propofol delivery was stopped, the subject's MOAA/S increased to a 2 (moderate sedation). The procedure was completed and the endoscope removed; the procedure lasted 7.8 minutes. Recovery time was not recorded for this subject; however, as seen in the procedure graphs the subject's MOAA/S returned to a 5 less than 4 minutes after the procedure was completed.

The subject had no cardiorespiratory events. His oxygen saturation was 95% or greater throughout the procedure.

4.5.11 Tertiary Analyses

A series of tertiary analyses were conducted to further explore the effects of SEDASYS System relative to the current standard of care. A complete summary of results may be found in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study.*

4.5.11.1 Mean Propofol Maintenance Rate

FDA-approved propofol labeling recommends that most patients require an infusion of 25 to 75 μg/kg/min to be adequately sedated.

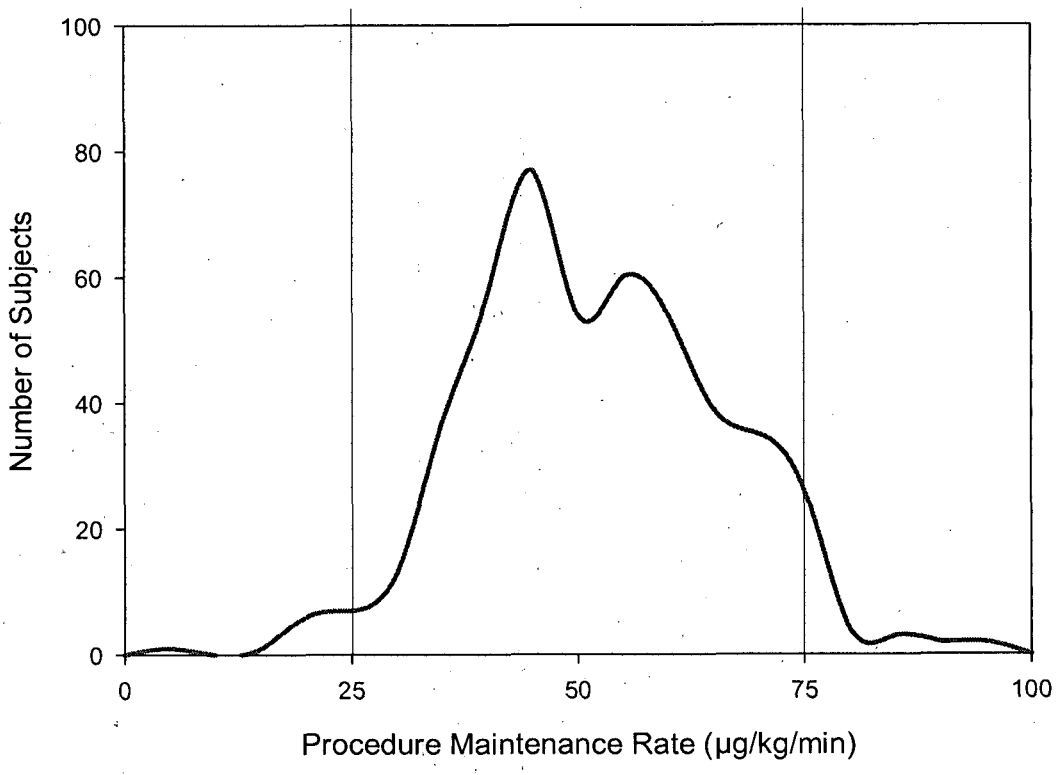
In the SDS group, subjects who underwent a colonoscopy received a mean propofol maintenance rate of 48 ± 13 μg/kg/min and subjects who underwent an EGD received a mean propofol maintenance rate of 54 ± 15 μg/kg/min (Table 26).

Table 26
Propofol Maintenance Rate During Procedure

Parameter	Colonoscopy	EGD
Propofol Maintenance Rate (μg/kg/min)	48 ± 13	54 ± 15

Figure 37 provides the distribution of mean propofol maintenance rates administered during the study. Most subjects (95%) had a maintenance rate within the dosing guidelines in propofol labeling: 25 to 75 μg/kg/min. The remaining subjects (5%) fall within the category of 'individualized and titrated to clinical response' as called out in propofol labeling.

Figure 37
Distribution of Mean Propofol Maintenance Rate



4.5.11.2 Clinical Staff Operating the SEDASYS System

The SEDASYS System was designed to be simple and intuitive to use, enabling it to be used without requiring a change to facility procedures regarding clinical staff involved with routine endoscopy procedures. During the pivotal study, data regarding clinical staff involved in the conduct of each procedure was recorded. Table 27 present data on the clinical staff required for completion of procedures during the study.

Table 27
Clinical Staff Conducting Procedures

Procedure with:	Colonoscopy		EGD	
	SDS	CSC	SDS	CSC
Endoscopist and nurse only	244 (70%)	252 (72%)	90 (68%)	95 (70%)
+1 tech/nurse	105 (30%)	98 (28%)	43 (32%)	41 (30%)

For both CSC and SDS groups, ~70% of procedure were completed with the endoscopist/nurse team. Approximately 30% of the time a third person (typically a technician or nurse) was involved in the conduct of the procedure (e.g., assisting with biopsies). The data demonstrate that the SEDASYS System can be used without requiring changes to facility standard practices.

4.5.12 Adverse Events

A listing of adverse events (by CRF Verbatim Text) can be found in Exhibit A, *Statistical Analysis of the Pivotal Clinical Study.*

4.5.12.1 Summary of Adverse Events – Colonoscopy Procedure

Of a total of 721 subjects who were randomized in this study and underwent a colonoscopy, 50 subjects reported one or more adverse events. Of the 358 subjects in the SDS group, 21 (5.9%) subjects had at least one adverse event reported, while 29 of 363 (8.0%) subjects in the CSC group had at least one adverse event reported (Table 28).

Table 28
Summary of Subjects with Adverse Events and Serious Adverse Events
Colonoscopy Procedure

Number and percent of subjects with:	SDS	CSC
One or more adverse events	21 (5.9%)	29 (8.0%)
Serious adverse events	0	1 (0.3%)

4.5.11.2 Clinical Staff Operating the SEDASYS System

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Number and percent of subjects with:	**SDS**	**CSC**
One or more adverse events	21 (5.9%)	29 (8.0%)
Serious adverse events	0	1 (0.3%)

The most frequently reported adverse event in the CSC group was oxygen desaturation (4.7%; 17 of 363 subjects). The most frequently reported adverse events in the SDS group were nausea, (1.4%; 5 of 358 subjects) and abdominal pain (1.1%; 4 of 358 subjects).

No subject experienced a serious adverse event in the SDS group. One subject in the CSC group experienced a serious adverse event.

In general, the types of adverse events and the percent of subjects reporting adverse events in the SDS group were not different from the CSC group. Of note, investigators reported most adverse events as mild (21) in the SDS group and moderate (23) in the CSC group (Table 29).

Table 29
Summary of Adverse Events by Severity
Colonoscopy Procedure

Severity	SDS	CSC
All adverse events	26	32
Mild adverse events	*21*	*8*
Moderate adverse events	*4*	*23*
Severe adverse events	*1*	*1*

In general, the causality of adverse events in relation to study procedure was similar between both groups (Table 30).

Table 30
Summary of Adverse Events by Causality to Procedure
Colonoscopy Procedure

Relationship	SDS	CSC
All adverse events	26	32
Not Related	*15*	*24*
Possibly	*5*	*3*
Probably	*5*	*4*
Definitely	*0*	*1*
Unknown	*1*	*0*

There were a greater number of adverse events in the CSC group related to study drug when compared to SDS group (Table 31).

Table 31
Summary of Adverse Events by Causality to Drug
Colonoscopy Procedure

Relationship	SDS	CSC
All adverse events	26	32
Not Related	*17*	*13*
Possibly	*5*	*2*
Probably	*1*	*4*
Definitely	*2*	*13*
Unknown	*1*	*0*

There were no device-related adverse events in either study group.

4.5.12.2 Summary of Adverse Events – EGD Procedure

Of a total of 279 subjects who were randomized in this study and underwent an EGD, 23 subjects reported one or more adverse events. Of the 138 subjects in the SDS group, 8 (5.8%) subjects had at least one adverse event reported, while 15 of 141 (10.6%) subjects in the CSC group had at least one adverse event reported (Table 32).

Table 32
Summary of Subjects With Adverse Events and Serious Adverse Events
EGD Procedure

Number and percent of subjects with:	SDS	CSC
One or more adverse events	8 (5.8%)	15 (10.6%)
Serious adverse events	0	0

The most frequently reported adverse events in the CSC group were oxygen desaturation (7.1%; 10 of 141 subjects), pharyngolaryngeal pain (2.1%; 3 of 141 subjects), and nausea (1.4%; 2 of 141 subjects). There were no reported adverse events in the SDS group with a frequency $\geq$ 1.0%.

In general, the types of adverse events and the percent of subjects reporting adverse events in the SDS group were not different from the CSC group. Of note, investigators reported most of the adverse events as mild (7) in the SDS group and moderate (13) in the CSC group (Table 33).

Table 33
Summary of Adverse Events by Severity
EGD Procedure

Severity and Causality	SDS	CSC
All adverse events	8	16
Mild adverse events	*7*	*3*
Moderate adverse events	*1*	*13*
Severe adverse events	*0*	*0*

In general, the causality of adverse events in relation to study procedure was similar between both groups (Table 34).

Table 34
Summary of Adverse Events by Causality for Procedure
EGD Procedure

Relationship	SDS	CSC
All adverse events	8	16
Not Related	*4*	*9*
Possibly	*4*	*5*
Probably	*0*	*1*
Definitely	*0*	*1*
Unknown	*0*	*0*

There were a greater number of adverse events in the CSC group related to study drug when compared to SDS group (Table 35).

Table 35
Summary of Adverse Events by Causality for Drug
EGD Procedure

Relationship	SDS	CSC
All adverse events	8	16
Not Related	*6*	*6*
Possibly	*1*	*0*
Probably	*0*	*3*
Definitely	*1*	*7*
Unknown	*0*	*0*

There were no device-related adverse events in either study group.

4.5.12.3 Over-Sedation Related Rescue Interventions

One subject in the CSC group undergoing a colonoscopy procedure required bag-mask ventilation due to an oxygen desaturation adverse event, which was rated as moderate in severity by the investigator.

No other over-sedation related rescue interventions occurred during this study in either group or procedure type.

4.5.12.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths and Other Significant Adverse Events
No deaths or other significant adverse events occurred in this study. No subjects were withdrawn from the study due to an adverse event. No unanticipated adverse device effects occurred in this study.

Other Serious Adverse Events
One serious adverse event occurred in the CSC group in a [redacted] undergoing a colonoscopy. No serious adverse event occurred in the SDS group.

Narratives of Serious Adverse Event
[redacted] is a 24-year old male with Crohn's disease. The subject was status post ileal resection in 1995 (at age 13) and lysis of adhesions in February 2006.

On 23 August 2007, this subject underwent a CSC colonoscopy. The subject was found to have a near-obstructing lesion at his anastomosis. Air became trapped above this and he developed an incomplete small bowel obstruction due to the presence of this lesion. During the procedure, the subject vomited; no intervention was done. The subject experienced abdominal pain, nausea, vomiting and abdominal distention at home after the procedure and went to the hospital, where he was admitted to the intensive care unit on 24 August 2007.

The subject was hospitalized for two days and during this time underwent a computerized tomography scan showing no evidence of perforation, but markedly distended small bowel. The subject was treated with intravenous corticosteroids and nasogastric tube suction. Output from the nasogastric tube suction rapidly declined over 24 hours. The subject's white count fell from 18.3 to 8 and his abdominal x-ray showed decreased small bowel distention. The nasogastric tube was clamped on 25 August 2007. The subject tolerated a clear liquid diet and the nasogastric tube was removed the following morning. On 26 August 2007, the subject was feeling well and moved his bowels. The subject had no more nausea, vomiting, or abdominal pain.

On 26 August 2007, at the time of discharge, the subject's laboratory data shows: white count 8, hematocrit 41, platelet count 282, 67 polyps, 18 lymphocytes, sodium 139, potassium 3.5, chloride 104, bicarbonate 27, BUN 11, creatinine 0.7, glucose 90, AST 14, ALT 12, alkaline phosphatase 46, total bilirubin 0.4, albumin 3.3, ESR 4, CRP less than 5.

At the time of discharge, the subject's medication included: Medrol Dosepak, azathioprine 500 mg daily, potassium 1 gbid, and Imodium prn for diarrhea.

The subject responded well to conservative therapy, was discharged within 48 hours, and instructed to follow-up with his physician.

4.5.13 System Malfunctions

There were 23 system malfunctions during the pivotal study.

- 1 failure of the high-pressure relief valve in the Procedure Room Unit oxygen manifold. The failure occurred prior to the first procedure of the day, while setting up the SEDASYS System. The failure was caused by user error: the pressure regulator, on the oxygen tank, was inadvertently opened to maximum pressure exceeding the system's rated input specification.

  This failure did not lead to an unsafe condition because, in response to a failure of any part of the oxygen delivery module, the SEDASYS System stops, or prevents, propofol infusion. To prevent further occurrences of this failure during the study, each site was trained on the proper handling of the pressure regulators on the oxygen tanks.

- 2 failures of the pulse oximeter module in the SEDASYS System. The failures occurred at the start of day, prior to the conduct of any procedure. These failures were caused by 'invalid' values coming from the OEM pulse oximeter board during the Bedside Monitoring Unit's 'power-on self test'.

  These failures did not lead to an unsafe condition because the Bedside Monitoring Units would not allow entry into a new case. Additionally, if an 'invalid' value is detected after power-on, the SEDASYS System stops, or prevents, propofol infusion. To enable continuation of the study at this site, the Bedside Monitoring Units were replaced.

- 1 failure of the Procedure Room Unit display monitor module. The failure was caused by a damaged power control chip in the Procedure Room Unit display power circuit. The failure occurred prior to initiation of sedation.

  This failure did not lead to an unsafe condition because, with the Procedure Room Unit display inactive, the user could not initiate sedation. To enable continuation of the study at this site, the Procedure Room Unit was replaced.

- 3 failures of the Bedside Monitoring Unit wireless printer module. The failures occurred prior to the conduct of a procedure. These failures were caused by a communication conflict between the wireless printer module in the Bedside Monitoring Unit and the facility's wireless network.

  These failures did not lead to an unsafe condition because the Bedside Monitoring Unit could not be used. To prevent further occurrences of this failure during the study, one site changed the location where they conducted the procedures, and the printing option on the Bedside Monitoring Units at the second site was disabled.

- 1 failure of the Procedure Room Unit. The failure occurred when connecting the Bedside Monitoring Unit to the Procedure Room Unit. The failure was caused by the Bedside Monitoring Unit collecting a large amount of pre-procedure data, which overwhelmed the buffer allocated for storing this data on the Procedure Room Unit upon connection.

  This failure did not lead to an unsafe condition because the Procedure Room Unit was shut down and propofol infusion could not begin.

- 6 failures in the Bedside Monitoring Unit power management subsystem. Five of these failures occurred prior to the start of a procedure; the sixth occurred after completion of a procedure. These failures were caused by a surge in the external line current resulting in the blowing of a fuse. The Bedside Monitoring Unit's batteries would continue to drain and would not charge.

  These failures did not lead to an unsafe condition because the Bedside Monitoring Unit could not be used. To enable continuation of the study at these sites, the Bedside Monitoring Units were replaced.

- 9 failures of the oral/nasal cannula. These failures occurred prior to initiating sedation. These failures were caused by misalignment of a gasket when the oral/nasal cannula is connected to the Bedside Monitoring Unit. Not all nine cannulas were available for analysis; the ones that were exhibited the misaligned gasket.

  These failures did not lead to an unsafe condition because propofol delivery is not permitted during an apnea alarm.

None of these system failures resulted in an adverse event. For more detail on these malfunctions, see Exhibit A, *Statistical Analysis of the Pivotal Clinical Study.*

4.5.14 Pivotal Study Discussion

4.5.14.1 Safety Assessment

In the pivotal study, patient safety was assessed by evaluating the following parameters:

- AUC_{Desat}
- Level of sedation
- Adverse events

The area-under-the-curve of oxygen desaturation results in this study were in favor of the SDS group, indicating that administration of propofol via the SEDASYS System reduced the risks associated with over-sedation compared to the current standard of care. For colonoscopy procedures, the results were statistically significantly in favor of the SEDASYS System. For EGD procedures, the results were directionally better, but not statistically, likely due to a smaller sample size.

The design of the SEDASYS System, coupled with the pharmacokinetic profile of propofol, is responsible for the differences observed. For example, with declining oxygen saturation, a

sign of over-sedation, the SEDASYS System reduces the rate of propofol delivery, increases supplemental oxygen, and instructs the patient to "*take a deep breath.*" In contrast, the current standard of care relies on the physician/nurse team to recognize the declining oxygen saturation and to take appropriate action, such as increasing supplemental oxygen and instructing the patient to breathe deeply. Further, the slower pharmacokinetic properties of midazolam will lengthen the duration of over-sedation.

The prevalence of adverse events in the study was low in both the SDS and CSC groups. Most of the events in the SDS group were classified as 'mild' and the majority of events in the CSC group were classified as 'moderate.' There were no rescue interventions or serious adverse events in the SDS group while in the CSC group there was one rescue intervention and one serious adverse event (neither device nor drug related).

The occurrence of deep sedation/general anesthesia (MOAA/S = 1 or 0) in both the SDS and CSC groups was very low with the vast majority (> 99%) of the MOAA/S scores falling in the minimal-to-moderate range of the ASA Sedation Continuum. These findings are unremarkable with respect to the CSC group as the literature is replete with references equating the use of benzodiazepines and opioids with moderate sedation. What is notable is that consistent levels of minimal-to-moderate sedation were achieved with propofol, delivered with the SEDASYS System, since the literature contains references equating propofol sedation with deep sedation and general anesthesia. The results from this study demonstrate conclusively that SEDASYS System enables physician/nurse teams to administer minimal-to-moderate sedation with propofol.

In sum, the data gathered in this study demonstrate that physician/nurse teams can safely administer propofol sedation with the SEDASYS System to patients undergoing colonoscopy and EGD procedures.

4.5.14.2 Effectiveness Assessment

In this pivotal study, device effectiveness was assessed by evaluating the following parameters:

- CSSI
- PSSI
- Recovery time

The satisfaction of the clinician administering sedation was considered an important variable in assessing the effectiveness of the SEDASYS System. The impact of the SEDASYS System on conduct of procedures and quality of sedation was captured with the CSSI questionnaire. There was a statistically significant difference favoring the SDS group with respect to the mean CSSI score.

Patient satisfaction did not achieve statistical significance between groups. Patients in both groups were very satisfied with the sedation they received.

Subjects in the SDS group recovered from sedation significantly faster than those in the CSC group; specifically, two times faster. More important than the absolute difference in time was the predictability of the recovery. To illustrate, approximately 99% of patients in the SDS group recovered within 10 minutes compared to approximately 75% of subjects in the CSC group. A few CSC subjects took longer than 35 minutes to recover.

In sum, the data gathered in this study demonstrate that physician/nurse teams can effectively administer propofol sedation with the SEDASYS System to patients undergoing colonoscopy and EGD procedures.

4.5.14.3 Support for EGD Indication

Demonstrating statistical superiority of the SEDASYS System over current standard of care is not a regulatory requirement to gain approval for EGD indication. Rather, per the Code of Federal Regulations, 21 CFR 860.7, the regulatory burden is to provide reasonable assurance of safety and effectiveness with the results being clinically significant.

Justification for the approval of EGD follows:

EGD Data In Aggregate Are Clinically Significant
The EGD data in aggregate are clinically significant when compared to subjects in the CSC group. Subjects in the SDS group:

- Had a lower incidence of oxygen desaturation
- Had a lower mean area-under-the-curve of oxygen desaturation
- Were predominantly minimally-to-moderately sedated
- Had fewer and less severe adverse events
- Recovered from the effects of sedation faster
- Recovered their psychomotor skills faster
- Were very satisfied with the sedation they received
- Had a more satisfied physician

Additionally, no SEDASYS System subject experienced a serious adverse event or a rescue intervention.

To put the above in context, there are ~5,000,000 EGD procedures performed annually in the US with current standard of care sedation. The above results, when compared to current standard of care, are clinically meaningful. If current standard of care sedation is considered safe and effective, then it can certainly be expected that sedation with the SEDASYS System must also be safe and effective.

Colonoscopy and EGD Are Similar Procedures
Routine EGD and colonoscopy procedures, while involving different parts of the anatomy, are fundamentally quite similar. Both utilize identical monitoring and endoscopic equipment; require similar skills by the endoscopist and supportive nursing staff; involve administration of similar sedative and analgesics; and take place in identical facilities. While colonoscopy procedures tend to have more challenging sedation requirements, there is no medical reason to expect the SEDASYS System to be less safe or effective in one procedure versus the other. If the SEDASYS System is shown to be safe and effective for colonoscopy, it must also be safe and effective for EGD procedures.

Colonoscopy and EGD LS Means Are Similar
The modeled means and confidence intervals confirm similarities between colonoscopy and EGD procedures. Examination of the least square means and corresponding 95% confidence intervals generated from the analysis of variance model for area-under-the-curve of oxygen desaturation (treatment and site included in the models), suggests the true population mean is similar for SEDASYS System subjects, regardless of the procedure that was performed (Table 36). The 95% confidence interval for EGD is subsumed by the interval for colonoscopy; and the least-squares means of colonoscopy and EGD fall within the 95% confidence intervals for both procedures.

Table 36
Least Squares Means and 95% CI for AUC_{Desat} (seconds·%)
EGD and Colonoscopy Procedures

Treatment	Procedure	LS Mean	95% CI
SDS	Colonoscopy	29	(0, 74)
	EGD	36	(6, 67)

Procedure Effect Analysis Shows No Difference Between Colonoscopy and EGD
To examine the consistency of results across colonoscopy and EGD procedures, analyses of the pooled colonoscopy and EGD subject data were conducted. All primary and secondary analysis ANOVAs were rerun on the entire database, using ANOVA with factors for treatment (SEDASYS System/current standard of care), procedure (EGD/colonoscopy), study site, and treatment-by-procedure interaction. Including factors for procedure and treatment-by-procedure interaction facilitates examination of the potential differences between procedures as well as differences in the treatment effect moderated by the procedure type. For the recovery time endpoint, a Cox Proportional Hazard model was conducted with factors for treatment with procedure as a covariate.

The procedure effects for each pooled analysis are presented in Table 37.

Table 37
Procedure Effect p-values
Colonoscopy and EGD Pooled Data

Analysis	Procedure Effect p-value
AUC_{Desat}	0.3501
CSSI	0.9764
PSSI	0.1638
Duration of Deep Sedation	0.4931
Recovery Time	0.0605

For all analyses, the effects for procedure and treatment-by-procedure interaction were not statistically significant. These results indicate that the observed treatment effect is not dependent upon the procedure performed, indicating that the safety and effectiveness of the SEDASYS System is not different between colonoscopy and EGD.

The above data taken in totality provide reasonable assurance of the safety and effectiveness of the SEDASYS System for EGD procedures. Therefore, Ethicon Endo-Surgery is seeking approval for EGD in addition to colonoscopy.

4.5.15 Pivotal Study Conclusion

This large, multi-center study provides substantial scientifically valid evidence that demonstrates physician/nurse teams can safely and effectively administer propofol for minimal-to-moderate sedation to subjects undergoing colonoscopy and EGD procedures. The SEDASYS System was tested in a well controlled investigation by physician/nurse teams, under expected conditions of use, with both clinically and statistically significant results. The safety findings coupled with benefits in patient satisfaction, clinician satisfaction, and recovery time give the SEDASYS System a very favorable benefit risk profile.

5.0 POST-APPROVAL RISK MINIMIZATION PLAN

In anticipation of FDA approval, Ethicon Endo-Surgery will implement a plan to minimize risk and maximize patient safety. This plan is comprehensive and includes a controlled, deliberate launch of the SEDASYS System, clear requirements that must be met at the facility level, and an extensive device training program. Device performance will be closely monitored and a post-approval study will be conducted to provide additional assurance of patient safety under real-world use conditions.

5.1 Controlled Launch

The results of the clinical program provide substantial evidence establishing the safety and effectiveness of the SEDASYS System for its intended use. Consistent with the methodical development of the SEDASYS System, Ethicon Endo-Surgery will conduct a progressive, phased-launch plan. This plan will ensure core processes meet customer needs.

Initially, the SEDASYS System will be placed at no more than 20 facilities. These facilities will be large, established endoscopy centers that typically conduct in excess of 5000 procedures annually. Only after review of the feedback from these sites will the device be made available to additional facilities.

In addition to collecting information validating our core processes, FDA reporting obligations such as adverse events, product complaints and device malfunctions will be collected and reviewed monthly by Ethicon Endo-Surgery Corrective and Preventative Action Council, which includes the Medical Director, an anesthesiologist.

5.2 Facility and User Requirements

The SEDASYS System will only be placed in accredited/licensed facilities (e.g., those certified by The Joint Commission [TJC], formerly known as JCAHO). Accrediting bodies, such as TJC, required individuals to:[25]

- Have appropriate credentials to manage patients at whatever level of sedation is achieved, either intentionally or unintentionally.
- Have a minimum competency-based education, training and experience in the following:
  - Evaluating patients before performing sedation,
  - Rescuing patients who slip into deeper-than-intended level of sedation or analgesia,
  - Managing a compromised airway, and
  - Providing adequate oxygenation and ventilation.

[25] The Joint Commission. 2009. Standards For Ambulatory Surgery Centers.

In addition, Ethicon Endo-Surgery will require prospective users to be trained in minimal-to-moderate sedation, including airway management, before being allowed to use the device. This training must include techniques such as:

- Chin lift
- Jaw thrust
- Bag-mask ventilation
- Insertion of oral or nasal airway

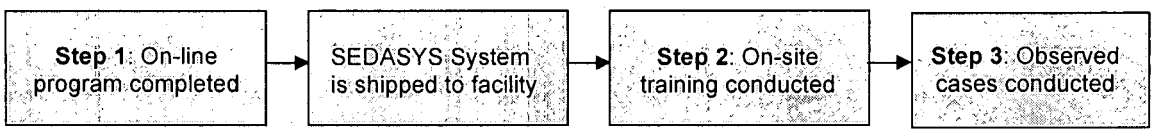
Many hospitals have programs, designed by anesthesiologists, to train non-anesthesiologists in minimal-to-moderate sedation including these airway management skills. For facilities that do not have their own program, there are existing educational programs in minimal-to-moderate sedation, being provided by anesthesiologists. As part of the controlled launch, Ethicon Endo-Surgery will refer facilities to these existing educational programs to help them obtain the required training.

Individual facility protocols will be followed related to necessary privileging and credentialing for use of the SEDASYS System. Facilities will need to sign documentation acknowledging the above requirements have been met. This acknowledgement enables prospective users to proceed to the device training program.

5.3 Device Training Program

Ethicon Endo-Surgery will implement a comprehensive 3-step SEDASYS System training program for prospective users. Consistent with the device and clinical development programs, anesthesiologists were consulted throughout the development of the training process and curriculum. In addition, Ethicon Endo-Surgery engaged gastroenterologists, registered nurses, and education specialists to understand and meet the educational needs of intended users.

Below is an overview of the training program with a detailed description of each step of the program to follow:



Step 1: On-line Program
The first step of device training consists of an on-line program that contains a series of self-guided, interactive, learning modules designed to teach prospective users about all aspects of the SEDASYS System.

The on-line program covers the following:

- Product labeling describing indications, contraindications, warnings and precautions
- Device hardware including the infusion pump and patient monitors (pulse oximeter, capnometer, automated responsiveness monitor and oxygen delivery; NIBP and ECG monitors)
- Device software with focus on the drug delivery algorithms and control systems to maximize patient safety (alarms and system advisories)
- Operational setup of the Bedside Monitoring Unit, Procedure Room Unit, Multiple Patient Use components, and Single Patient Use components
- Clinical safety and effectiveness data gathered during the pivotal study
- Basic propofol and fentanyl pharmacology
- Clinical signs and risks related to each level of sedation as defined and adopted by the ASA
- Airway management techniques
- Patient selection consistent with labeling

Prospective users must complete all modules and pass a final test before being allowed to progress to the second step of the training program. Importantly, successful completion and documentation of the on-line training is a pre-requisite to initiate shipment of the SEDASYS System to the facility.

Step 2: On-site Instructor-Led Training
Upon receipt of the SEDASYS System, an Ethicon Endo-Surgery representative will set up the device at the facility. Then an Ethicon Endo-Surgery clinical education specialist will conduct training to reinforce and enhance the knowledge that prospective users have in operating the device.

The instructor-led training includes:

- Reinforcement of key information covered in the on-line program
- Participation in interactive exercises and self assessments
- Completion of simulated hands-on case scenarios (no drug delivered)

To maximize retention, participants will be required to demonstrate various aspects of the SEDASYS System functionality. At the conclusion of this training, all prospective users will document their participation in the training and verify that they are ready to use the SEDASYS System.

Step 3: Hands-on Patient Cases
After prospective users have participated in the on-site instructor-led training, they will proceed with the final phase of the device training program. During this final training step, physicians and nurses will conduct colonoscopy and EGD procedures under the observation of the clinical education specialist. Ethicon Endo-Surgery will maintain records of all trained users.

In addition to the 3-step training program, Ethicon Endo-Surgery intends to make additional training resources and learning opportunities available to users on an on-going basis.

5.4 Post-approval Vigilance

Ethicon Endo-Surgery is committed to patient safety and to the continuous improvement of the SEDASYS System. To minimize risk throughout the life of the product:

- Any serious adverse event associated with the device, including malfunctions, will be investigated and reported to FDA.
- Customer complaints will be diligently tracked and investigated, and as appropriate, corrective action will be taken.
- If there is a question of patient safety, a health hazard analysis will be conducted. If warranted, a Quality Review Board is convened comprising of representatives from medical, clinical, science, quality assurance, engineering, regulatory, and marketing to determine the corrective and preventative action.

5.5 Post-approval Study

Ethicon Endo-Surgery is currently discussing a post-approval study with the FDA's Office of Surveillance and Biometrics. This study will provide additional assurance of the safety of the SEDASYS System and the effectiveness of the device training program under real-world use conditions. An outline of the proposed study is included in Exhibit F, *Post-Approval Study Outline*.

5.6 Conclusion

Ethicon Endo-Surgery has designed a multi-faceted risk minimization plan to help ensure the safe and effective use of the SEDASYS System post approval. Key mitigations include a controlled launch, facility and user requirements that emphasize that only properly trained physicians and nurses operate the SEDASYS System, a comprehensive device training program, and conduct of a post-approval study.

6.0 PROPOSED LABELING

This section contains key elements of the proposed labeling for the SEDASYS® System, including indications for use, contraindications, and warnings. Also provided is an important clarification to labeling to eliminate confusion in the marketplace regarding who can use the device (located on the first page of the Clinical User Guide/Operator's Manual). The entire Clinical User Guide/Operator's Manual can be found electronically on the compact disk (CD) provided in Exhibit E, *Clinical User Guide/Operator's Manual and Device Video.*

6.1 Indications for Use

The SEDASYS System is indicated for the intravenous administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal-to-moderate sedation, as defined by the American Society of Anesthesiologists Continuum of Depth of Sedation, in adult patients (American Society of Anesthesiologists physical status I and II) undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

6.2 Contraindications

The SEDASYS System is contraindicated in the following:

- Patients with a known hypersensitivity to 1% propofol injectable emulsion or its components
- Patients with allergies to eggs, egg products, soybeans or soy products
- Patients with a known hypersensitivity to fentanyl
- Pregnant or lactating women
- Delivery of any drug other than 1% propofol injectable emulsion
- Patients with a full stomach

6.3 General Use Warnings

For readability, warnings are bulleted and, when applicable, supporting rationale can be found below the warning.

- The SEDASYS System should only be used by physician/nurse teams who have received prior training in the administration of minimal-to-moderate sedation including airway management, provided by their facility or a certified third party, and who have completed an Ethicon Endo-Surgery-approved device training program. It should be noted that the Ethicon Endo-Surgery-approved device training program does not replace formalized training in minimal-to-moderate sedation. This training must be completed before users administer propofol with the SEDASYS System.

Rationale: This warning alerts prospective users to the requirement that they must have prior training in the administration of minimal-to-moderated sedation including airway management to be eligible for device training.

- As with any medical procedure, the safety of the patient is the responsibility of the physician. The primary role of the physician is to conduct the endoscopic procedure. A nurse, under the direction of the physician, should assist the physician and tend to the patient in accordance with ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists (2002).

  Rationale: Based on feedback from gastroenterologists and anesthesiologists during device development, this warning was created to clarify the responsibility of the physician and nurse. This warning is consistent with the "Availability of an Individual Responsible for Patient Monitoring" recommendation found on page 1009 of the 2002 ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists that reads, *"A designated individual, other than the practitioner performing the procedure, should be present to monitor the patient throughout procedures performed with sedation/analgesia. During deep sedation, this individual should have no other responsibilities. However, during moderate sedation, this individual may assist with minor, interruptible tasks once the patient's level of sedation–analgesia and vital signs have stabilized, provided that adequate monitoring for the patient's level of sedation is maintained."*

- The safety and effectiveness of the SEDASYS System has not been established in the following patient populations:
  - ASA physical status III
  - Patients using a fentanyl patch
  - Patients with abnormal airway or diagnosed sleep apnea
  - Patients with gastroparesis
  - Patients with Body Mass Index ≥ 35
  - Patients undergoing both colonoscopy and esophagogastroduodenoscopy during the same procedure visit
  - Patients undergoing emergent colonoscopy or esophagogastroduodenoscopy Procedures

  Rationale: It is important that prospective device users be aware that the safety and effectiveness of the SEDASYS System has not been established in these populations. Placing this statement in the Warnings section signifies the importance.

- Practitioners should consult an anesthesiologist when the ASA classification is unclear, the patient is medically compromised or unstable, or a difficult airway is anticipated (e.g., sleep apnea or Mallampati airway classification III or IV).

  Rationale: This warning makes users aware of conditions when an anesthesiologist, who is better able to address these conditions, should be consulted.

- Rescue medications (i.e., narcotic reversal agents) and equipment for maintenance of the patient's airway, positive pressure ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available.
- Do not supplement propofol administered by the SEDASYS System with additional manual bolus doses of any other sedative (e.g., midazolam) as this may result in overdosing and respiratory depression.

6.4 Drug Warnings Applicable to the SEDASYS System

Propofol

- Use of 1% propofol injectable emulsion has been associated with both fatal and life-threatening anaphylactic and anaphylactoid reactions.
- Carefully review all aspects of the propofol package insert, especially the warning and precaution sections, before using the SEDASYS System to administer 1% propofol injectable emulsion.
- Only use 1% (10 mg/mL) propofol injectable emulsion in new 10 or 20 mL vials. Do not use an expired or previously used vial.
- Do not supplement propofol administered by the SEDASYS System with additional manual bolus doses of propofol as this may result in overdosing and respiratory depression.

Fentanyl

- Users should carefully review all aspects of the fentanyl package insert, especially the warning and precaution sections, before administering this drug.
- Only a **single** pre-procedure dose of fentanyl should be administered. Administration of additional doses of fentanyl beyond the start of the procedure increases the risk of severe respiratory depression.
- Do not administer fentanyl until all of the patient monitors are connected.

6.5 Labeling Clarification Statement

The Food and Drug Administration (FDA) has approved the use of the SEDASYS System, a Computer-Assisted Personalized Sedation device, for the administration of propofol by a physician/nurse team. This team must be trained in the administration of minimal-to-moderate sedation (sometimes referred to as conscious sedation) to use the SEDASYS System. This team does not need to be trained in the administration of general anesthesia. The FDA reached this determination based upon the review of clinical data provided by Ethicon Endo-Surgery and understands this is a departure from the approved labeling of Diprivan and other generic forms of propofol. Administration of propofol sedation by a physician/nurse team not trained in the administration of general anesthesia, by any means other than with the SEDASYS System, has not been approved by the FDA. For more information about propofol, including warnings and precautions, consult the approved package insert of this drug.

Rationale: The overall purpose of this part of the labeling is to ensure Adequate Directions for Use. It addresses the warning 'trained in the administration of general anesthesia' in the propofol package insert that is familiar to prospective users of the SEDASYS System. Stating that it is not necessary for users of the SEDASYS System to be trained in the administration of general anesthesia is necessary to minimize or eliminate confusion among physicians and nurses.

7.0 OVERALL SUMMARY AND CONCLUSIONS

The technical and clinical information provided demonstrate that the SEDASYS System enables trained physician/nurse teams to safely and effectively administer minimal-to-moderate propofol sedation to patients undergoing colonoscopy and EGD procedures.

The SEDASYS System design mitigates the risks of over-sedation and subsequent ventilatory depression including stringent adherence to the dosing guidelines in FDA-approved propofol labeling and the use of lock-out timers to enforce titration to clinical effect. Additionally, the system contains a full suite of monitors, consistent with the ASA Practice Guidelines for Sedation by Non-anesthesiologists. These monitors are integrated with propofol delivery through alarms that reduce/stop propofol delivery at signs of respiratory depression. The SEDASYS System also includes mandatory oxygen delivery that automatically increases at the first sign of oxygen desaturation. The inclusion of capnometry, automated responsiveness monitoring, ECG and mandatory oxygen delivery represents an enhancement in safety over what is used today in the current practice of sedation.

The SEDASYS System is a safe and effective alternative to current benzodiazepine-based sedation with benefits as evidenced by lower area-under-the-curve of oxygen desaturation and fewer adverse events in the pivotal study. In addition, patients experienced faster recovery and were very satisfied with the sedation they received. Clinicians were able to titrate propofol to achieve and maintain a level of sedation specific to the needs of the patient, leading to overall higher clinician satisfaction.

In anticipation of FDA approval, Ethicon Endo-Surgery has designed a plan to further minimize risk and maximize patient safety. This plan is comprehensive and includes a controlled launch of the SEDASYS System, clear requirements that must be met at the facility level, and extensive device training program. In addition, a post-approval study will be conducted to provide further assurance of the safety of the SEDASYS System under real-world use conditions.

Device design, clinical program results, and post-approval mitigations give the SEDASYS System a favorable benefit/risk profile for both colonoscopy and EGD. Accordingly, Ethicon Endo-Surgery respectfully requests the panel render a recommendation for approval for both indications.

Exhibit A
Statistical Analysis of the Pivotal Clinical Study

1.0 SUMMARY OF STATISTICAL ANALYSES

1.1 Sample Size Rationale

1.1.1 Determination of Sample Size - 1000 Subjects

The study's primary endpoint, area-under-the-curve of oxygen desaturation (AUC_{Desat}), is a relatively new measure and as a result, there are no published studies of procedural sedation that utilized AUC_{Desat} as a measure of sedation risk. Therefore, a sample size could not be calculated from published AUC_{Desat} data.

Unpublished AUC_{Desat} data are available from Ethicon Endo-Surgery study CI-02-0004 which was summarized in Section 4.3. AUC_{Desat} was assessed for benzodiazepine-based sedation in 148 subjects undergoing colonoscopy and/or EGD. A sample size calculation based on data from the CI-02-0004 study coupled with AUC_{Desat} data from the two feasibility studies (CI-04-0005 and CI-05-0002, summarized in Section 4.4) was conducted. Only subjects from those studies who received routine supplemental oxygen and had a body mass index < 35 were included in the analysis. In order to have a 90% chance of detecting a difference between area-under-the-curves, a sample size of ~100 subjects per treatment group would be required, using effect size estimates of 0.375 to 0.45 derived from the feasibility studies. Clearly, studies of this size would be too small to assess the safety and effectiveness of the SEDASYS System.

If a sample size calculation were to be based on published literature, it would require an assumption that the incidence of oxygen desaturation is a reasonable predictor for AUC_{Desat} Even with this assumption, the published data are collected using a variety of study designs (e.g., oxygen desaturation was not the primary variable, supplemental oxygen was not always used, varying endoscopic procedures, etc.). These studies show a wide range of incidence of oxygen desaturation (< 90%), from as low as 2.4% to as high as 58%. If an estimated mid-value of 25% is used for incidence in benzodiazepine-based sedation, a comparison made to the SEDASYS System (data from feasibility studies: CI-04-0005 and CI-05-0002), would require a sample size of ~150 subjects per treatment group. Again, the size is too small to adequately address effectiveness and safety.

Therefore, in discussion with the Ethicon Endo-Surgery Anesthesia Advisory panel and the Agency, it was decided that a 1000 subject study would be sufficient to demonstrate that physician/nurse teams could safely and effectively administer propofol for minimal-to-moderate sedation to patients undergoing colonoscopy and EGD procedures.

1.1.2 More Colonoscopies Than EGDs

It is generally considered that, compared to EGDs, colonoscopies present a greater challenge for sedation. The procedures are longer than EGDs, there is more discomfort due to insufflation of the colon, and there is the potential for more anatomical challenges due to prior abdominopelvic surgeries.

This difference was clearly seen in the risk study (CI-02-0004). Twenty-three (40%) subjects (with body mass index < 35 and receiving supplemental oxygen) who had a colonoscopy experienced at least one desaturation event; 56 events total. Whereas, for EGD, only 7 subjects (25%) (with body mass index < 35 and receiving supplemental oxygen) had at least one desaturation event (12 events total).

In order to evaluate the SEDASYS System in more challenging procedures, it was decided to enroll more colonoscopy subjects (~700) than EGD subjects (~300).

1.2 Planned Statistical Analyses

1.2.1 Primary Analysis

The primary analysis for both colonoscopy and EGD procedures was a between group comparison of the mean area-under-the-curve of oxygen desaturation. The oxygen desaturation area-under-the-curves were analyzed using analysis of variance. A linear model was used including terms for group and for study site. An F test was conducted to test the hypothesis:

$$H_0 : \mu_{SDS} = \mu_{CSC} \quad vs. \quad H_A : \mu_{SDS} \neq \mu_{CSC}, \tag{1}$$

where μ_{SDS} and μ_{CSC} were the area-under-the-curve means for the SDS device and CSC groups, respectively. The F test was conducted at the two-sided, $\alpha = 0.05$ level of significance.

1.2.2 Secondary Analysis

In order to maintain an overall α=0.05 probability of a Type I error, the analyses of the four secondary endpoints for both colonoscopy and EGD were conducted at the Tukey multiplicity adjusted $\alpha = 0.0253$ significance level.

Between group comparisons for duration of deep sedation/general anesthesia, as measured by the occurrence (each occurrence = 2 minutes) of all MOAA/S scores of 1 or 0 during a procedure, were conducted using analysis of variance methods with an appropriate linear model.

Between group comparisons for Patient Satisfaction with Sedation Instrument and Clinician Satisfaction with Sedation Instrument scores were conducted using analysis of variance methods with an appropriate linear model.

Time to recovery from sedation was analyzed using a Cox proportional hazards regression model to determine the treatment effect on recovery time. Graphical displays of survival curves were constructed for the two groups.

1.2.3 Tertiary Analyses

Summary statistics were computed for all additional measures. For categorical measures, the data was summarized using counts and percentages. For continuous measures, summary statistics (mean, median, standard deviation, minima, and maxima) were computed by group.

1.2.4 Safety Data Analysis

Adverse events were coded using the current version of the medical dictionary for regulatory activities (MedDRA®) and summarized by treatment for the number of subjects reporting the adverse event and the number of adverse events reported. Frequencies of each adverse event were summarized within group by MedDRA preferred term within system organ class, by severity and by relation to treatment. A by-subject adverse event data listing including verbatim term, coded term, group, severity, and relationship to treatment is provided.

2.0 RANDOMIZATION AND STUDY POPULATIONS

2.1 Randomization

Consecutive patients presenting for a colonoscopy or EGD were considered for enrollment into the study. Patients were deemed enrolled into this study (Figure 38) at the time they signed informed consent. They were then randomized to treatment following successful screening. Subjects were considered part of the Intent-to-Treat population at the time they were randomized to a group (SDS or CSC).

Figure 38
Subject Randomization

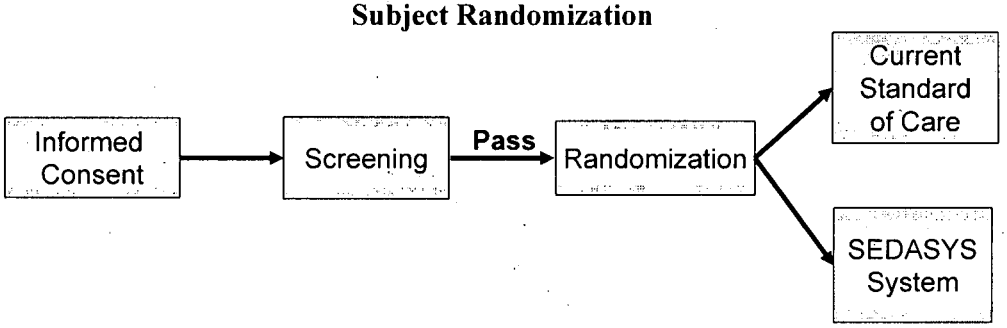
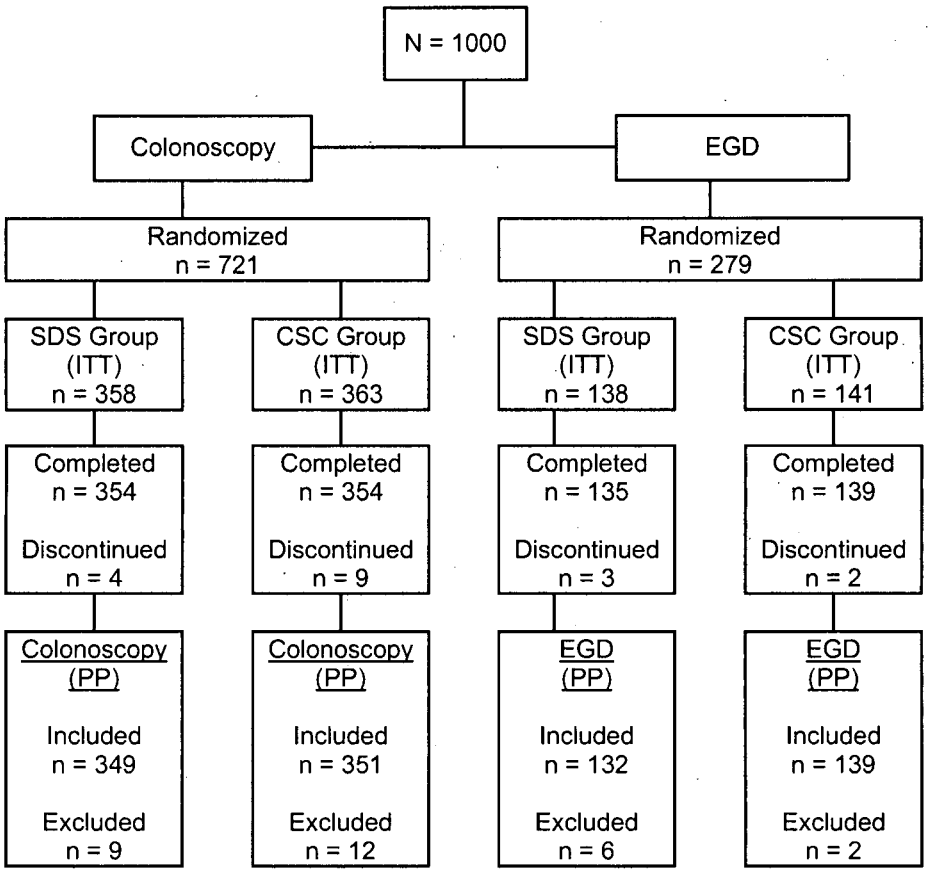


Figure 39 is a flow diagram of subject progress from randomization through final analysis.

Figure 39
Subject Accountability Flow Diagram



In all cases, the Per Protocol (PP) dataset did not substantively differ from the ITT dataset. Therefore, all results reported are based upon the ITT data set using all subjects with data available for analysis (the mITT population).

2.2 Analysis Populations

All safety analyses were conducted on the ITT population. For the effectiveness analysis, two populations were analyzed, ITT and Per Protocol. The ITT population was the primary analysis for effectiveness. The analysis populations were defined as follows:

ITT Populations
The ITT population includes all patients who were randomized to treatment. In the event that subjects were randomized to one treatment group (CSC or SDS) but received the incorrect treatment, the subject's data was analyzed according to the treatment actually received. This

is due to the fact that the primary analysis, AUC_{Desat}, is a safety measure rather than an effectiveness measure. If a subject was stratified according to one procedure (colonoscopy or EGD) but actually received the other procedure, that subject's data was summarized according to the procedure actually preformed.

There were three subjects who were randomized to the SDS group but treated in the CSC group. In accordance with the planned statistical analysis, those three subjects were included in the CSC group within the ITT analysis.

Due to factors not associated with the functioning of the sedation device or characteristics of treatment regimen assigned, several subjects had missing data for the primary and secondary outcome measures. The resulting analyses are based upon ITT subjects with complete data, effectively a modified ITT (mITT) population. Tables 38 and 39 summarize the number of subjects used for each analysis.

Table 38
Number of Subjects with Data Available for Primary and Secondary Analysis
Colonoscopy

		SDS	CSC
ITT	Randomized	358	363
mITT	AUC_{Desat}	349	350
	CSSI	355	353
	PSSI	287	281
	Recovery Time	336	334
	Duration Deep/General Sedation	356	356

Table 39
Number of Subjects with Data Available for Primary and Secondary Analysis
EGD

		SDS	CSC
ITT	Randomized	138	141
mITT	AUC_{Desat}	133	136
	CSSI	135	138
	PSSI	106	116
	Recovery Time	127	131
	Duration Deep/General Sedation	135	139

The majority of data missing is attributable to malfunctioning or incorrect operation of the Data Acquisition System (DAQ). This is a unit appended to the sedation device for purposes of clinical data capture only. It has no effect on the device nor will it be part of the final marketed product. A detailed listing of missing data for the primary outcome measure, AUC_{Desat}, is provided in Tables 40 and 41.

In all cases, the missing data is neither associated with the treatment assigned nor the outcomes of the patient. Therefore, it is reasonable to assume that no bias has been introduced into the analysis through attrition.

Table 40
Reasons for Missing AUC_{Desat} Data
Colonoscopy

Subject	Treatment	Reason missing AUC_{Desat} Data
[redacted]	CSC	Randomized, but never treated; missing all procedure data.
[redacted]		Missing all DAQ data
[redacted]		Randomized, but never treated; missing all procedure data.
[redacted]		Missing all DAQ data
[redacted]		Randomized, but never treated; missing all procedure data.
[redacted]		Randomized, but never treated; missing all procedure data.
[redacted]		Missing all DAQ data
[redacted]		Missing all DAQ data
[redacted]		Missing all DAQ data
[redacted]		Missing all DAQ data
[redacted]		Randomized, but never treated; missing all procedure data.
[redacted]		Randomized, but never treated; missing all procedure data.
[redacted]		Randomized, but never treated; missing all procedure data.

Subject	Treatment	Reason missing AUC_{Desat} Data
[redacted]	SDS	Randomized, but never treated; missing all procedure data.
		Missing all DAQ data
		Missing all DAQ data
		Randomized, but never treated; missing all procedure data.
		Missing all DAQ data
		Missing all DAQ data
		Missing all DAQ data
		Missing all DAQ data
		Missing all DAQ data

Table 41
Reasons for Missing AUC_{Desat} Data
EGD

Subject	Treatment	Reason missing AUC_{Desat} Data
[redacted]	CSC	Missing all DAQ data
		Randomized, but never treated; missing all procedure data.
		Missing all DAQ data
		Randomized, but never treated; missing all procedure data.
		Missing all DAQ data
[redacted]	SDS	Missing all DAQ data
		Missing all DAQ data
		Randomized, but never treated; missing all procedure data.
		Randomized, but never treated; missing all procedure data.
		Randomized, but never treated; missing all procedure data.

Examination of the missing data confirms that no discernable trends for missing data exist. The number and reasons for missing data are approximately equally distributed across the treatment groups. Examination of the outcomes for the secondary analyses was consistent with this examination of the missing data for AUC_{Desat}.

There are 210 subjects with missing PSSI data, evenly divided between CSC and SDS. Two factors contribute to this number. First, 53 subjects were enrolled under protocol Amendment 3, which had PSSI being completed at time of recovery. In protocol Amendment 4, the time of completion was changed to 24-to-48 hours after discharge. In addition to treating the 53 subjects enrolled under Amendment 3 as having missing data for PSSI, many subjects were unable to be reached for completion of the PSSI at a 24-to-48 hour follow-up.

Protocol Amendment 4 also had a different definition of Recovery Time. Therefore, the 53 subjects enrolled under Amendment 3 are treated as having missing data for recovery time.

Per-Protocol Population
For the colonoscopy subjects, the Per-Protocol population includes all patients who have met all inclusion and exclusion criteria, had no major protocol deviations, and whose physician was able to cross the splenic flexure during the procedure.

For the EGD subjects, the Per-Protocol population includes all patients who have met all inclusion and exclusion criteria, had no major protocol deviations, and whose physician was able to reach the duodenum during the procedure.

In all cases, analyses of the Per-Protocol population confirm the results of the ITT population.

2.2.1 Colonoscopy Procedure – Per-Protocol Subjects

Table 42 shows the distribution of the subject data among the analysis sets for subjects who underwent a colonoscopy. Of the nine subjects excluded from the SDS group Per-Protocol population:

- 2 subjects were excluded due to the inability to cross the splenic flexure.
- 5 subjects were excluded due to major protocol deviations.
- 2 subjects were discontinued from the study prior to the colonoscopy procedure.

Of the twelve subjects excluded from the CSC group Per-Protocol population:

- 1 subject was excluded due to the inability to cross the splenic flexure.
- 4 subjects were excluded due to major protocol deviations
- 3 subjects were excluded due to violation of inclusion/exclusion criteria.
- 5 subjects were discontinued from the study prior to the colonoscopy procedure.

Table 42
Analysis Sets for Randomized Subjects – Colonoscopy Procedure

Analysis Set	SDS (N = 358)	CSC (N = 363)	Total (N = 721)
Intent-to-Treat population	358 (100%)	363 (100%)	721 (100%)
Per-protocol population	349 (97%)	351 (97%)	700 (97%)

2.2.2 EGD Procedure – Per-Protocol Subjects

Table 43 shows the distribution of the subject data among the analysis sets for subjects who underwent an EGD. Of the six subjects excluded from the SDS group Per-Protocol population:

- 1 subject was excluded due to the inability to reach the duodenum.
- 3 subjects were excluded due to violation of inclusion/exclusion criteria.
- 2 subjects were discontinued from the study prior to the EGD procedure.

The two subjects excluded from the CSC group Per-Protocol population were discontinued from the study prior to the EGD procedure.

Table 43
Analysis Sets for Randomized Subjects – EGD Procedure

Analysis Set	SDS (N = 138)	CSC (N = 141)	Total (N = 279)
Intent-to-treat population	138 (100%)	141 (100%)	279 (100%)
Per-protocol population	132 (96%)	139 (99%)	271 (97%)

Analysis Subgroup Definitions

Subgroup analyses of subjects experiencing the event of interest for a given analyses were planned for the Per-Protocol population for the following tertiary variables:

- Mean oxygen desaturation duration and magnitude
- Mean apnea duration
- Mean bradycardia duration and magnitude
- Mean hypotension duration and magnitude
- Mean interruption duration
- Number of polyps per subject

2.3 Sensitivity Analysis and Examination of Center Effect for Primary Endpoint

2.3.1 Sensitivity Analysis

The primary colonoscopy analysis is based upon all Modified Intent-to-Treat (mITT) subjects with AUC_{Desat} data (n = 699). In order to assess the degree to which the primary colonoscopy analysis is dependent upon values for the missing data, a series of sensitivity analyses were conducted. A complete description of the 22 subjects, who underwent a colonoscopy, with missing AUC_{Desat} data can be found in Table 40.

The first imputation of missing values involved the computed confidence intervals for each treatment group. In the SDS group, the 95% confidence interval for AUC_{Desat} for colonoscopy subjects was (0 to 74). Therefore, any SDS subjects with missing data received the worst value in the confidence interval, 74. Similarly, for the CSC group, the 95% confidence interval for AUC_{Desat} for colonoscopy subjects was (65 to 154). Therefore, any CSC subjects with missing data received the best value in the confidence interval, 65. After imputation, the primary analysis was rerun with the complete n = 721 ITT data set. The treatment effect remained significant, p = 0.004.

A more conservative approach was taken to imputing missing values – the worst case scenario by-site. For each site, the minimum and maximum values were computed for SDS and CSC groups. SDS subjects with missing values were assigned the value of the worst SDS observed case (highest AUC_{Desat}) of the site that enrolled the subject. CSC subjects with missing data were assigned the best CSC observed case (smallest AUC_{Desat}) at their site of enrollment. In all cases, this resulted in an $AUC_{Desat} = 0$ imputed for all CSC cases with missing data. After imputation, the primary analysis was rerun with the complete n = 721 ITT data set. The treatment effect again remained significant, p = 0.009.

As a final sensitivity analysis, the worst possible case was assumed. That is, the CSC subjects with missing data were assigned an $AUC_{Desat} = 0$ and SDS subjects with missing data were assigned the worst observed AUC_{Desat} value in the SDS group, 1741 seconds·%. Data were imputed and the primary colonoscopy analysis rerun on the complete n = 721 ITT data set. In this case, the treatment effect was not significant, p = 0.277.

Results of the sensitivity analyses demonstrate the robustness of the colonoscopy primary analysis to potential values of the missing data. When an imputation is based upon the confidence intervals computed for the observed data or based upon a worst case scenario by site, the treatment effect remains significant. Results confirmed that SDS subjects have significantly lower AUC_{Desat} values. In fact, it isn't unless one imputes the best observed value for CSC subjects and the worst observed value, independent of site, for SDS subjects that the treatment effect becomes non significant. Being that this scenario does not take into account the statistically significant difference between sites, the robustness of the results to potential values for the missing data is confirmed.

2.3.2 Examination of Center Effect

While recruiting centers for the study, one objective was to enroll investigators with different endoscopic/sedation practices. The intent was to evaluate the SEDASYS System under conditions representative of the spectrum of current practice. Tables 44 and 45 present AUC_{Desat} data by center for colonoscopy and EGD, respectively. The data shows that there are differences in the center's AUC_{Desat} for both SDS and CSC. At each center, for both colonoscopy and EGD, the AUC_{Desat} in the SDS group was lower, or equivalent, to the CSC group.

Table 44
AUC_{Desat} (seconds·%) – By Center, Colonoscopy

Center Number	SDS	CSC
Site 0 (n = 112)	3 ± 21	13 ± 47
Site 2 (n = 59)	2 ± 12	40 ± 125
Site 3 (n = 145)	2 ± 11	39 ± 108
Site 4 (n = 126)	85 ± 281	378 ± 1102
Site 5 (n = 18)	50 ± 151	460 ± 758
Site 6 (n = 24)	0	0
Site 7 (n = 96)	0	3 ± 14
Site 8 (n = 119)	3 ± 20	23 ± 100

Table 45
AUC_{Desat} (seconds·%) – By Center, EGD

Center Number	SDS	CSC
Site 0 (n = 30)	19 ± 61	4 ± 17
Site 2 (n = 12)	0	136 ± 359
Site 3 (n = 49)	0	0
Site 4 (n = 66)	141 ± 346	187 ± 271
Site 5 (n = 7)	0	223 ± 283
Site 6 (n = 0)	NA[a]	NA
Site 7 (n = 36)	10 ± 25	7 ± 27
Site 8 (n = 69)	0	0

[a] Site 6 did not conduct any EGD procedures.

In order to examine the effect of sedation practice differences on the observed treatment effect, a series of *post hoc* analyses were conducted.

First, a mixed effects model was conducted. The model examines the relationship between treatment (fixed), center (random) and the primary outcome of AUC_{Desat}. Table 46 contains the results for the treatment effect for this model. These statistical results are similar to the initial analysis, with LS Mean for SDS colonoscopy ($p = 0.004$) remaining significantly different than that for CSC.

Table 46
Mixed Effects Model: AUC_{Desat} (seconds·%)

	SDS LS Mean	CSC LS Mean	Difference LS Mean	95% CI	p-value
Colonoscopy	23.0	103.0	80.2	26.3 – 134.0	0.004
EGD	35.8	56.9	21.0	-19.5 – 61.5	0.307

Inherent to this fixed effect model is the assumption of equal variances between centers (i.e., the model includes equal variances along the diagonal of the variance/covariance matrix). So, an additional exploratory analysis was conducted that relaxes the equal variance assumption so that variances for each center are modeled separately. Due to the complexity of this model, convergence was not achieved using the raw data. Therefore, grouping of study centers was required. Examination of the residuals plotted by study center in the original analysis suggested two groupings:

- Study centers 0, 2, 3, 6, 7, and 8 in one group
- Study centers 4 and 5 in a second group

So, the heterogeneous variance model was conducted using the two groups of study centers rather than the original study center variable.

Table 47 contains the results for the treatment effect for this model. The results are similar to the initial analysis, with colonoscopy ($p < 0.001$) remaining statistically significantly different.

Table 47
Heterogeneous Variance Model: AUC_{Desat} (seconds·%)

	SDS LS Mean	CSC LS Mean	Difference LS Mean	95% CI	p-value
Colonoscopy	113.8	134.9	21.2	10.9 – 31.4	< 0.001
EGD	80.5	88.0	7.5	-12.3 – 27.2	0.457

The results from these different models indicate the treatment effect remains statistically significant for colonoscopy, regardless of the modeling method used. Therefore, whether one assumes the study center effect is allowed to vary by center, or whether one assumes the study centers may be grouped and variances estimated within these groupings of study centers separately, the results confirm the significant effect for treatment.

The results of the models differ in the magnitude of the estimated treatment effect. The models that allow heterogeneous variances between study centers increased the precision of estimate, but the magnitude of difference in mean AUC_{Desat} is decreased (80.2 vs. 21.2 %·seconds for colonoscopy and 21.0 vs. 7.5 %·seconds for EGD). It is questionable whether allowing the data to dictate groupings provides a more generalizable estimate of the treatment effect. That is, the improved model fit may result in a good fit to this sample data that cannot be expected to generalize to the population, particularly if the assumption of two groupings of study centers is not warranted.

As noted previously, sites were selected purposely to insure a diversity of sedation practices. Therefore, the model with a random effect for treatment seems warranted. This model confirms the results of the fixed effects model. However, the heterogeneous variance model, which requires pooling of centers in order to converge, likely over simplifies the diversity of sedation practices and therefore is not generalizable.

In an effort to further examine the potential effect of center differences on the treatment effect, Ethicon Endo-Surgery commissioned an independent examination of the data. This analysis employed a marginal regression model, which allows for heterogeneity of variances across centers/treatments. This analysis confirmed the results of the primary analysis. Specifically, the new analysis demonstrated a highly significant, 82% reduction in mean AUC_{Desat} for the SEDASYS System for colonoscopy and a non-statistically significant 35% reduction in mean AUC_{Desat} for EGD.

All of our statistical analyses indicate that there is a highly significant reduction in mean AUC_{Desat} in favor of the SEDASYS System for colonoscopy. Furthermore, there is an estimated reduction in mean AUC_{Desat} in favor the SEDASYS system for EGD, although the results are not statistically significant at the 0.05 level.

3.0 ADDITIONAL STUDY RESULTS

3.1 Additional Descriptive Statistics

A further examination of the data distributions of the primary and secondary outcomes are presented in the Tables 48 and 49 below:

Table 48
Descriptive Statistics for Primary and Secondary Endpoints for Colonoscopy

			Percentile			
	n	min	25th	50th	75th	Max
AUC_{Desat} (seconds·%)						
SDS	349	0	0	0	0	1741
CSC	350	0	0	0	0	7040
CSSI (range from 1 – 100 with 100 = very satisfied)						
SDS	355	27.1	84.4	96.9	100.0	100.0
CSC	353	25.0	63.5	80.2	87.5	100.0
PSSI (range from 1 – 100 with 100 = very satisfied)						
SDS	287	0.0	90.6	96.9	100.0	100.0
CSC	281	35.4	85.4	94.8	100.0	100.0
Recovery Time (minutes)						
SDS	336	0.0	1.0	2.0	4.0	15.0
CSC	334	0.0	1.0	3.0	10.0	37.0
Duration of Deep Sedation/General Anesthesia (minutes)						
SDS	356	0	0	0	0	16
CSC	356	0	0	0	0	22

Table 49
Descriptive Statistics for Primary and Secondary Endpoints for EGD

			Percentile			
	n	min	25th	50th	75th	Max
AUC_{Desat} (seconds·%)						
SDS	133	0	0	0	0	1771
CSC	136	0	0	0	0	996
CSSI (range from 1 – 100 with 100 = very satisfied)						
SDS	135	35.4	84.4	97.9	100.0	100.0
CSC	138	42.7	63.5	78.7	91.7	100.0
PSSI (range from 1 – 100 with 100 = very satisfied)						
SDS	106	24.0	88.5	93.8	100.0	100.0
CSC	116	39.6	81.3	91.7	99.0	100.0
Recovery Time (minutes)						
SDS	127	0.0	2.0	2.0	5.0	12.0
CSC	131	0.0	1.0	5.0	10.0	36.0
Duration of Deep Sedation/General Anesthesia (minutes)						
SDS	135	0	0	0	0	4
CSC	139	0	0	0	0	10

3.2 Special Populations: Primary Endpoint

The tables below provide AUC_{Desat} data by the following sub-populations:

- ASA Physical Status
- Age
- Body Mass Index
- Gender
- Minimum MOAA/S

Due to smaller sample sizes in several of these sup-populations, the tables provide AUC_{Desat} data for colonoscopy and EGD procedures pooled.

In addition to the summary data, all subjects in the study with an $AUC_{Desat} \geq 1000$ are identified per sub-population. There were 9 current standard of care subjects with $AUC_{Desat} \geq 1000$, compare to 3 SEDASYS System subjects. These 12 subjects, along with their demographic information are provided in Table 50.

Table 50
Subjects with $AUC_{Desat} \geq 1000$ seconds•%

Subject	Treatment Group	AUC_{Desat}	ASA	Age	BMI	Gender	Minimum MOAA/S
[redacted]	SDS	1771	III	71	29	M	2
[redacted]	SDS	1741	II	54	26	F	3
[redacted]	SDS	1319	I	19	19	F	2
[redacted]	CSC	7040	II	70	32	F	1
[redacted]	CSC	3411	I	52	32	F	3
[redacted]	CSC	2601	II	54	31	M	3
[redacted]	CSC	2599	II	70	20	F	1
[redacted]	CSC	2226	I	35	21	F	3
[redacted]	CSC	2070	I	70	33	F	2
[redacted]	CSC	1594	II	60	31	F	3
[redacted]	CSC	1478	II	55	33	M	3
[redacted]	CSC	1328	I	76	29	F	4

All subjects had a colonoscopy, except [redacted] who had an EGD.

3.2.1 ASA Physical Status

A stratification of all subjects by ASA physical status is presented in Figure 40.

Figure 40
Distribution of Subjects By ASA Status

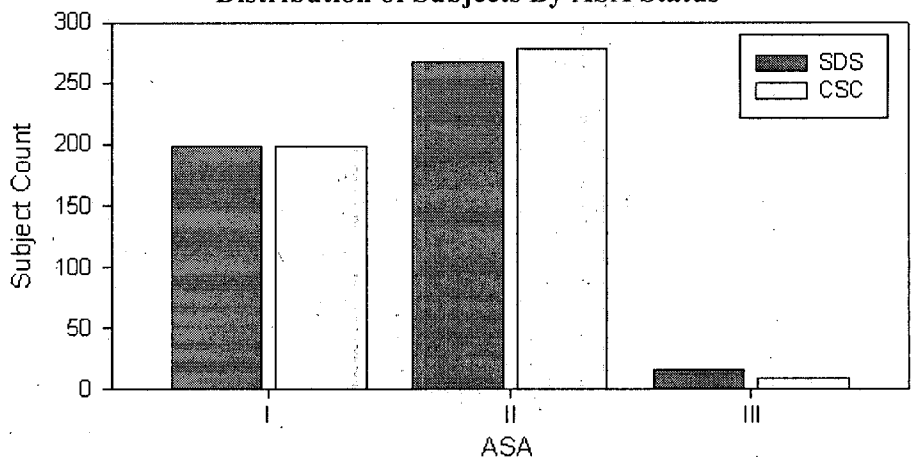


Figure 41 presents ASA physical status and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between ASA physical status and oxygen desaturation.

Figure 41
All Subjects With AUC_{Desat} > 0, Relationship to ASA Status

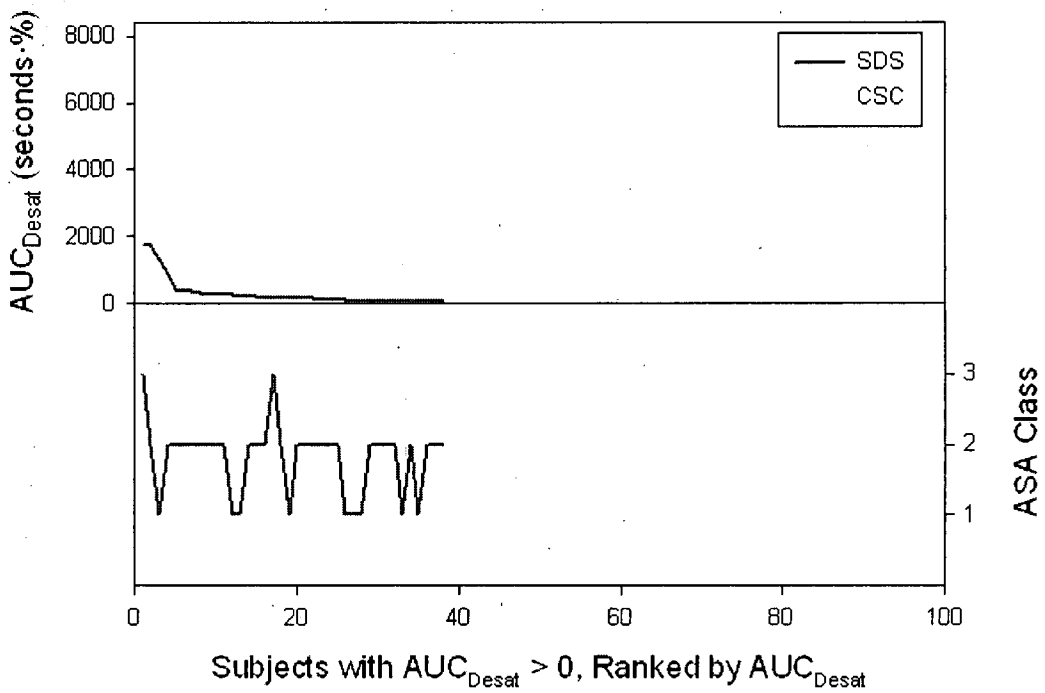


Table 51 presents the mean AUC_{Desat} data with subjects stratified by ASA physical status.

Table 51
AUC_{Desat} (seconds•%) – By ASA Physical Status

ASA Physical Status	SDS	CSC
I (n = 397)	12 ± 98	72 ± 350
II (n = 546)	26 ± 134	99 ± 506
III (n = 25)	122 ± 442	110 ± 132

Of the SEDASYS System subjects 16 (3.3%) were ASA III and of the current standard of care subjects 9 (1.9%) were ASA III. Of the 9 current standard of care subjects, 4 (44%) experienced and oxygen desaturation. The range of AUC_{Desat} for these 4 subjects was 192 to 283 seconds·%.

Of the 16 SEDASYS System subjects, 2 (13%) experienced an oxygen desaturation. [redacted] had an AUC_{Desat} of 1771 seconds·% and the other subject had an AUC_{Desat} of 179. The remaining 14 (88%) of SEDASYS System subjects had an AUC_{Desat} of 0.

3.2.2 Age

A stratification of all subjects by age is presented in Figure 42.

Figure 42
Distribution of Subjects By Age

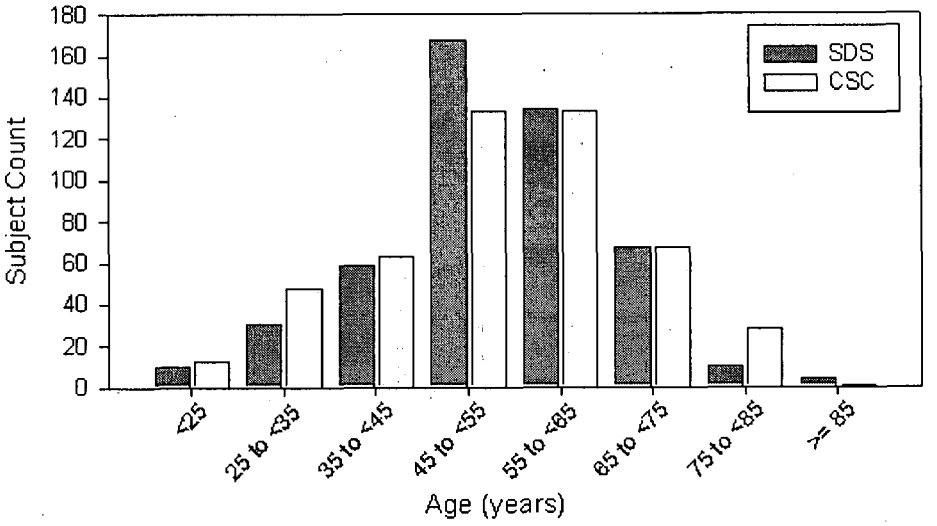


Figure 43 presents age and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between age and oxygen desaturation.

Figure 43
All Subjects With AUC_{Desat} > 0, With Relationship to Age

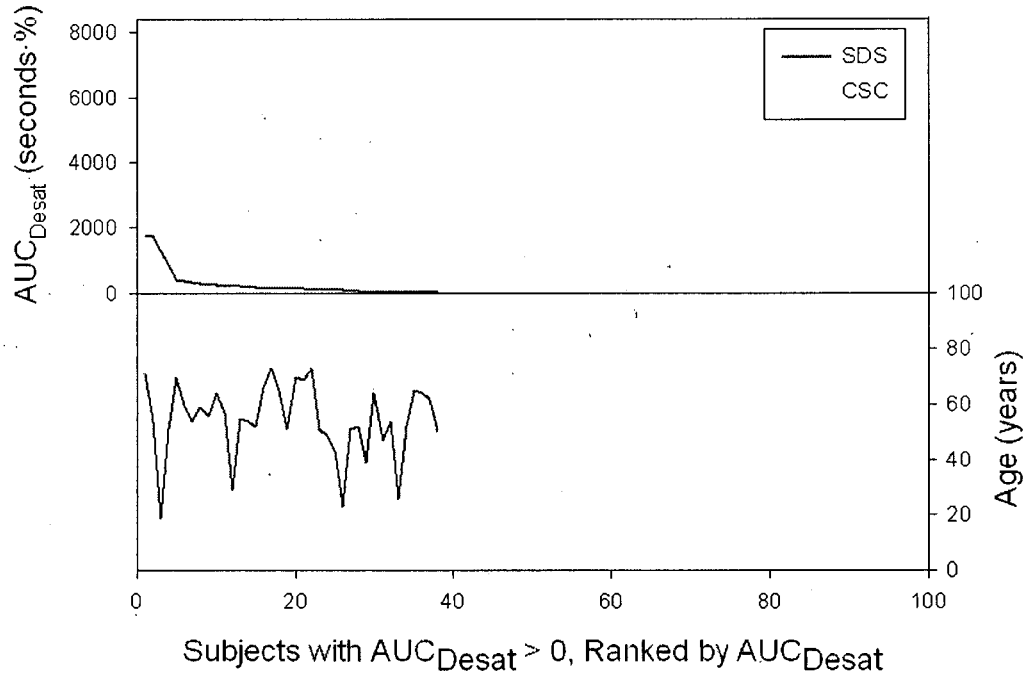


Table 52 presents the mean AUC_{Desat} data with subjects stratified by age.

Table 52
AUC_{Desat} (seconds•%) – By Age

Age (years)	SDS	CSC
< 55 (n = 524)	23 ± 149	62 ± 318
55 to < 65 (n = 267)	14 ± 63	50 ± 210
65 to < 75 (n = 134)	49 ± 225	243 ± 943
75 to < 85 (n = 38)	0	129 ± 335
≥ 85 (n = 5)	0	283[a]

[a] Standard deviation was undefined due to sample size of 1.

Of the 9 current standard of care subjects with an AUC_{Desat} ≥ 1000, 4 (44%) were older than 65 years. Three of these ([redacted] and [redacted]) had an AUC_{Desat} > 2000; the largest being 7040 seconds·%. A single SEDASYS System [redacted] older than 65 years had an AUC_{Desat} > 1000.

Of the 5 subjects 85 years, or older, 4 (80%) were SEDASYS System subjects.

3.2.3 Body Mass Index

A stratification of all subjects by BMI is presented in Figure 44.

Figure 44
Distribution of Subjects By BMI

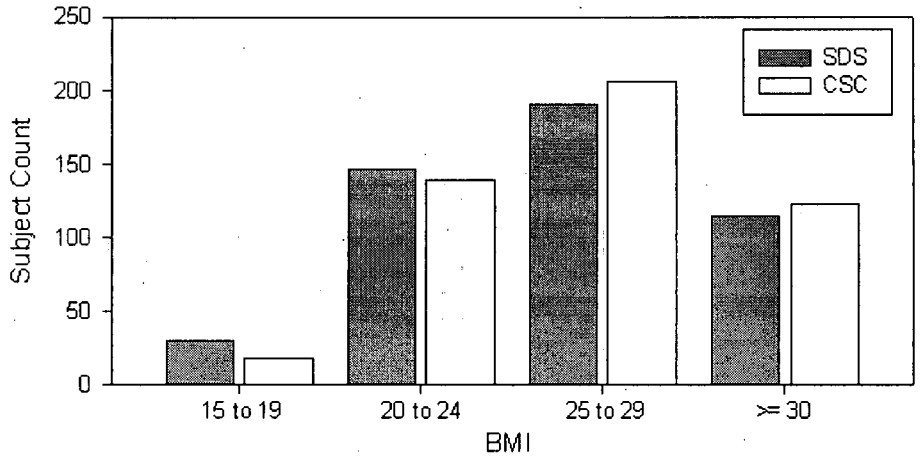


Figure 45 presents BMI and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between BMI and oxygen desaturation.

Figure 45
All Subjects With $AUC_{Desat} > 0$, With Relationship to BMI

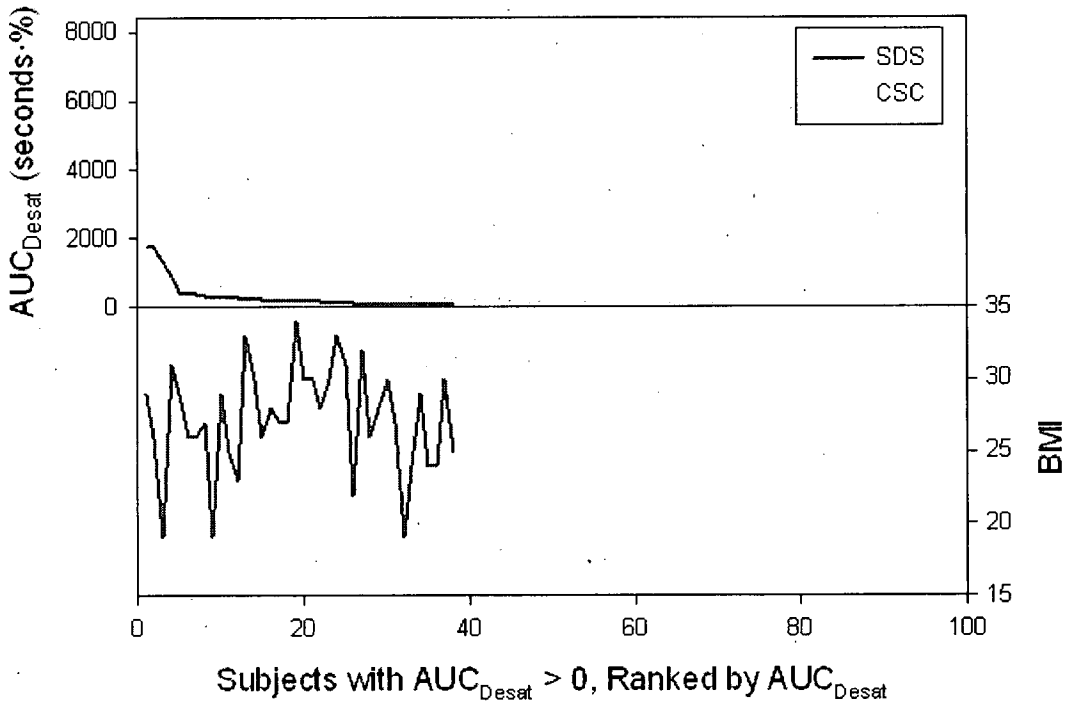


Table 53 presents the mean AUC_{Desat} data with subjects stratified by BMI.

Table 53
AUC_{Desat} (seconds•%) – By BMI

BMI (kg/m²)	SDS	CSC
15 – 19 (n = 48)	55 ± 244	0
20 – 24 (n = 287)	4 ± 24	56 ± 301
25 – 29 (n = 395)	36 ± 190	53 ± 174
> 30 (n = 238)	21 ± 95	196 ± 782

Of the 9 current standard of care subjects with an $AUC_{Desat} \geq 1000$, 6 (67%) had a BMI greater than 30 kg/m^2. Four of these subjects ([redacted] and [redacted] had an AUC_{Desat} > 2000; the largest being 7040 seconds·%. None of the SEDASYS System subjects with an $AUC_{Desat} \geq 1000$ had a BMI greater than 30 kg/m^2.

One of the SEDASYS System [redacted] with an $AUC_{Desat} \geq 1000$, had a BMI less than 20. Only 2 other SEDASYS System subjects with a BMI less than 20 had an oxygen desaturation; their AUC_{Desat} were 64 and 275 seconds·%. All 3 of these subjects had a BMI of 19 kg/m^2.

Of the 48 subjects with a BMI between 15 and 19 kg/m^2, 30 (63%) were SEDASYS System subjects. Of these 30 SEDASYS System, 2 had a BMI of 16 kg/m^2; 2 had a BMI of 17; and 8 had a BMI of 18. None of the 12 subjects with a BMI < 19 kg/m^2 had an oxygen desaturation.

A substantial amount of the difference seen in AUC_{Desat} between the SEDASYS System and current standard of care in subjects with low BMI can be attributed to the arbitrary selection of BMI intervals. Since there were no subjects in the study with a BMI of 15 kg/m^2, the intervals for this sub-population analysis could have started with BMI 16 – 20. This would have added a total of 29 subjects (with BMI = 20) to the first interval; 15 current standard of care and 14 SEDASYS System.

None of the 14 additional SEDASYS System subjects had an oxygen desaturation event; thereby reducing the mean AUC_{Desat} for this sub-population from 55 to 38 seconds·%. Whereas, 3 of the additional current standard of care subjects had an oxygen desaturation; increasing the AUC_{Desat} for this sub-population from 0 to 113 seconds·%. One of these current standard of care [redacted] had an AUC_{Desat} of 2599. This subject was the only subject in the study that required bag-mask ventilation.

3.2.4 Gender

A stratification of all subjects by gender is presented in Figure 46.

Figure 46
Distribution of Subjects By Gender

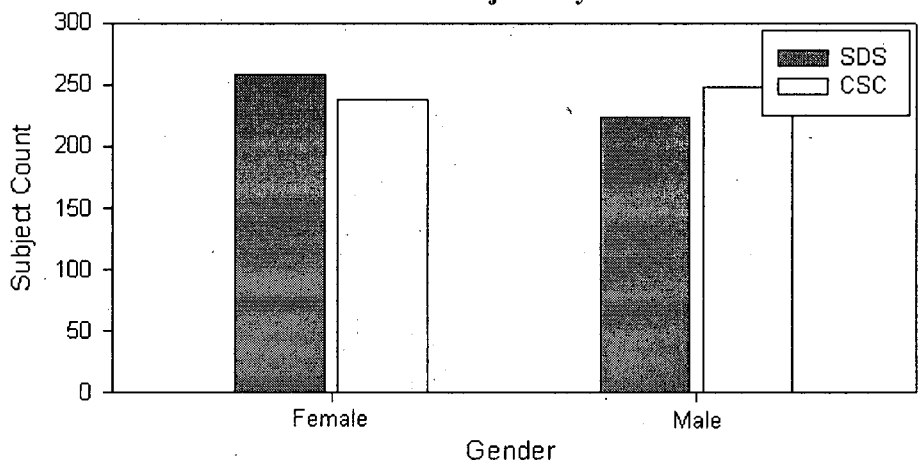


Figure 47 presents gender and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between gender and oxygen desaturation.

Figure 47
All Subjects With $AUC_{Desat} > 0$, With Relationship to Gender

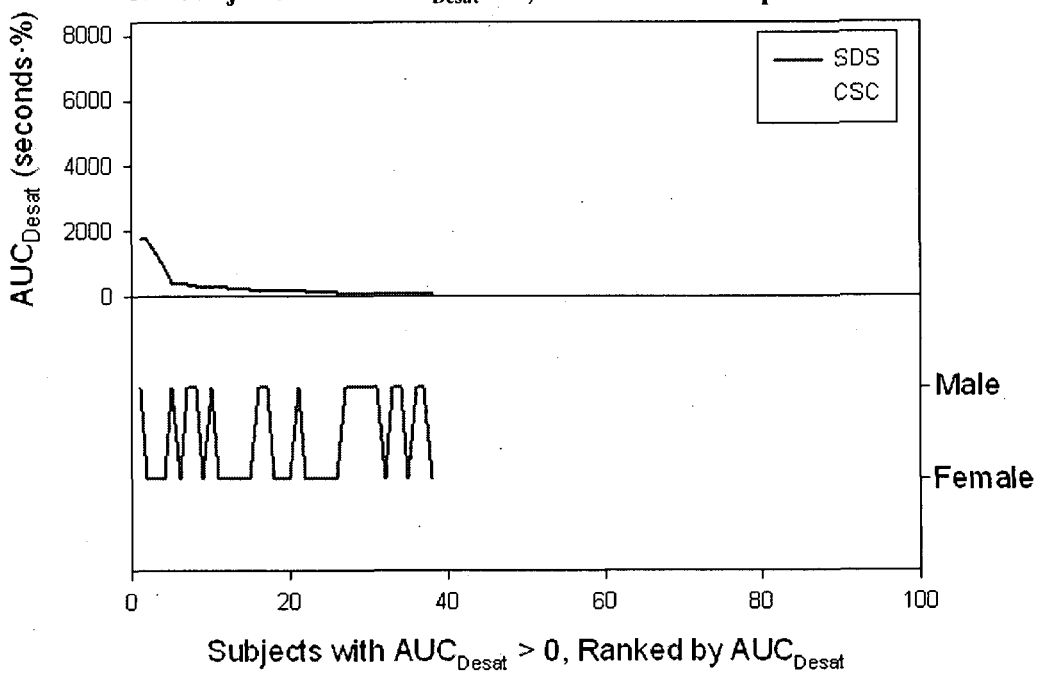


Table 54 presents the mean AUC_{Desat} data with subjects stratified by gender.

Table 54
AUC_{Desat} (seconds•%) – By Gender

ASA Physical Status	SDS	CSC
Male (n = 472)	19 ± 129	41 ± 214
Female (n = 496)	27 ± 154	137 ± 592

Of the 9 current standard of care subjects with an $AUC_{Desat} \geq 1000$, 7 (78%) were female. Of the SEDASYS System subjects with an $AUC_{Desat} \geq 1000$, 2 (67%) were female.

3.2.5 Minimum Level of Sedation

A stratification of all subjects by minimum MOAA/S reached is presented in Figure 48.

Figure 48
Distribution of Subjects By Minimum Level of Sedation

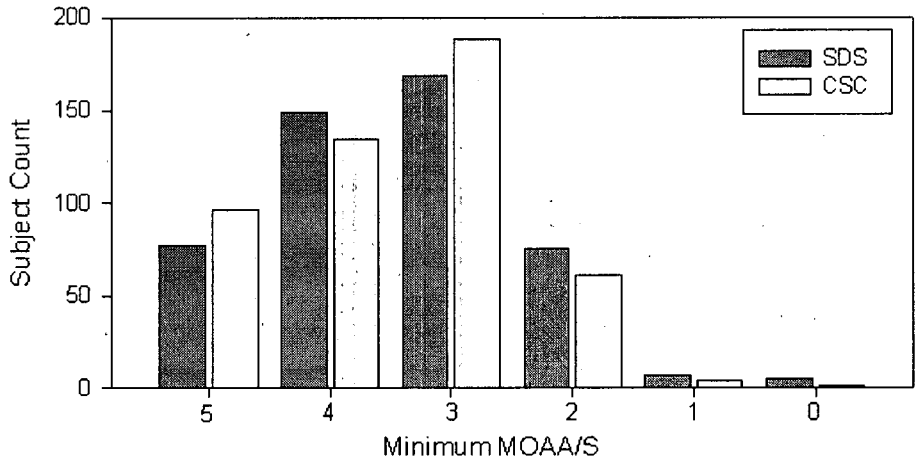


Figure 49 presents minimum MOAA/S reached and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between minimum level of sedation and oxygen desaturation.

Figure 49
All Subjects With AUC_{Desat} > 0, With Relationship to Level of Sedation

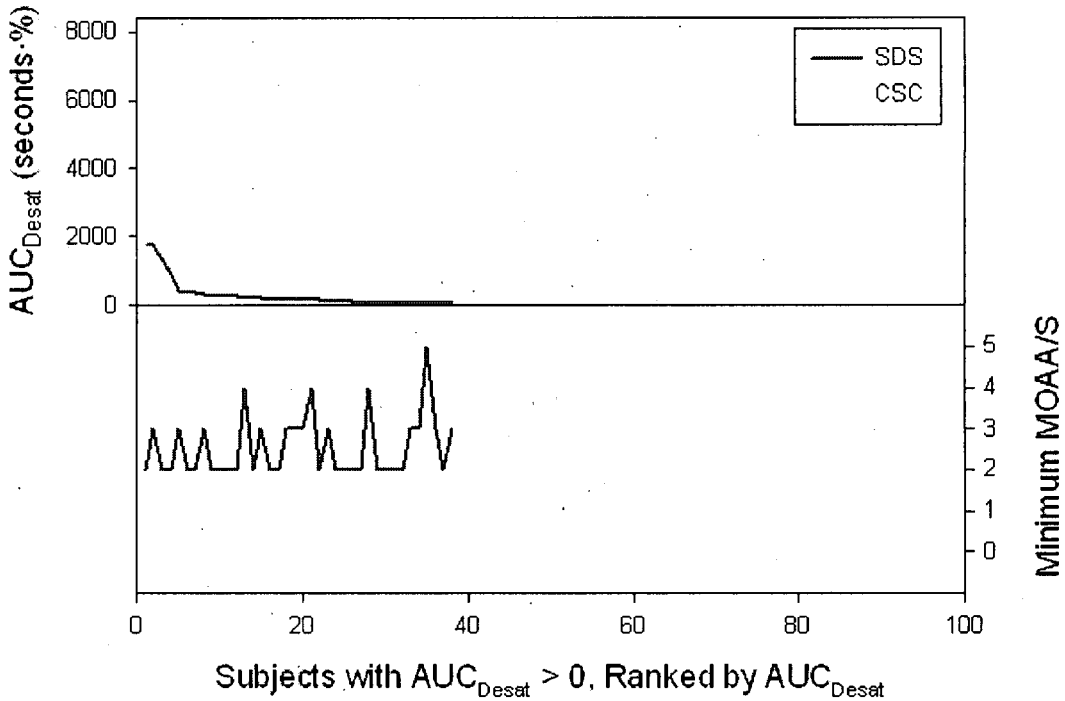


Table 55 presents the mean AUC_{Desat} data with subjects stratified by minimum MOAA/S reached.

Table 55
AUC_{Desat} (seconds•%) – By Minimum MOAA/S

Minimum MOAA/S	SDS	CSC
5 (n = 173)	1 ± 6	7 ± 52
4 (n = 283)	3 ± 24	25 ± 136
3 (n = 358)	21 ± 143	120 ± 404
2 (n = 136)	97 ± 280	86 ± 297
1 (n = 11)	0	2527 ± 3214
0 (n = 6)	0	841[a]

[a] Standard deviation was undefined due to sample size of 1.

Of the 6 subjects with a minimum MOAA/S of 0, 5 (83%) were SEDASYS System subjects. Of the 11 subjects with a minimum MOAA/S of 1, 7 (64%) were SEDASYS System subjects. None of these subjects had an oxygen desaturation.

Of the 5 current standard of care subjects with a minimum MOAA/S of 0 or 1, 4 (80%) had an oxygen desaturation. One of these [redacted] had an AUC_{Desat} of 7040 seconds·% and one [redacted] required bag-mask ventilation.

3.2.6 Duration of Procedure

A stratification of all subjects by the duration of procedure (first sedative/analgesic until scope-out) is presented in Figure 50.

Figure 50
Distribution of Subjects by Duration of Procedure

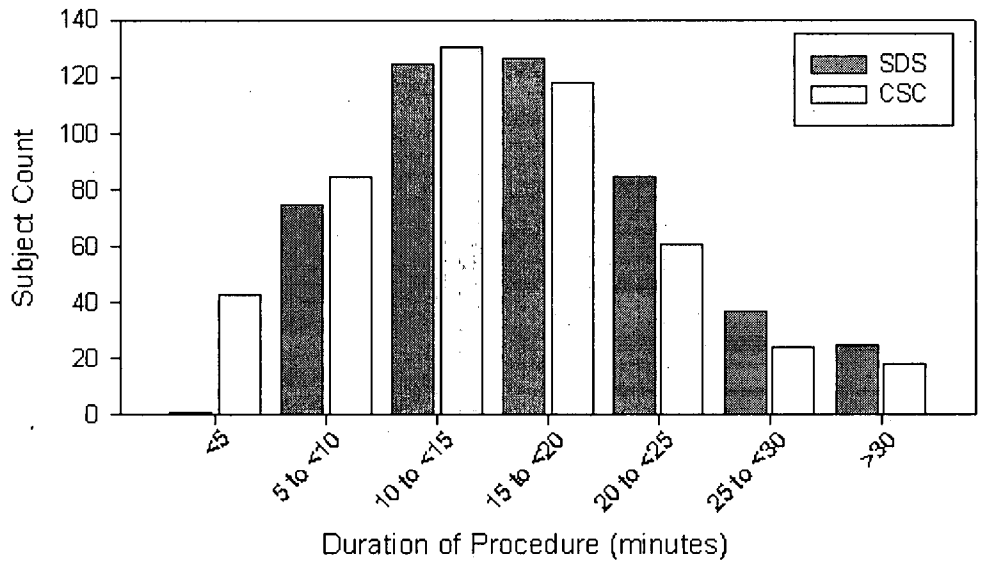


Figure 51 presents duration of procedure and AUC_{Desat} data for all subjects in the pivotal study that had an oxygen desaturation. The data suggests that there was no relationship between the duration of the procedure and oxygen desaturation.

Figure 51
All Subjects With $AUC_{Desat} > 0$, With Relationship to Duration of Procedure

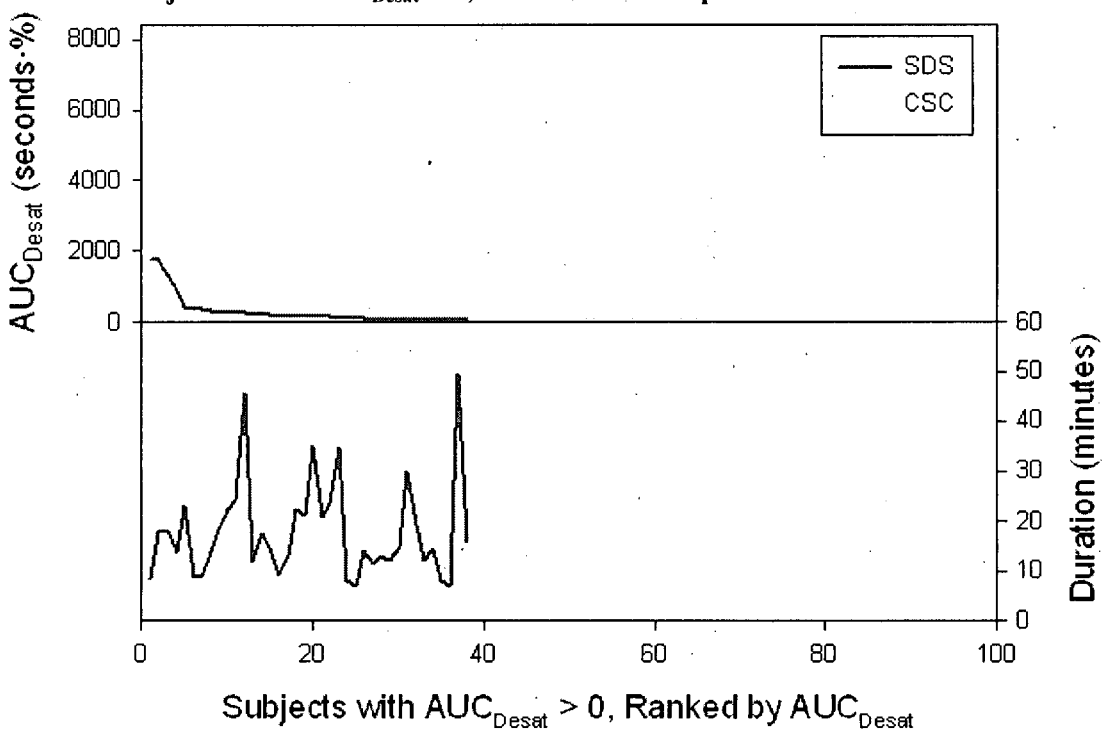


Table 56 presents the mean AUC_{Desat} data with subjects stratified the duration of the procedure.

Table 56
AUC_{Desat} (seconds•%) – By Duration of Procedure

Procedure Time (minutes)	SDS	CSC
< 5 (n = 44)	0	33 ± 154
5 to < 10 (n = 160)	41 ± 213	51 ± 133
10 to < 15 (n = 256)	19 ± 94	107 ± 354
15 to < 20 (n = 245)	29 ± 195	78 ± 375
20 to < 25 (n = 146)	19 ± 70	130 ± 903
25 to < 30 (n = 61)	2 ± 11	126 ± 434
> 30 (n = 42)	24 ± 63	150 ± 612

In the CSC group, there appears to be an upward trend in AUC_{Desat} with increasing duration of procedure. Whereas, the trend is not seen in the SDS group.

3.3 Mean Sedative and Analgesic Dose

Colonoscopy

Table 57 summarizes the mean dose of sedatives (propofol and midazolam) and analgesics (fentanyl and meperidine) administered to subjects undergoing a colonoscopy during the study.

Table 57
Amount of Sedatives and Analgesics Administered
Colonoscopy Procedure

Medication	SDS	CSC
Propofol (mg)	106 ± 57	1.0 ± 11
Midazolam (mg)	0	4.8 ± 2.2
Fentanyl (µg)	74 ± 23	111 ± 40[a]
Meperidine (mg)	0	44 ± 16[b]

[a] 5 sites used fentanyl as the analgesic for CSC.
[b] 3 sites used meperidine as the analgesic for CSC.

EGD

Table 58 summarizes the mean dose of sedatives (propofol and midazolam) and analgesics (fentanyl and meperidine) administered to subjects undergoing an EGD during the study.

Table 58
Amount of Sedatives and Analgesics Administered
EGD Procedure

Medication	SDS	CSC
Propofol (mg)	70 ± 37	0
Midazolam (mg)	0	4.3 ± 2.1
Fentanyl (µg)	66 ± 22	69 ± 51[a]
Meperidine (mg)	0	42 ± 19[b]

[a] 5 sites used fentanyl as the analgesic for CSC.
[b] 3 sites used meperidine as the analgesic for CSC.

Propofol Dose Details

Table 59 summarizes the mean dose of propofol by maintenance rate (MR) and loading dose (LD). For colonoscopy subjects, 73% of the total propofol dose was from the maintenance rate and 27% from PRNs. For EGD subjects, 62% of the total propofol dose was from the maintenance rate and 38% from PRNs.

Table 59
Summary of Propofol Dose
Colonoscopy and EGD Procedures

Parameter	Colonoscopy	EGD
Total Dose (mg)	105 ± 54	70 ± 37
Total MR Dose (mg)	77 ± 37	43 ± 22
Total PRN Dose (mg)	28 ± 28	27 ± 21

3.4 Cardiorespiratory Measures

Assessments of cardiorespiratory measures were performed on subjects who underwent a colonoscopy or EGD, both prior to and following the removal of artifact events, using both subject means and worst case.

The following analysis was conducted on:

- Subgroup per-protocol population (subjects that had an event)
- With artifact removed
- Using worst case events from each subject

Oxygen desaturation events were defined as oxygen saturation less than 90% that lasted longer than 15 seconds.

Apnea events were defined as the absence of respiratory activity for 30 seconds or longer.

Bradycardia events were defined as a heart rate less than 50 beats per minute, or 80% of baseline (whichever is lower) that lasted longer than 30 seconds.

Hypotension events were defined as two (or more) consecutive systolic blood pressure measurements less than 80 mmHg, or 80% of baseline (whichever is lower).

Colonoscopy

Table 60 summarizes the oxygen desaturation, apnea, bradycardia, and hypotension events for those subjects who had an event while undergoing a colonoscopy.

Table 60
Summary of Cardiorespiratory Events
Worst Case Events with Artifact Removed
Colonoscopy Procedure

Parameter	SDS	CSC
Desaturation		
Subjects (n)	18	56
Duration of events (seconds)	40 ± 30	68 ± 70
Magnitude of events (%)	82 ± 4.3	82 ± 9.2
Apnea		
Subjects (n)	127	119
Duration of events (seconds)	50 ± 15	51 ± 23
Bradycardia		
Subjects (n)	10	4
Duration of events (seconds)	72 ± 32	121 ± 89
Magnitude of events (beats per minute)	43 ± 3.6	41 ± 3.4
Hypotension		
Subjects (n)	8	5
Duration of events (seconds)	371 ± 195	184 ± 93
Magnitude of events (mmHg)	67 ± 8.2	71 ± 4.3

There were 3 times as many subjects in the CSC group who had an oxygen desaturation event, compared to the SDS group.

EGD
Table 61 summarizes the oxygen desaturation, apnea, bradycardia, and hypotension events for those subjects who had an event while undergoing an EGD.

Table 61
Summary of Cardiorespiratory Events
Worst Case Events with Artifact Removed
EGD Procedure

Parameter	SDS	CSC
Desaturation		
Subjects (n)	17	24
Duration of events (seconds)	38 ± 23	58 ± 43
Magnitude of events (%)	80 ± 8.5	82 ± 5.0
Apnea		
Subject (n)	52	57
Duration of events (seconds)	49 ± 18	55 ± 23
Bradycardia		
Subjects (n)	2	0
Duration of events (seconds)	138 ± 8.5	0
Magnitude of events (beats per minute)	40 ± 4.2	0
Hypotension		
Subjects (n)	0	0

Oxygen desaturation, apnea, and hypotension events were similar for subjects in both treatment groups who underwent an EGD.

3.5 Completed Procedures

Colonoscopy
The cecum was reached in 346 (97%) subjects in the SDS group and to 344 (95%) subjects in the CSC group.

The duration of time required to reach the cecum was similar for both groups (7.4 ± 4.3 minutes and 6.9 ± 3.6 minutes, in the SDS and CSC groups, respectively).

The review of listing data revealed that 4 of 9 subjects in the SDS group reported as not reaching the cecum were because those subjects had no cecum due to prior surgery. Five of 11 subjects in the CSC group reported as not reaching the cecum were because those subjects had no cecum due to prior surgery.

EGD
The duodenum was reached in 134 (97%) subjects in the SDS group and to 139 (99%) subjects in the CSC group.

There was no difference between groups in the duration of time required to reach the duodenum (1.3 ± 1.1 minutes and 1.4 ± 1.0 minutes in the SDS and CSC groups, respectively).

The review of listings revealed that the subject in the SDS group, reported as not reaching the duodenum was because that subject had no duodenum due to prior surgery.

3.6 Procedure Time

Colonoscopy
The mean procedure time (scope-in to scope-out) was similar for both groups (13.4 ± 5.7 minutes and 13.3 ± 5.6 minutes, in the SDS and CSC groups, respectively).

The maximum procedure times were 41.6 minutes in the SDS group and 51.5 in the CSC group.

EGD
The mean procedure time (scope-in to scope-out) was similar for both groups (3.7 ± 2.2 minutes and 3.9 ± 2.4 minutes, in the SDS and CSC groups, respectively).

The maximum procedure times were 12.6 minutes in the SDS group and 15.9 in the CSC group.

3.7 Detection of Polyps

Colonoscopy
There was no difference in the number of subjects (121 [34%]) undergoing a colonoscopy in the SDS group who were found to have polyps, when compared with the CSC group (125 [35%]). In the subjects with polyps, the number of polyps per subject was 1.8 ± 1.6 in the SDS group and 2.0 ± 1.5 in the CSC group.

EGD
There was no difference in the number of subjects (5 [3.5%]) undergoing an EGD in the CSC group who were found to have polyps, when compared with the SDS group (2 [1.4 %]). In the subjects with polyps, the number of polyps per subject was 2.0 ± 2.2 in the CSC group and 1.5 ± 0.7 the SDS group.

3.8 Oxygen Delivery

The delivery of oxygen to subjects in the study was similar between treatment groups, when viewed on an L/min basis (Table 62). The SEDASYS System delivers supplemental oxygen at 2 L/min when the patient's oxygen saturation is greater than 96%. The system automatically increases oxygen delivery if the patient's saturation is less than, or equal to, 96%. This results in a mean oxygen delivery rate greater than 2 L/min, for both procedures.

Table 62
Mean Oxygen Delivery Rate

O_2 (L/min)	SDS	CSC
Colonoscopy	2.3 ± 0.8	2.2 ± 0.6
EGD	2.4 ± 0.7	2.1 ± 0.3

Per study protocol, all sites were required to deliver supplemental oxygen, at 2 L/min, in the current standard of care, even if was not part of there standard practice. Investigators increased the delivery of oxygen when they deemed clinically necessary, resulting in a mean delivery rate greater than 2 L/min, for both procedure.

A better way to view oxygen delivery is to look at oxygen delivered to those in need; i.e. subjects with an oxygen desaturation.

Colonoscopy
Table 63 presents data regarding oxygen delivery to colonoscopy subjects during an oxygen desaturation event (SpO_2 < 90% for > 15 seconds). Due to the automatic increase in oxygen delivery at SpO_2 = 96%, subjects in the SEDASYS System group were receiving oxygen at greater than 2 L/min during all 32 desaturation events; whereas, subjects in the current standard of care group did not receive additional oxygen during 53 (38%) of their 140 desaturation events.

Table 63
Oxygen Delivery During Oxygen Desaturation – Colonoscopy

	SDS	CSC
Desaturation Events	32	140
O_2 > 2 L/min	32 (100%)	61 (44%)
O_2 = 2 L/min, then increased during event	0	26 (19%)
O_2 = 2 L/min, with no increase during event	0	53 (38%)

Oxygen desaturation = SpO_2 < 90% for > 15 seconds.

EGD
Table 64 presents data regarding oxygen delivery to EGD subjects during an oxygen desaturation event (SpO_2 < 90% for > 15 seconds). Due to the automatic increase in oxygen delivery at SpO_2 = 96%, subjects in the SEDASYS System group were receiving oxygen at greater than 2 L/min during all 20 desaturation events; whereas, subjects in the current standard of care group did not receive additional oxygen during 30 (70%) of their 43 desaturation events.

Table 64
Oxygen Delivery During Oxygen Desaturation – EGD

	SDS	CSC
Desaturation Events	20	43
O_2 > 2 L/min prior	20 (100%)	4 (9%)
O_2 = 2 L/min prior, then increased during event	0	9 (21%)
O_2 = 2 L/min prior, with no increase during event	0	30 (70%)

Oxygen desaturation = SpO_2 < 90% for > 15 seconds.

3.9 Recovery of Psychomotor Skills

Colonoscopy
The mean change from baseline in psychomotor test scores was defined as the subject's baseline score subtracted from the subject's post sedation score. At the time of recovery, subjects in the SDS group had recovered greater than 99% of their baseline psychomotor skills, compared with the CSC group that recovered only 73% of their baseline psychomotor skills. This indicates that subjects in the SDS group recovered psychomotor skills more rapidly than subjects in the CSC group.

Thirty minutes after the time of recovery, subjects in the SDS group had surpassed their baseline psychomotor skills by 16% (probably due, in part, to a learned effect), compared to subjects in the CSC group who had only surpassed their baseline psychomotor skills by 3% (also probably due, in part, to a learned effect).

EGD
At the time of recovery, subjects in the SDS group had surpassed their baseline psychomotor skills by 8% (probably due, in part, to a learned effect), compared with the CSC group that recovered only 63% of their baseline psychomotor skills. This indicates that subjects in the SDS group recovered psychomotor skills more rapidly than subjects in the CSC group.

Thirty minutes after the time of recovery, subjects in the SDS group had surpassed their baseline psychomotor skills by 33%, compared to subjects in the CSC group who had just recovered their baseline psychomotor skills.

4.0 LISTING OF ADVERSE EVENTS BY CRF VERBATIM TEXT

4.1 Colonoscopy

Table 65
Listing of Adverse Events
Current Standard of Care – Colonoscopy

Subject	Time Period	CRF Verbatim Text	Action Taken	Procedure Related	Study Device Related	Drug Related	Severity	SAE?
[redacted]	Post-op	Worsening Abdominal Pain	Administered Methscopolamine	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Flatulence	Drug Therapy	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	IV Site Swelling	Dc'd IV Pressure Applied	Probably	Not Related	Not Related	Mild	No
[redacted]	Post-op	Vomiting	None	Possibly	Not Related	Possibly	Mild	No
[redacted]	Post-op	Atypical Chest Pain "Appeared To Be Related To GI Symptoms"	Drug Therapy	Probably	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Blood With Bowel Movement	None	Probably	Not Related	Not Related	Mild	No
[redacted]	Post-op	Diarrhea	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	None	Probably	Not Related	Possibly	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Oxygen Flow Increased	Not Related	Not Related	Definitely	Mild	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increase Oxygen Flew	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygenation	Not Related	Not Related	Definitely	Moderate	No

Subject	Time Period	CRF Verbatim Text	Action Taken	Procedure Related	Study Device Related	Drug Related	Severity	SAE?
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Worsening Oxygen Desaturation	Bag-Mask Ventilation	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Post-op	Hemmorroid	Drug Therapy	Possibly	Not Related	Not Related	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Oxygen Flow Increased	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Post-op	Nausea	Drug Therapy	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Diarrhea	Drug Therapy	Not Related	Not Related	Not Related	Mild	No
[redacted]	Intraop	Vomiting	None	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Crohn's Ileitis	Drug Therapy	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Partial Small Bowel Obstruction	Drug Therapy/Hospitalization	Definitely	Not Related	Not Related	Severe	Yes

Table 66
Listing of Adverse Events
SEDASYS System – Colonoscopy

Subject	Time Period	CRF Verbatim Text	Action Taken	Procedure Related	Study Device Related	Drug Related	Severity	SAE?
[redacted]	Pre-op	Headache	Drug Therapy	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Abdominal Bloating	Drug Therapy	Probably	Not Related	Not Related	Mild	No
[redacted]	Post-op	Gas	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Dizziness	None	Probably	Not Related	Possibly	Mild	No
[redacted]	Post-op	Nausea	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Intraop	Tingling At IV Site	None	Not Related	Not Related	Possibly	Mild	No
[redacted]	Post-op	Sinus Headache	None	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Fever	Drug Therapy	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	Drug Therapy	Possibly	Not Related	Not Related	Mild	No
[redacted]	Intraop	Apnea	Rub Sternum	Not Related	Not Related	Probably	Mild	No
[redacted]	Post-op	Abdominal Cramping	None	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	None	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	None	Probably	Not Related	Not Related	Mild	No
[redacted]	Post-op	Vomiting	None	Probably	Not Related	Not Related	Mild	No
[redacted]	Pre-op	Hypotension	None	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Abdominal Pain	Drug Therapy	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Vomiting	None	Not Related	Not Related	Not Related	Moderate	No
[redacted]	Intraop	Hypertension	None	Not Related	Not Related	Possibly	Mild	No
[redacted]	Post-op	Abdominal Cramping	Drug Therapy	Probably	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Abdominal Pain	Drug Therapy	Not Related	Not Related	Not Related	Severe	No
[redacted]	Post-op	Stiff Neck	Drug Therapy	Not Related	Not Related	Not Related	Mild	No
[redacted]	Pre-op	Burning At IV Site	None	Not Related	Not Related	Possibly	Mild	No
[redacted]	Intraop	Head Tremors	None	Not Related	Not Related	Definitely	Mild	No
[redacted]	Intraop	Right Hand Tremors	None	Not Related	Not Related	Definitely	Mild	No
[redacted]	Intraop	Body Trembling	Reduced Propofol Infusion	Unknown	Not Related	Unknown	Mild	No

4.2 EGD

Table 67
Listing of Adverse Events
Current Standard of Care – EGD

Subject	Time Period	CRF Verbatim Text	Action Taken	Procedure Related	Study Device Related	Drug Related	Severity	SAE?
[redacted]	Post-op	Sore Throat	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Intraop	Infiltration At IV Site Right Antecubital	Hot Compresses And Elevation Of Right Arm	Definitely	Not Related	Not Related	Mild	No
[redacted]	Post-op	Nausea	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Sore Throat	Drug Therapy	Probably	Not Related	Not Related	Moderate	No
[redacted]	Post-op	Nausea	Drug Therapy	Possibly	Not Related	Not Related	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Possibly	Not Related	Probably	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Oxygen Desaturation	Increased Oxygen Flow	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Post-op	Sore Throat	None	Possibly	Not Related	Not Related	Moderate	No

Table 68
Listing of Adverse Events
SEDASYS System EGD

Subject	Time Period	CRF Verbatim Text	Action Taken	Procedure Related	Study Device Related	Drug Related	Severity	SAE?
[redacted]	Intraop	Vomiting Worsening	None	Possibly	Not Related	Possibly	Mild	No
[redacted]	Intraop	Anxiety	None	Not Related	Not Related	Not Related	Mild	No
[redacted]	Post-op	Dizziness	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Hoarse Voice	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Post-op	Esophageal Pain	None	Possibly	Not Related	Not Related	Mild	No
[redacted]	Intraop	Oxygen Desaturation	Tongue Depressor	Not Related	Not Related	Definitely	Moderate	No
[redacted]	Intraop	Worsening Hypertension	Drug Therapy	Not Related	Not Related	Not Related	Mild	No
[redacted]	Intraop	Rash On Chest And Back	Drug Therapy	Not Related	Not Related	Possibly	Mild	No

5.0 SYSTEM MALFUNCTIONS

Additional details regarding the 23 clinical study device failures and related post-study device modifications are provided in Table 69. In addition, the clinical implications of each of the failures, *had* they occurred during a procedure, are described. The discussions regarding "*the clinical implications of each failure if they had occurred during a procedure*" are based on the design of the SEDASYS System, prior to any modification based on the failures seen in the pivotal study.

Table 69
Device Malfunctions During Pivotal Study

Device Malfunction	Clinical Implications Had Failure Occurred During a Procedure	Post-Study Device Modification
Failure of the high-pressure relief valve in the PRU oxygen manifold. The failure was caused by user error: the pressure regulator on the oxygen tank was inadvertently opened to maximum pressure; exceeding the SEDASYS System's rated input specification.	This failure could only have occurred during a procedure if the pressure regulator on the oxygen source was manually adjusted, during the procedure, to a pressure greatly exceeding the system's input specifications. The failure would have been obvious to the user as compressed oxygen rushed through the damaged relief valve, producing a loud "hissing". Additionally, the system would have alerted the clinical team through an Advisory that there was a problem with the oxygen delivery module. The failure would not have lead to an unsafe condition because, in response to a failure of any part of the oxygen delivery module during a procedure, the SEDASYS System would have stopped propofol infusion (see original PMA submission *Section 5.5.2 Safety Shell*). All physiological monitoring would have continued without interruption.	No post-study device modifications have been made to address this failure. However, detailed instructions have been added to of the Clinical User Guide/Operator's Manual for the SEDASYS System that describes the proper method of connecting the PRU to an oxygen source.

Device Malfunction	Clinical Implications Had Failure Occurred During a Procedure	Post-Study Device Modification
Failure of the pulse oximeter module. The failures (2) occurred at the start of day, prior to the conduct of any procedure. These failures were caused by 'invalid' values coming from the OEM pulse oximeter board during the BMU's 'power-on self test'.	If the pulse oximeter module had failed during a procedure due to 'invalid' data, the SEDASYS System would have stopped the propofol. The failure would have been obvious to the user as the system would have alerted the clinical team through an Advisory that the pulse oximeter had failed. All other physiological monitoring would have continued without interruption.	No post-study device modifications have been made to address these failures. The failure mode was not able to be reproduced in subsequent testing. Additionally, when the "invalid' data was communicated, the BMU software behaved as expected per design requirements: preventing entry into a new case.
Failure of the PRU display monitor module. The failure was caused by a damaged power control chip in the PRU display power circuit.	For this failure to have occurred during a procedure, the umbilical cable would have to have been disconnected and re-connected during the procedure. If the failure had occurred during a procedure it would have been immediately obvious to the clinical team; the PRU monitoring screen would have been blank. Without an active user interface through the PRU, the user would have terminated the propofol infusion via the BMU. The patient would have continued to be monitored by the BMU until discharge from the facility.	The hot swap circuit on the PRU System I/O board was modified to limit current surge during connection of the BMU to the PRU via the umbilical cable. A surge could damage components and cause a drop in the 28 VDC supply rail resulting in lock up of sub-modules.
Failure of the BMU wireless printer module. These failures (3) were caused by a communication conflict between the wireless printer module in the BMU and the facility's wireless network.	This failure could not have occurred during a procedure. The BMU configures the wireless network only during the power-up sequence.	In summary, due to an issue in the wireless LAN driver in the BMU software, an infinite loop was triggered while trying to configure the network and the system would lock-up during the power up sequence. The wireless LAN driver has been updated to correct this issue.

Device Malfunction	Clinical Implications Had Failure Occurred During a Procedure	Post-Study Device Modification
Failure of data transfer between the BMU and PRU. The failure was caused by the BMU collecting a large amount of pre-procedure data, overwhelming the fixed buffer allocated for storing on the PRU upon connection.	This failure could not have occurred during a procedure. Pre-procedure data transfer from the BMU to the PRU occurs pre-procedure, at connection of the BMU to the PRU via the umbilical cable.	The PRU software has been modified to replace the fixed memory partition allocated for storing pre-procedure data with dynamic allocation of memory depending on the size of the pre-procedure case log received from the BMU at connection.
Failure in the BMU power management subsystem. These failures (6) were caused by a current surge in the power input circuit resulting in the blowing of an internal fuse. The BMU's batteries would continue to drain and would not charge.	This failure could not have occurred during a procedure. For the failure to occur, the BMU battery voltage level must be well below the threshold where the system software would allow a new case to begin. Further, it can only occur at connection of the BMU to an external power supply.	The BMU battery charger circuit has been modified to prevent inadvertent fuse damage while continuing to provide short circuit protection. A trickle current is provided to the battery to get the battery out of safety cut-off prior to allowing the normal battery charging to take place. This prevents the overvoltage protection circuit from seeing an open circuit charger voltage higher than expected which could result in a blown fuse.

Device Malfunction	Clinical Implications Had Failure Occurred During a Procedure	Post-Study Device Modification
Failure of the oral/nasal cannula. These failures (9) were caused by misalignment of a gasket when the oral/nasal cannula is connected to the BMU resulting in the inability of the system to detect respiration rate.	For this failure to have occurred during a procedure the oral/nasal cannula would have to have been disconnected and re-connected during the procedure. Had the cannula been disconnected and re-connected during the procedure, resulting in a damaged gasket, the SEDASYS System would have been unable to detect respiration rate. This would have triggered an apnea alarm and stopped propofol delivery. In response, the clinical team could have replaced the damaged oral/nasal cannula, restoring accurate measurement of respiration rate. Or they could have continued the procedure without delivering a maintenance infusion of propofol (i.e., already in the scope withdrawal phase of the procedure) due to the absence of a respiration rate. All other physiological monitoring would have continued without interruption.	The oral/nasal cannula connector has been modified to prevent the capnometry sampling interface gaskets from being damaged during connection to the BMU. Specifically, the connector portion of the oral/nasal cannula was modified to ensure that the rigid alignment pins would engage the mating BMU feature prior to engagement of the flexible gasket, especially during off-axis connection.

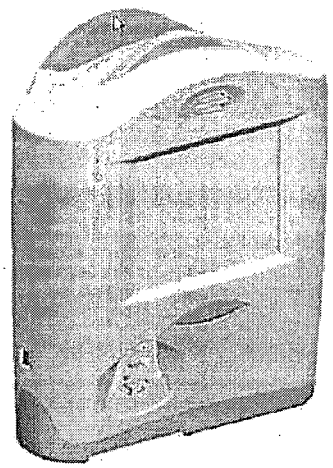
Exhibit B
Additional Device Descriptions

1.0 DEVICE COMPONENTS

1.1 Bedside Monitoring Unit

The Bedside Monitoring Unit monitors patient physiologic parameters during all phases of the clinical procedure. It is self-powered allowing it to stay with the patient throughout the procedure flow from the pre-procedure room, to the procedure room, and finally the recovery room. While in the procedure room, it is connected to the Procedure Room Unit and the physiologic parameters monitored by it are displayed on the Procedure Room Unit. The Bedside Monitoring Unit contains hardware and software to allow it to monitor patient arterial saturation (SpO_2), blood pressure (NIBP), and heart rate (and display of the ECG). It also contains the hardware and software to monitor the patient's responsiveness utilizing the novel automated responsiveness monitor. Figure 52 is an illustration of the Bedside Monitoring Unit.

Figure 52
Bedside Monitoring Unit

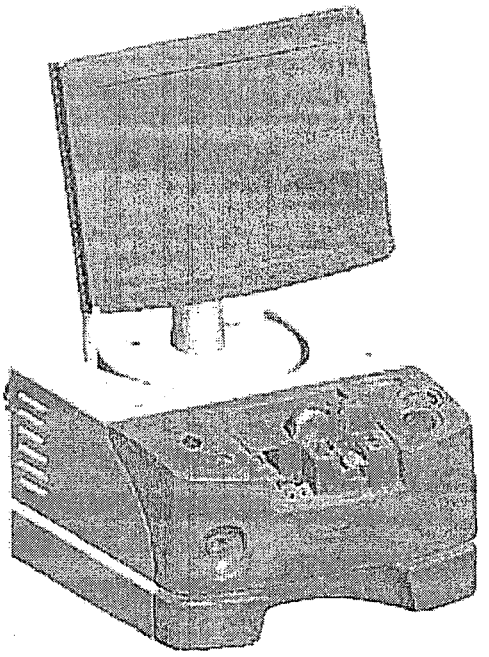


1.2 Procedure Room Unit

The Procedure Room Unit is designed to remain in the procedure room. It contains the drug delivery unit, which includes the infusion pump and algorithms (drug delivery algorithms and safeguards) that drive the delivery of 1% propofol injectable emulsion. Capnometry is incorporated into the system to monitor the patient's respiration rate and end-tidal carbon dioxide. An oxygen regulator provides oxygen delivery during procedures. The Procedure Room Unit contains the primary user interface, displaying all patient monitored patient data and providing means for user input of propofol dose rate. Figure 53 is an illustration of the Procedure Room Unit.

The Procedure Room Unit contains a battery-powered backup system that allows up to 10 minutes of use to complete or terminate the procedure should AC power be lost.

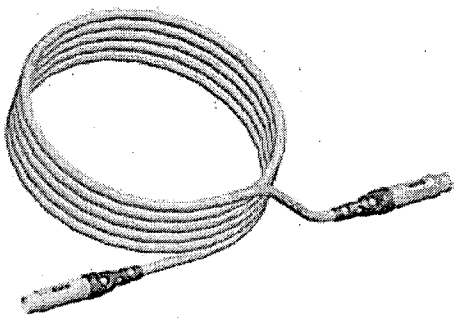
Figure 53
Procedure Room Unit



1.3 Umbilical Cable

The umbilical cable provides communication, power, and pneumatic connections between the Procedure Room Unit and the Bedside Monitoring Unit. The connectors on either end of the umbilical cable are identical. Therefore, either end of the cable can be connected to the Bedside Monitoring Unit or the Procedure Room Unit. The umbilical cable is connected to the Procedure Room Unit at all times. Figure 54 is an illustration of an umbilical cable.

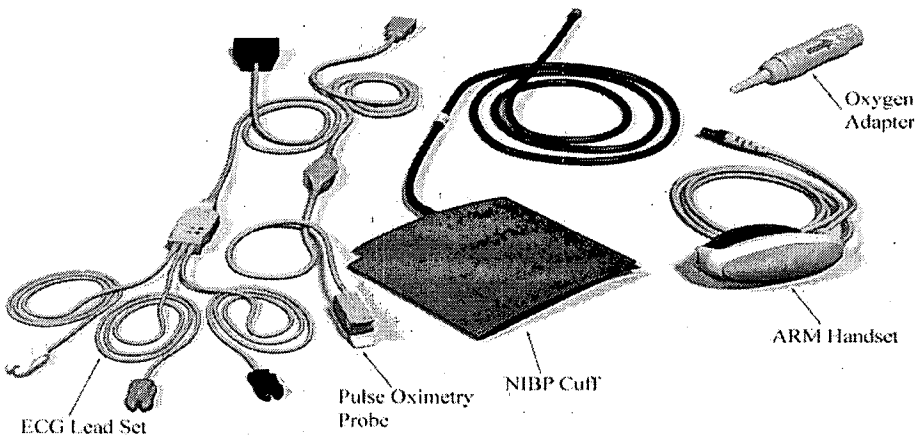
Figure 54
Umbilical Cable



1.4 Multiple Patient Use Items

The SEDASYS System utilizes five Multiple Patient Use items: 1) pulse oximetry probe (and extension cable), 2) ECG lead set (and extension cable), 3) NIBP cuff (and extension tubing), 4) automated responsiveness monitor (ARM) handset, and 5) an oxygen adapter, allowing connection of the Bedside Monitoring Unit directly to an oxygen source. Figure 55 is an illustration of the Multiple Patient Use items.

Figure 55
Multiple Patient Use Items



Pulse Oximetry Probe – The pulse oximetry probe is a clip-on type finger probe sensor utilizing infrared light to measure the patient's arterial oxygen level (SpO_2) and heart rate.

ECG Lead Set – The SEDASYS System uses a three lead ECG for measuring the patient's heart rate and display of the ECG waveform.

NIBP Cuff – Four different adult sized cuffs are supplied.

ARM Handset – The automated responsiveness monitor (ARM) handset provides mild tactile stimulus to the patient and feedback to the SEDASYS System as to the level of patient responsiveness. The ARM handset is ergonomically designed to fit comfortably in the patient's hand and includes a strap to retain the handset in the palm of the hand.

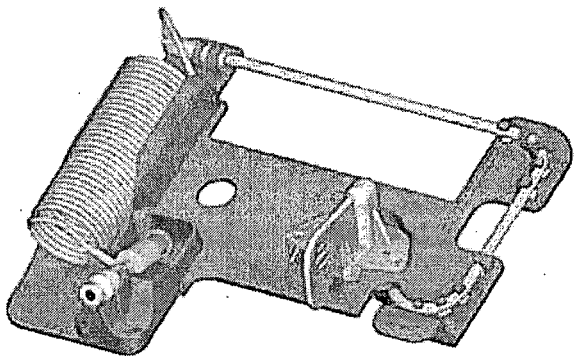
Oxygen Adapter – The oxygen adapter provides a means for connecting the Bedside Monitoring Unit to an oxygen supply when the Bedside Monitoring Unit is not connected to the Procedure Room Unit. The oxygen adapter includes a barbed fitting to connect to tubing from a facility oxygen supply.

1.5 Single Patient Use Items

The SEDASYS System uses three Single Patient Use disposable items; 1) a drug delivery cassette for delivering propofol to the patient; 2) an oral/nasal cannula for supplying oxygen to, and collecting exhaled gases from, the patient; and 3) a bite block for use with EGD patients.

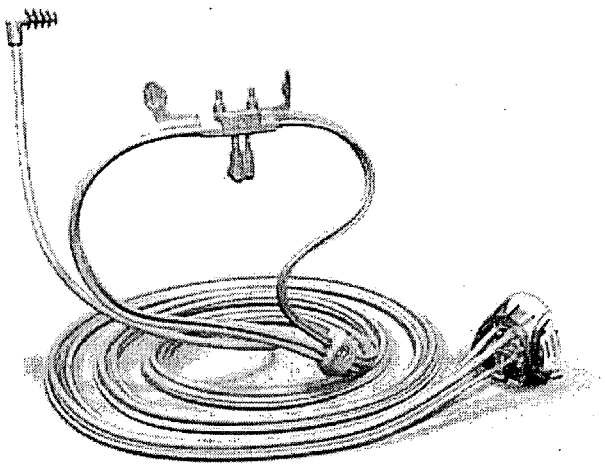
Drug Delivery Cassette – The drug delivery cassette is used for delivering 1% propofol to the patient directly from the drug vial. It is comprised of a rigid plastic base, vial spike with protective cover, infusion tubing, and t-site connector. The entire assembly is packaged sterile. Figure 56 is an illustration of the Drug Delivery Cassette.

Figure 56
Drug Delivery Cassette



Oral/Nasal Cannula – The oral/nasal cannula consists of three gas sampling ports (the left and right nares and the mouth) for carbon dioxide analysis. There are outlets on both the nasal and oral side of the cannula for oxygen delivery. Figure 57 is an illustration of the Oral/Nasal Cannula.

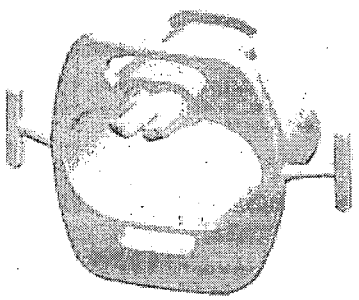
Figure 57
Oral/Nasal Cannula



The ear piece is made of a soft pliable plastic that can be comfortably fitted into the patient's ear. Approximately six feet of PVC tubing extends between the oral/nasal cannula face piece (and ear piece) and a connector designed to securely attach the oral/nasal cannula assembly to the Bedside Monitoring Unit.

Bite Block – The bite block is used to ensure function of the oral/nasal cannula in the presence of an endoscope or esophageal dilator during EGD procedures. Figure 58 is an illustration of the Bite Block.

Figure 58
Bite Block



1.6 Printing

A printed record of current patient physiology and current propofol dosing information can be obtained, on a wireless printer, at any time during a procedure. Figure 59 is a sample of the printout.

Figure 59
Sample Procedure Printout

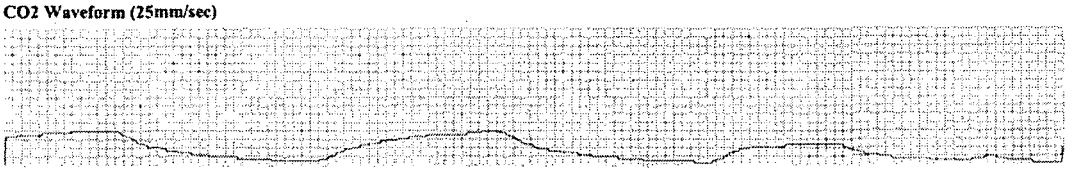
STAT Print - PRU

ID: 15M89 **Weight (kg): 30** **Date: August 30, 2007** **Time: 02:03:27 PM** **Page 1 of 1**

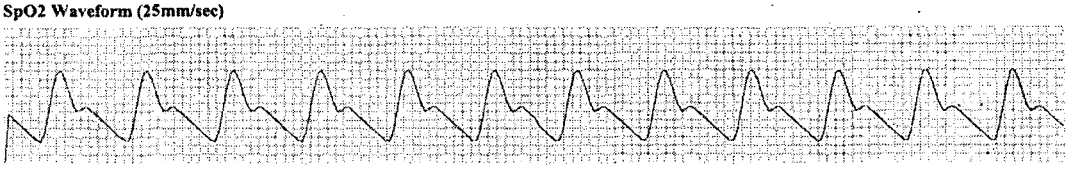
SpO2 (%)	HR (bpm)	Systolic (mmHg)	Diastolic (mmHg)	RR (breaths /min)	EtCO2 (mmHg)	O2 (Lpm)	Response	Dose Rate (mcg/kg/min)	PRN (mg)	Total Propofol (mg)
96	75	122	82	17	17	5	2 sec	---	---	---

[**]Alarm Event [---]Data Not Available [D]Drug Change Event [♥]HR from ECG

CO2 Waveform (25mm/sec)



SpO2 Waveform (25mm/sec)



ECG Waveform (25mm/sec)

At the completion of a case, a printed summary of the procedure is sent to the wireless printer. The printed record contains patient physiology and propofol delivery information collected throughout the procedure at the selected data collection interval. Figure 60 is a sample of the printed record.

Figure 60
Sample End Case Summary Printout

End Case Summary

ID: [redacted] **Weight (kg): 30** **Date: August 29, 2007** **Time: 23:12:23** **Page 1 of 2**

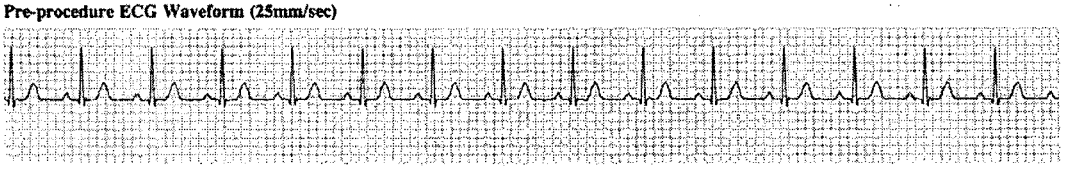
Time	SpO2 (%)	HR (bpm)	Systolic (mmHg)	Diastolic (mmHg)	RR (breaths /min)	EtCO2 (mmHg)	O2 (Lpm)	Response	Dose Rate (mcg/kg/min)	PRN (mg)	Total Propofol (mg)
Pre-procedure											
23:05:47	95	100	120	80	---	---	---	---	---	---	---
23:06:38	95	100	120	80	---	---	---	---	---	---	---
Procedure											
23:08:20	95	100	120	80	12	38	5	Yes	---	---	---
23:09:20	95	100	120	80	12	38	5	Yes	---	---	---
23:10:20	95	100	120	80	12	38	5	Yes	---	---	---
Post-procedure											
23:12:07	95	100	120	80	---	---	---	---	---	---	---
23:12:23	95	100	120	80	---	---	---	---	---	---	---

[**]Alarm Event [---]Data Not Available [D]Drug Change Event [♥]HR from ECG

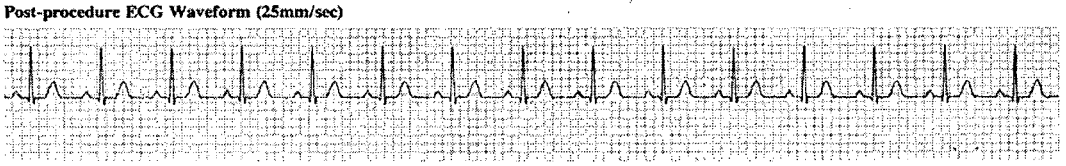
End Case Summary

ID: [redacted] **Weight (kg): 30** **Date: August 29, 2007** **Time: 23:12:23** **Page 2 of 2**

Pre-procedure ECG Waveform (25mm/sec)



Post-procedure ECG Waveform (25mm/sec)



1.7 Packaging and Sterilization

1.7.1 Bedside Monitoring Unit and Procedure Room Unit

This capital equipment is placed in a polyethylene plastic bag and then in a corrugated shipper box.

1.7.2 Multiple Patient Use Items

- The automated responsiveness monitor handset is packaged in a polyethylene bag and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The pulse oximeter probe is packaged in a white board box. It is placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The pulse oximeter cable is wrapped in anti-static bubble wrap and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The ECG leads are packaged in a polyethylene zip lock bag and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The ECG trunk cable is packaged in a polyethylene zip lock bag and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The NIBP cuffs are individually packaged in a polyethylene zip lock bag and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.
- The NIBP extension tube is packaged in a polyethylene zip lock bag and placed within the divider set of the Bedside Monitoring Unit/Multiple Patient Use shipping case.

1.7.3 Single Patient Use Items

- Each oral/nasal cannula is packaged in a polyethylene bag with a special "Unitear" opening feature. Packaged oral/nasal cannulas are packed 20 units to a corrugated shipping case lined with a polyethylene bag.
- The drug delivery cassette is the only item shipped sterile. Each cassette is packaged in a Flexible Tyvek/Film peel pouch. Packaged drug delivery cassettes are packed 20 units to a corrugated shipping case lined with a polyethylene bag. The drug delivery cassettes are Gamma radiation sterilized at a minimum dose of 25 kGy and maximum dose of 45 kGy. The package product has a Sterility Assurance Level (SAL) of 10^{-6}.
- Each bite block (both large and small) with retention strap attached, is packaged in a polyethylene bag. Packaged bite blocks are packed 50 units to a corrugated shipping case that is lined with a polyethylene bag.

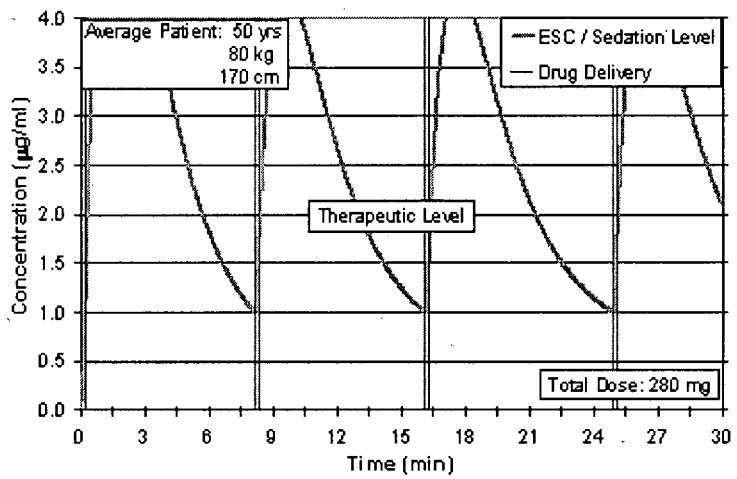
2.0 Rationale for Drug Delivery Algorithms

2.1 Loading Dose and Maintenance Rate

The objective of sedation is to produce a clinically desired time course of minimal-to-moderate sedation, while minimizing undesirable side effects. This time course is rapid onset, smooth maintenance, and rapid recovery.[26,27]

In the current practice of sedation, most clinicians employ the intermittent bolus technique. This technique results in excessive drug effect at the time of the bolus, inadequate drug effect before the next bolus, or both.[28] Figure 61 demonstrates, using a pharmacokinetic model[29,30] the intermittent bolus technique, using large boluses of propofol. In Figure 61, ESC stands for the effect-site concentration of propofol. As can be seen, there are extended periods where the patient would have been under-sedated and larger periods where the patient was over-sedated, and therefore, at greater risk. This clearly does not represent "smooth maintenance" of sedation.

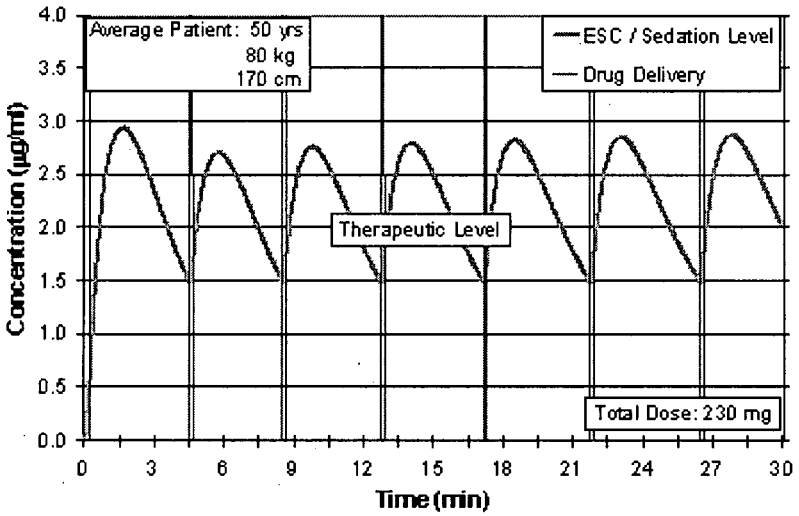
Figure 61
Sedation With Intermittent Bolus Technique



[26] Miller RD (ed). 2000. *Anesthesia (5th Edition).* Philadelphia: Churchill Livingstone. Chapters 2, 9, and 11.
[27] Barash PG, Cullen BF, and Stoelting RK (eds). 2001. *Clinical Anesthesia (4th Edition).* Philadelphia: Lippincott Williams & Wilkins. Chapters 11 and 13.
[28] Stoelting RK. 1999. *Pharmacology & Physiology in Anesthetic Practice (3rd Edition).* Philadelphia: Lippincott-Raven. Chapters 1 and 6.
[29] Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. 1998. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 88:1170-82.
[30] Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. 1999. The influence of age on propofol pharmacodynamics. *Anesthesiology* 90:1502-16.

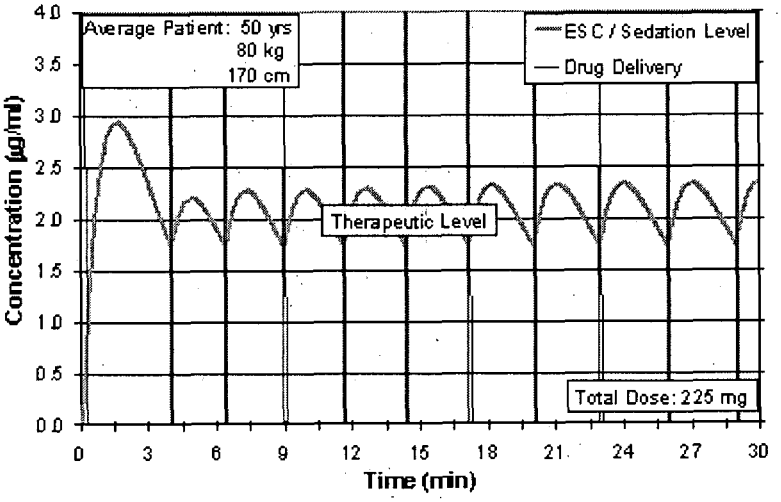
To reduce the periods of under- and over-sedation, the clinician can deliver smaller boluses more frequently. In Figure 61, the initial bolus was 100 mg and the subsequent boluses 60 mg. Figure 62 shows the intermittent bolus technique with an initial bolus of 50 mg and subsequent boluses of 30 mg. Not only are the periods of over-sedation reduced, the amplitude of over-sedation is significantly smaller. In addition, the total amount of propofol delivered to the patient was reduced from 280 mg to 230 mg.

Figure 62
Sedation With Intermittent Bolus Technique



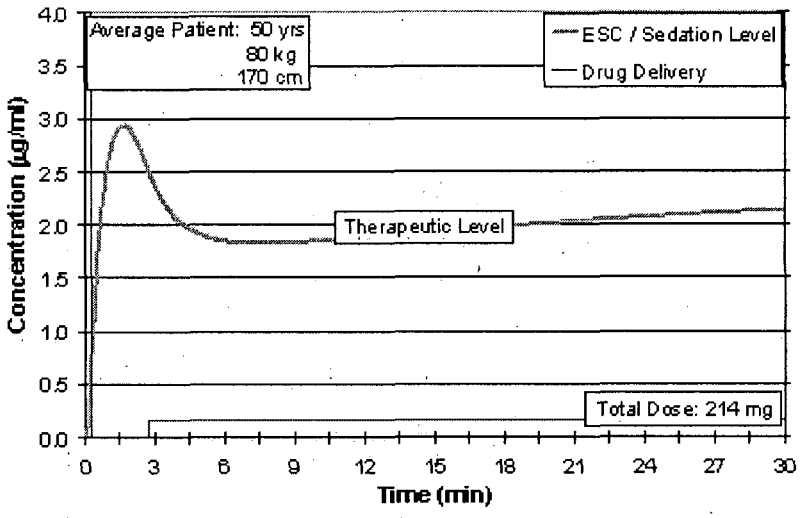
Further improvements can be achieved with even smaller, more frequent boluses. Figure 63 shows the intermittent bolus technique with an initial bolus of 50 mg and subsequent boluses of 17 mg. There is now virtually no under- or over-sedation, outside of the over-sedation resulting from the initial bolus. However, in order to accomplish this, the clinician had to administer a propofol bolus approximately every 3 minutes, or 10 times during a typical 30-minute procedure. This becomes very tedious and increases the risk of inadvertent overdose.

Figure 63
Sedation With Intermittent Bolus Technique



Extending the concept of reducing the size of subsequent boluses and increasing their frequency yields an initial bolus to rapidly achieve the required level of sedation followed by a continuous infusion to maintain the level of sedation. Figure 64 shows an example of this, incorporating the same initial bolus from the two previous examples (50 mg) followed by a 75 µg/kg/min infusion. In this example, the bolus is not representative of the loading dose the SEDASYS System is designed to deliver. As a 'true' bolus, excessive overshoot of the therapeutic level occurred. The SEDASYS System delivers a loading dose, over 3 minutes, rather than a 'bolus', eliminating the excessive overshoot.

Figure 64
Sedation With Continuous Infusion



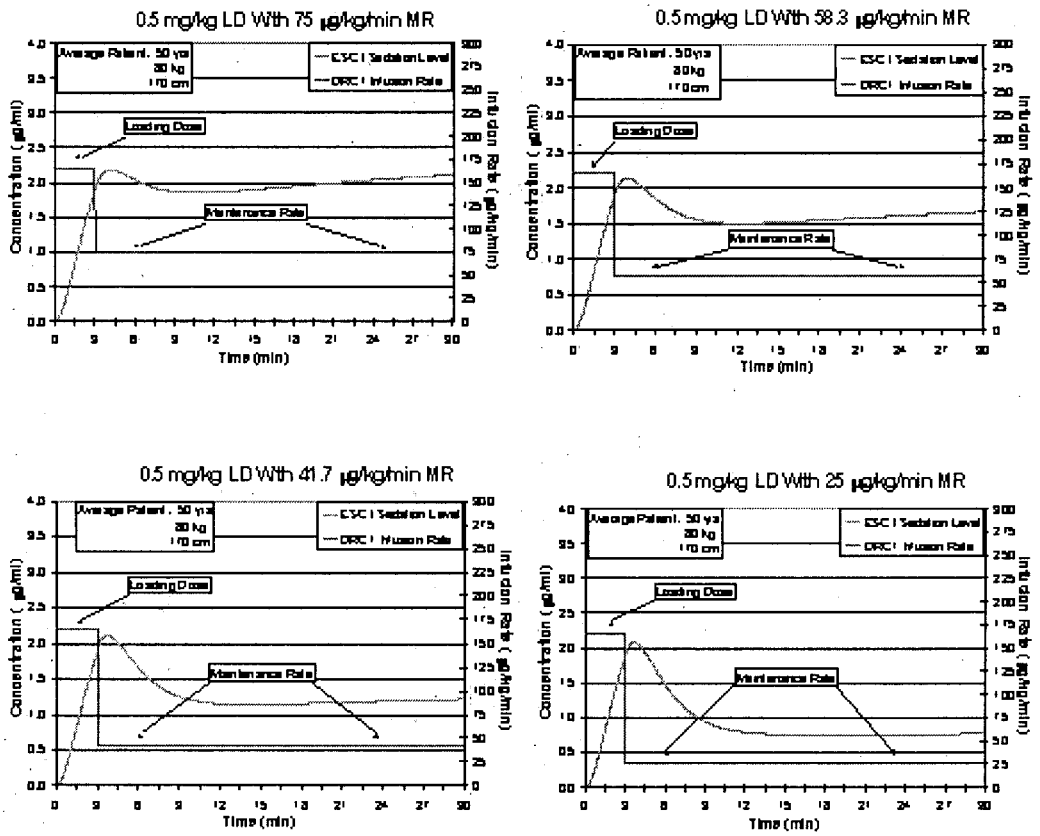
In summary, these four examples clearly demonstrate that a continuous infusion is the best way to achieve a "smooth maintenance" of sedation. This, combined with the recommendation in the propofol labeling[31] to avoid the intermittent bolus technique, led to the decision to provide a continuous infusion of propofol in the SEDASYS System.

[31] APP Pharmaceuticals, LLC. February 2008. DIPRIVAN (propofol) 1% Injectable Emulsion for I.V. Labeling.

2.2 Loading Dose Sized to Maintenance Rate

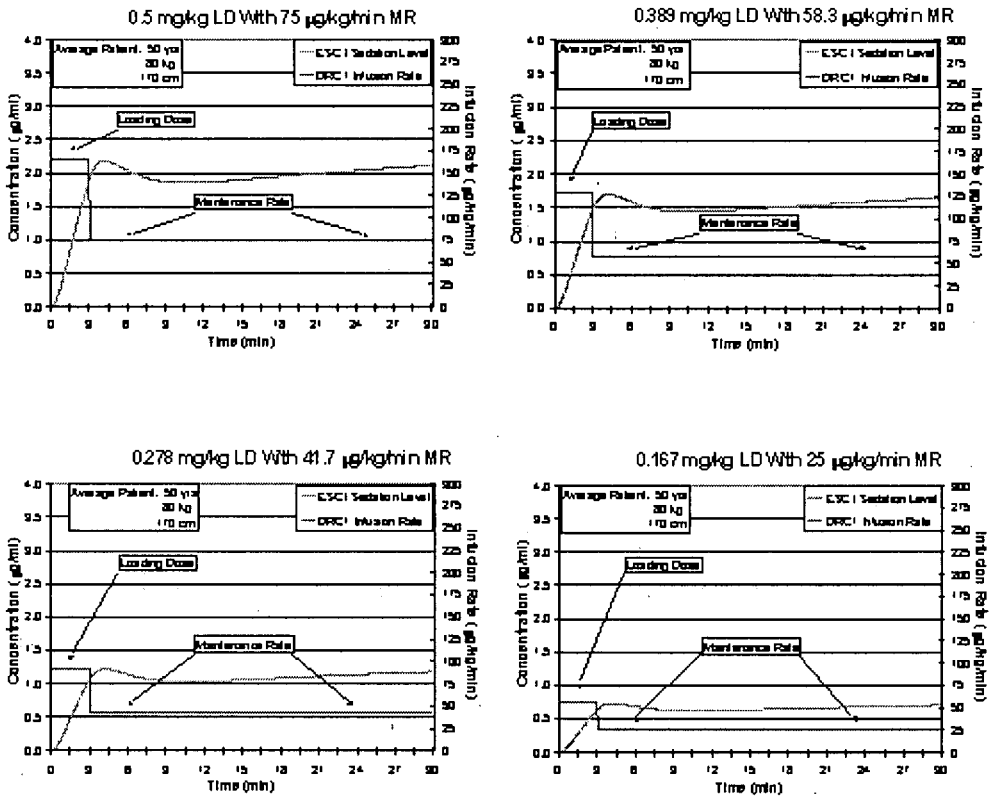
FDA-approved propofol labeling recommends an infusion range (25 to 75 µg/kg/min) to maintain sedation, but only a single value (0.5 mg/kg) to initiate sedation. However, pharmacokinetic principles suggest that it is inappropriate to deliver a "one-size-fits-all" loading dose. The loading dose should be tailored to the desired level of sedation. Figure 65 demonstrates, via computer simulations, the effect of using a "one-size-fits-all" loading dose for any desired level of sedation. For the purpose of these simulations, the desired level of sedation is represented by the effect site concentration maintained by the maintenance rate. Notice that the smaller the maintenance rate, the greater the overshoot of the desired level of sedation. At a maintenance rate of 25 µg/kg/min, this overshoot is almost 200%. This could put the patient at a significant risk of over-sedation.

Figure 65
One Size Fits All Loading Dose



Over clinically relevant ranges, the pharmacokinetics of most drugs are linear. Schnider *et al.*[32] found that the "pharmacokinetics of propofol are linear for clinically relevant infusion rates (25 to 200 µg/kg/min)." Therefore, a linear function was employed to determine the appropriate loading dose for each maintenance rate. By correlating the maximum initiation dose (0.5 mg/kg) to the maximum maintenance rate (75 µg/kg/min), a specific loading dose can be determined for any maintenance rate through linear interpolation. Figure 66 demonstrates the effect of sizing the loading dose to the selected maintenance rate. For each maintenance rate, the desired level of sedation is achieved within 3 minutes with very little overshoot, and the level of sedation is smoothly maintained.

Figure 66
Loading Dose Sized to Maintenance Rate



[32] Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. 1998. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 88:1170-82.

The simulations presented above, as well as all subsequent simulations, were performed using a standard three compartment pharmacokinetic model[33,34] with an added effect site compartment.[35] The model's parameters, specific to propofol, were taken from the work of Schnider *et al.*[36,37] This parameter set was recommended by the Ethicon Endo-Surgery Anesthesia Advisory Panel as the most accurate for propofol.

From these data, which are based on accepted propofol pharmacokinetic models, Ethicon Endo-Surgery concluded that a linear relationship between loading dose and maintenance rate would quickly and accurately achieve the intended level of sedation. These simulations demonstrate that a simple linear correlation of loading dose to maintenance rate can provide a safe initiation of sedation. Therefore, the SEDASYS System automatically calculates an appropriately sized loading dose for the maintenance rate entered by the clinician using the same equation used for the simulations above to reflect the linear relationship:

$$LD = 0.5 * (MR / 75) * Weight$$

Additionally, the loading dose will be delivered over three minutes.

2.3 Negative Loading Dose

If the maintenance rate is decreased, the incremental loading dose will be negative. It is impossible to withdraw drug from a patient, so a truly negative loading dose is not feasible. However, if a negative loading dose is not accounted for in the actual drug administration, then the drug delivery algorithm's incremental loading dose calculation will be corrupted for any subsequent maintenance rate increases. In addition to the corruption of the algorithms, not providing a negative loading dose will result in a slow decrease in sedation level. Figure 67 depicts a maintenance rate decrease without a negative loading dose. It takes approximately 9 minutes to decrease to the "desired level" of sedation.

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[33] Stoelting, RK. 1999. *Pharmacology & Physiology in Anesthetic Practice (3rd edition).* Philadelphia: Lippincott-Raven. Chapters 1 and 6.

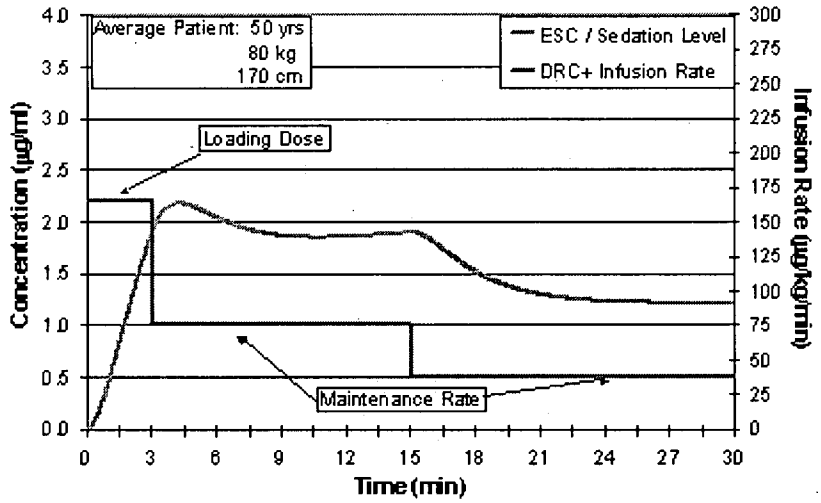
[34] Barash, PG, Cullen, BF, and Stoelting, RK(eds). 2001. *Clinical Anesthesia (4th edition).* Philadelphia: Lippincott Williams & Wilkins. Chapters 11 and 13.

[35] Miller, RD (ed). 2000. *Anesthesia (5th edition).* Philadelphia: Churchill Livingstone. Chapters 2, 9, and 11.

[36] Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. 1998. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 88:1170-82.

[37] Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. 1999. The influence of age on propofol pharmacodynamics. *Anesthesiology* 90:1502-16.

Figure 67
Rate Decrease Without Negative Loading Dose



It is important to rapidly decrease the level of sedation, since the decrease may be in reaction to an over-sedated patient. The decrease seen in Figure 67, without a negative loading dose, is a function of the redistribution of propofol from the blood and effect site, into the peripheral compartments (muscle, fat, etc.) and the metabolism of propofol. In "steady-state" conditions, the redistribution and metabolism of propofol is equal to the infusion rate. When the infusion rate is increased, there is an increase in drug in the blood as the new rate is higher than the rate of redistribution and metabolism. When the infusion rate is decreased, there is a decrease in the blood levels of propofol as the redistribution and metabolism are now higher than the infusion rate. The larger the decrease in infusion rate the greater the difference between the redistribution and metabolism versus the infusion rate. Therefore, to get the most rapid decrease in sedation level, the infusion rate should be temporarily stopped, creating the largest possible difference.

How long the infusion rate should be stopped is a function of the absolute value of the maintenance rate decrease and the pharmacokinetics of propofol. The dominant aspect of the decrease in blood concentration of propofol following short duration infusions is the redistribution. Theoretically, the inter-compartment clearances of a pharmacokinetic model could be used to determine the time the pump should be stopped. However, this would assume *a priori* knowledge of the patient; knowledge that does not exist.

Instead, a "steady-state" assumption is used to calculate the period the infusion rate should be stopped. As mentioned above, in "steady-state" the redistribution and metabolism of propofol equals the infusion rate (no net change in blood concentration). Under this assumption, if the infusion rate is stopped, the amount of drug eliminated from the blood is equivalent to the integral of the "steady-state" infusion rate over the period the infusion rate

is stopped. This, in essence, becomes a linear approximation of the exponential inter-compartment clearances. Figure 68 demonstrates the effectiveness of this approach in rapidly decreasing the level of sedation in response to a maintenance rate decrease. Compare the 3 minutes required to decrease to the new level of sedation with the 9 minutes it took without a "negative" loading dose.

Figure 68
Rate Decrease With Negative Loading Dose

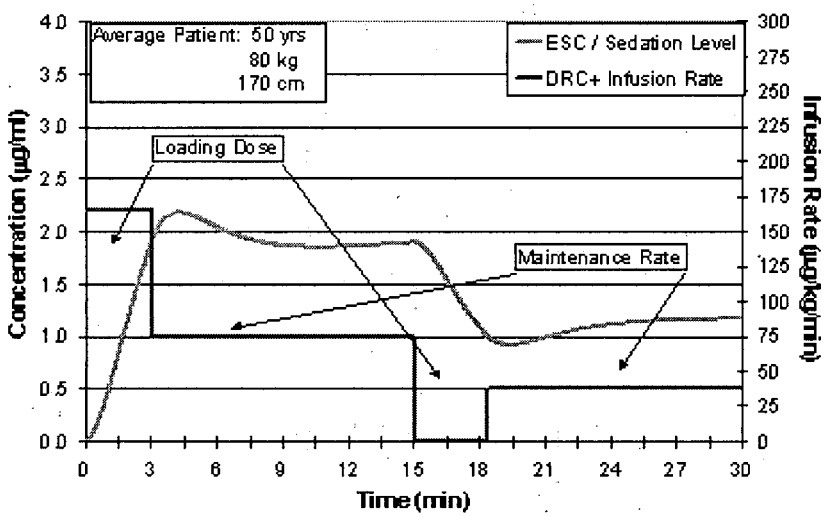
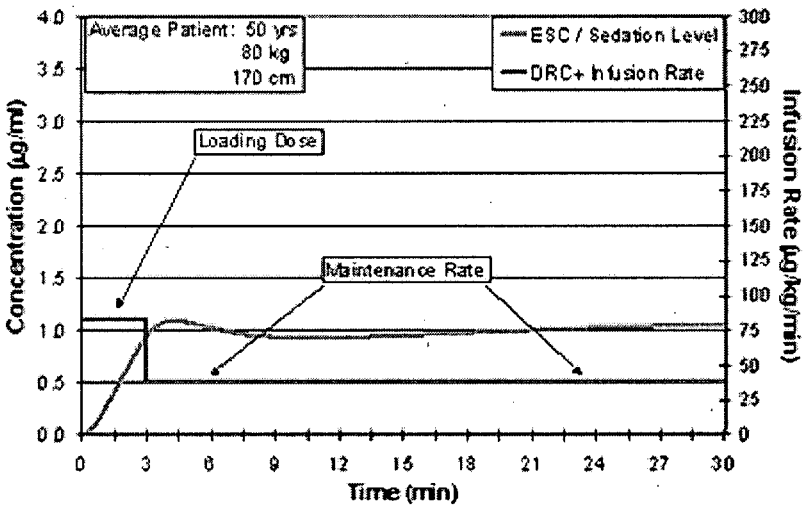


Figure 69 shows what the sedation level would have been, if the user had selected 37.5 µg/kg/min from the start. Three minutes after the maintenance rate decrease in Figure 69, the two ESCs are equivalent.

Figure 69
Sedation Level With Maintenance Rate of 37.5 µg/kg/min



Based on the concepts discussed above, a "negative" loading dose will be accomplished by stopping the infusion of propofol for a specified period of time. This period of time is calculated as:

$$Time_zero = -60{,}000 * LD_incremental / (MR_current * Weight)$$

Where the 60,000 is a conversion factor incorporating the conversions from minutes to seconds (60) and mg to µg (1,000), and MR_current is the maintenance rate prior to the requested decrease.

2.4 PRN

As mentioned above, propofol labeling suggests a loading dose of up to 0.5 mg/kg to initiate sedation. In addition it mentions that if the intermittent bolus technique is used to maintain sedation, doses of 10 to 20 mg can be used.

During a procedure, the patient may experience transient episodes of agitation or discomfort, such as when the scope is passing through the splenic flexure during a colonoscopy. Increasing the propofol maintenance rate to treat this transient episode could result in over-sedation when the extra stimulus ends. The clinician would then have to reduce the maintenance rate in response.

The PRN feature allows the clinician to treat transient episodes of discomfort with a transient increase in the sedation effect. This can be done when the clinician observes patient discomfort, or can be used in advance to prevent discomfort when the clinician knows a particularly uncomfortable part of the procedure is approaching.

Therefore, the PRN is not being used to initiate sedation, nor simply maintain it. Rather it is being used for something in between; specifically treating transient increases in patient discomfort. Therefore, it should not be as large a dose as an initial loading dose, nor should it be as small as the doses used to maintain sedation.

A 100 kg patient, with initial maintenance rate of 75 μg/kg/min, would receive a loading dose of 50 mg. If the clinician subsequently increased the maintenance rate by 25 μg/kg/min to treat an increase in discomfort, the patient would receive an incremental loading dose of 17 mg. Heavier patients would receive more and lighter patients less.

The PRN dose is 0.25 mg/kg. For the 100 kg patient the PRN dose would be 25 mg. This is similar in size to the incremental loading dose for an increase in maintenance rate from 75 to 100 μg/kg/min. The PRN dose will be larger for heavier patients, and less for lighter patients, just like the incremental loading dose.

The PRN is delivered slowly, at a pump rate of 450 mL/hour. For the 100 kg patient the PRN will be delivered in 20 seconds. For the 50 kg and 150 kg patients the dose will be delivered in 10 and 30 seconds, respectively. The slow infusion technique is used to deliver the PRN to prevent the high plasma levels of propofol that could occur with a rapid bolus technique.

3.0 SUMMARY OF PRECLINICAL STUDIES

A series of preclinical studies were conducted to demonstrate the SEDASYS System meets its requirements, conforms to international safety standards, and is safe and suitable for its intended use. A summary of the major studies follows.

3.1 Design Safety, Electrical Safety, and Electromagnetic Compatibility

Design safety, electrical safety, and electromagnetic compatibility were demonstrated by evaluating compliance with the relevant portions of the following standards:

- UL 60601-1; 2003, Medical Electrical Equipment – General Requirements for Safety
- IEC 60601-1-2; 2001, Medical Electrical Equipment, Part 1: General Requirements for Safety, Section 1.2 Collateral Standard: Electromagnetic Compatibility – Requirements and Tests

The SEDASYS System complies with the relevant sections of the standards.

3.2 Software Testing

In accordance with the FDA Guidance Document entitled "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices," the SEDASYS System software level of concern was major. Documentation per this level of concern was supplied. Validation testing of system performance and functionality was performed to demonstrate that the device meets it requirements, and performs as intended.

All software testing passed the acceptance criteria.

3.3 Performance Requirements

A series of system and subsystem level testing was performed to demonstrate the performance and functionality of the SEDASYS System. Table 70 summarizes the major tests.

Table 70
Summary of the Performance and Functionality Testing

Subsystem Performance	Method	Result
Drug Delivery Accuracy	Drug delivery accuracy (± 5%) was measured over a range of flow rates (1.2, 25.2, and 90 mL/hr).	Pass
Oxygen Saturation by Pulse Oximeter	Oxygen saturation accuracy was measured over the range of 70–100% using a calibrated reference device. A minimum accuracy of ± 2% SpO_2 was required.	Pass
Heart Rate Accuracy by Pulse Oximeter	Heart rate accuracy was measured over the range of 30–240 beats per minute using a calibrated reference device. A minimum accuracy of ± 3 beats per minute was required.	Pass
Respiration Rate by Capnometry	Respiration rate was measured using a simulator over a range of 2–40 breaths per minute with and without supplemental oxygen. The required accuracy was ± 5% or 1 breath per minute, whichever was greater.	Pass
Audio System by Automated Responsiveness Monitor	The automated responsiveness monitor audio volume level was measured to demonstrate it provides an audio output between 50–110 dBA ± 5%.	Pass
Subsystem Performance	**Method**	**Result**
Tactile Stimulus by Automated Responsiveness Monitor	The automated responsiveness monitor handset was evaluated for its ability to deliver a tactile stimulus (vibration), to detect patient actuation, and not self-actuate.	Pass
Heart Rate by ECG	Heart rate accuracy was measured over the range of 30–240 beats per minute using a calibrated reference device. A minimum accuracy of ± 3 beats per minute was required.	Pass
Blood Pressure	Blood pressure monitoring capabilities were measured in accordance with ANSI/AAMI SP10.	Pass
Oxygen Delivery	Oxygen delivery was measured in a test simulator over a range of 1 to 12 liters per minute. Required accuracy was ± 1 liter per minute or ± 15%, which ever was greater.	Pass

3.4 Human Factors Engineering

Comprehensive human factors engineering was performed throughout the product development process to optimize the design and its user interfaces. Studies evaluated the design and its usability. Multiple rounds of usability testing were conducted with the target end-users (gastroenterologists and nurses) and experts in human factors engineering. These studies demonstrated that the user interfaces successfully enable the proper operation of the device.

3.5 Biocompatibility

Materials biocompatibility was evaluated in accordance with ISO 10993-1 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing" and the FDA General Program Memorandum #G95-1: Use of International ISO-10993. Materials with patient or user contact were classified into one of the following two categories:

- Surface devices with less than 24 hours of skin contact (i.e., contact category is "Limited Surface Contact – Skin")
- Externally communicating devices with indirect blood contact of less than 24 hours (i.e., "Limited Tissue Contact")

Materials used in the device with Limited Surface Contact (Skin) were evaluated at a minimum for:

- Cytotoxicity
- Irritation
- Sensitization

Materials used in the device with Limited Tissue Contact (indirect blood) were evaluated at a minimum for:

- Cytotoxicity
- Irritation
- Sensitization
- Acute systemic toxicity
- Pyrogenicity
- Hemocompatibility

The evaluations demonstrated the biocompatibility of the device materials.

3.6 Material Compatibility with Propofol

Materials that contact 1% (10 mg/mL) propofol injectable emulsion were selected and evaluated for compatibility with propofol. These fluid path materials were demonstrated to be compatible.

3.7 Ship Testing

The fully packaged capital equipment of the SEDASYS System was subjected to standardized ASTM shock and vibration testing to simulate commercial transportation. The devices were tested for performance before packaging, subjected to the shock and vibration testing, then evaluated for performance again and visually inspected. The devices met the requirements of this test; the devices operated normally after exposure to the shock and vibration test conditions.

Similarly, the fully packaged single patient use components of the SEDASYS System were subjected to standardized ASTM shock and vibration testing to simulate commercial transportation. The devices were tested for performance before packaging, subjected to the shock and vibration testing, then evaluated for performance again, and package integrity. The devices met the requirements of this test and packaging integrity was not compromised after exposure to the shock and vibration test conditions.

3.8 Storage Condition Testing

The SEDASYS System was subjected to temperature extremes of potential storage conditions. The limits chosen for storage conditions were temperature 0 to 40°C and relative humidity of 20 to 90%.

3.9 Sterilization

The drug delivery cassette is provided sterile. The gamma radiation sterilization cycle was validated in accordance with ANSI/AAMI/ISO11137-2:2006 to achieve a minimum sterility assurance level of $1x10^{-6}$.

Exhibit C
Clinician and Patient Satisfaction with Sedation Instrument Questionnaires

CLINICIAN SATISFACTION WITH SEDATION INSTRUMENT (CSSI)

INSTRUCTIONS: This survey asks for your views about the sedation you administered during your most recent procedure. **Circle one answer for every question**. If you are unsure about how to answer a question, please give the best answer you can.

For this procedure, please rate your level of satisfaction with each of the following... (Circle one response on each line.)

	Very Satisfied	Satisfied	Somewhat Satisfied	Neither Satisfied Nor Dissatisfied	Somewhat Dissatisfied	Dissatisfied	Very Dissatisfied
1. Ease of use of the sedation delivery	1	2	3	4	5	6	7
2. Convenience with the sedation delivery	1	2	3	4	5	6	7
3. Rapidity in achieving appropriate level of sedation	1	2	3	4	5	6	7
4. Difficulty with the sedation administration	1	2	3	4	5	6	7
5. Ability to adjust the dosage during the procedure	1	2	3	4	5	6	7
6. Ease at which level of sedation was maintained	1	2	3	4	5	6	7
7. Rapidity of patient recovery	1	2	3	4	5	6	7
8. Effectiveness of the sedation received	1	2	3	4	5	6	7
9. Effect the sedation had on the procedure	1	2	3	4	5	6	7
10. Effectiveness of the monitoring system	1	2	3	4	5	6	7
11. Ability to recognize potential problems	1	2	3	4	5	6	7
12. Ease of use of the monitoring system	1	2	3	4	5	6	7
13. Patient's ability to communicate post operatively	1	2	3	4	5	6	7
14. Patient's ability to retain post operative information	1	2	3	4	5	6	7
15. Recovery time associated with the sedation	1	2	3	4	5	6	7
16. Post operative side effects from the sedation received	1	2	3	4	5	6	7

PATIENT SATISFACTION WITH SEDATION INSTRUMENT (PSSI)

INSTRUCTIONS: This survey asks for your views about the sedation that you received during your most recent procedure. **Circle one answer for every question**. If you are unsure about how to answer a question, please give the best answer you can.

Thinking about the sedation you most recently received, how satisfied or dissatisfied are you with each of the following? (Circle one response on each line.)

	Very Satisfied	Satisfied	Somewhat Satisfied	Neither Satisfied Nor Dissatisfied	Somewhat Dissatisfied	Dissatisfied	Very Dissatisfied
1. Ease of the sedation administration	1	2	3	4	5	6	7
2. Pain associated with the sedation delivery	1	2	3	4	5	6	7
3. Amount you remember during the procedure	1	2	3	4	5	6	7
4. Amount of drowsiness with the medication	1	2	3	4	5	6	7
5. Amount of sedation you received (enough to make you drowsy or go to sleep)	1	2	3	4	5	6	7
6. Pain associated with the procedure	1	2	3	4	5	6	7
7. Abdominal discomfort after the procedure	1	2	3	4	5	6	7
8. Amount of nausea after the procedure	1	2	3	4	5	6	7
9. Amount you remember about the procedure	1	2	3	4	5	6	7
10. Length of time you felt the effects of the sedation received	1	2	3	4	5	6	7
11. Drowsiness after the procedure	1	2	3	4	5	6	7
12. Grogginess after the procedure	1	2	3	4	5	6	7
13. How tired you felt after the procedure	1	2	3	4	5	6	7
14. Your ability to think clearly after the procedure	1	2	3	4	5	6	7
15. Ease of recovery after the procedure	1	2	3	4	5	6	7
16. How fast you returned to your usual daily activities (things you do everyday)	1	2	3	4	5	6	7

Exhibit D
Ethicon Endo-Surgery Anesthesia Advisory Panel Members

The Ethicon Endo-Surgery Anesthesia Advisory Panel is chaired by Steven Shafer, MD (Department of Anesthesiology, Columbia University). The table below lists all panel members.

Name	Affiliation	Expertise
Steven Shafer, MD *(Chairman)*	Columbia University	Helped develop Diprivan dosing guidelines
Charles Cote, MD	Massachusetts General Hospital	Participated in panel for ASA guidelines on sedation for non-anesthesiologists, including propofol
Talmage Egan, MD	University of Utah	Expert in clinical pharmacology of sedatives and analgesics
Peter Glass, MD	SUNY Stony Brook	Expert in depth of anesthesia/sedation monitoring
Jeff Gross, MD	University of Connecticut	Chaired panel for ASA guidelines on sedation for non-anesthesiologists, including propofol
James Jacobs, MD, PhD	Syracuse University	Developed computer-assisted drug administration algorithm (CACI)
Jerry Reves, MD	Medical University of South Carolina	Developed computer-assisted drug administration algorithm (CACI)
Michael Roizen, MD	Cleveland Clinic	Expert on sedation and anesthesia devices
Dwayne Westenskow, PhD	University of Utah	Expert on anesthesia devices and human factors engineering
Paul White, MD, PhD	University of Texas Southwestern at Dallas	Clinical investigator for studies supporting Diprivan labeling and expert in intravenous anesthesia.

Exhibit E
Clinical User Guide / Operator's Manual and Device Video

Exhibit E is included on the CD provided in the front of this binder behind tab "CD and List of Contents."

Volumes 3-5_Exhibit E_Operators Manual
Volume 6_Exhibit E_Device Video

Exhibit F
Post-Approval Study Outline

POST-APPROVAL SAFETY ASSESSMENT OF THE SEDASYS SYSTEM IN ROUTINE CLINICAL PRACTICE AND EVALUATION OF TRAINING EFFECTIVENESS

A. Objectives with study hypotheses

The objectives of this study are to evaluate the safety of the SEDASYS System when used in routine clinical practice under marketed conditions and to evaluate the effectiveness of the device training program over time.

Hypothesis: The incidence of SEDASYS System related airway rescue interventions (insertion of artificial airways, bag-mask ventilation or administration of reversal agents) will be no more than the current reported incidence (1/500 prevalence of morbidity reported as rescue interventions for airway management) with benzodiazepine/opioid based sedation.

The SEDASYS System users will also be tested for competency in device use at different time points to evaluate training effectiveness.

B. Background

The SEDASYS System is currently indicated for the intravenous administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal-to-moderate sedation, as defined by the American Society of Anesthesiologists (ASA) Continuum of Depth of Sedation, in adult patients (ASA physical status I and II) undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

The pivotal study was a multi-center, randomized (1:1), comparative study of propofol sedation with SEDASYS System versus benzodiazepine-based sedation in subjects undergoing colonoscopy or EGD procedures. Four hundred ninety-six subjects were randomized to the SEDASYS System Group. The primary endpoint was the area-under-the-curve of oxygen desaturation (AUC_{Desat}) (SpO_2 < 90% saturation for >15 seconds), a surrogate measure for the risks associated with over-sedation. Results for AUC_{Desat} were in favor of the SEDASYS System Group, indicating that administration of propofol via the SEDASYS System reduced the risks associated with over-sedation when compared to the current standard of care (benzodiazepine-based sedation). For colonoscopy procedures, the results were statistically significantly in favor of the SEDASYS System. For EGD procedures, the results were directionally better. The results of the pivotal study (coupled with the results from two feasibility studies) provided evidence establishing the safety and effectiveness of the SEDASYS System for its intended use under the conditions of use described in the labeling.

The SEDASYS System training program includes on-line training, instructor-lead training and an observational period of approximately 10 cases conducted with oversight from an Ethicon Endo-Surgery education specialist.

The proposed post-approval study is larger in size than the pivotal study and utilizes actual morbidity/mortality as the study endpoint to confirm the previous findings of our surrogate measure, area-under-the-curve of oxygen desaturation. Additionally, this study will provide a more comprehensive understanding of the safety of the SEDASYS System and any complications that may not be spontaneously reported. Lastly, this study will provide an evaluation of the effectiveness of the SEDASYS training program over time.

C. Study design

The study is a single arm, non randomized, non-blinded, multi-center, prospective, safety study of colonoscopy, and EGD, performed in routine clinical practice.
Adult male and female patients scheduled for non-emergent endoscopy procedures during the study timeframe will be invited to participate in the study.

Facilities that have had no prior training or experience using the SEDASYS System will be invited to participate in training evaluations at specified time points over the course of 1-year.

D. Study groups

This study is planned with two types of study groups , firstly subjects as part of the safety analysis will be enrolled based on the FDA-approved labeling for the SEDASYS System.

Inclusion Criteria:
According to the approved FDA labeling for the SEDASYS System as determined through assessment by principal investigator

Exclusion Criteria:
According to approved FDA labeling for the SEDASYS System. Subjects with any contraindications must be excluded.

Secondly, the target site selection criteria for analyzing training effectiveness will include sites that meet all requirements for the use of the SEDASYS System. This includes: accredited facilities (e.g., those certified by The Joint Commission [TJC], formerly known as JCAHO); requirements that all users be trained in minimal-to-moderate sedation, including airway management and all users must complete the Ethicon Endo-Surgery 3-Step training program.

Sites that participate in the training evaluation must have no prior training or experience using the SEDASYS System and have appropriate knowledge of Good Clinical Practice Guidelines.

E. Outcomes of interest

Primary Endpoint:
Rescue Interventions for airway management compared to the current standard of care as described in historical literature and pivotal study data

Rescue Interventions for airway management are defined as:

- Insertion of artificial airway

- Bag-Mask ventilation
- Administration of rescue medications
- Intubation

***Secondary Endpoints*:**

- Pharmacologic interventions for hemodynamic events. This will be defined as any concomitant therapy administered during the procedure, as the result of an hemodynamic physiologic event determined per physician judgment
- Training effectiveness as measured through simulations of device action to test aspects of user interface at baseline, post 3-part training program, 6-months post training and 12-months post training.
  - Competency to be defined as knowledge of device operation and appropriate adherence to the Clinical User Guide Operators Manual.

***Other Safety Endpoints*:**

- Oxygen saturation during the procedure reported every 5 minutes
- Level of sedation (as defined by the ASA continuum of sedation) reported at a range that is standard for gastrointestinal procedures.
- All AEs and SAEs will be reported and classified as unrelated or related to SEDASYS System sedation
  - Expected AEs for each procedure type, associated with the use of sedation and associated with the device will be listed in the protocol
- All product malfunctions will be reported; highlighting any product malfunctions leading to meaningful injury

F. Study size and Power calculations (based on study hypothesis)

Rational for prevalence of 1/500:
In a prospective study of 14,419 subjects the rate of cardiopulmonary complications, as defined by rescue intervention, was 2/1000[38]. A retrospective study done of 21,011 patients found the rate to be 5.4/1000 subjects[39]. The bounds of rescue interventions reported in these two articles (1/500 to 3/500) serve as the basis of the power analysis for the proposed study.

***Sample Size / Power Analysis*:**
A sample size of 1511 subjects will provide power = 80% to detect a difference between a rescue intervention rate of 1/500, the target rate, and a rate equivalent to the upper bound of the range cited above, 3/500 using a Fisher's exact test, one-tailed alpha=0.05. The analysis will test that the observed rate of interventions is not significantly greater than

[38] Quine MA, Bell GD, McCloy RF, Matthews HR. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing and sedation methods. Gut 1995;36:462-7
[39] Arrowsmith JB, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. Gastrointest Endosc 1991;37:421-7

1/500. 1511 subjects will provide sufficient power to detect a difference as small as 2/500 (ie. the difference between 1/500 and 3/500).

In addition to those 1511 subjects, we plan on including the data collected from the 496 subjects that were enrolled under the SEDASYS System group of the pivotal study proving a total data set of approximately 2000 subjects.

NOTE: this is a rough sample size that will be finalized during the interactive review process with FDA

Up to 20 sites will be recruited into the study. A minimum of 18 teams will be selected with 1-2 physician/nurse teams per site.

A McNemar's test (unconditional) for paired binomial proportions will have exact power = 82.7% to detect a difference between the pre-training and post-training proportion of "passes" when 18 teams are assessed. This calculation is anticipated to detect a difference in binomial proportions of 0.45 and assumes a proportion of discordant pairs = 0.60.

G. Sampling and recruitment strategy

Appropriate, willing, patients who meet all inclusion and exclusion criteria will sign an informed consent prior to study procedures. Eligible subjects will be consecutively enrolled into the study to minimize bias.

H. Data collection, follow-up schedule and plan to minimize loss to follow-up.

Data collection to include: Consent of subject, Medical History, Demographic data, concomitant therapy, Procedure type [Routine non-emergent colonoscopy or EGD with the SEDASYS System], airway rescue interventions, AEs, Product Complaints, and the rest of the secondary endpoints.

For subject data: data will be collected prior to and during use of SEDASYS System through 24 hours post discharge. AEs will be followed to resolution. No additional plan to minimize loss to follow-up is necessary for a 1-day study.

For training data: data will be collected at 4 time-points (prior to EES 3-part training program, post 3-part training program, 6-months post training and 12-months post training).

I. Statistical Analysis

Primary Measure:
One Sided Fisher's exact test (one sided) to demonstrate that the rate of rescue interventions is not significantly greater than 1/500 (Power 80%, a = 0.05)

Secondary Measures:

- Training Effectiveness-
  Competence will be assessed at 4 time points: prior to training, immediately post-training, 6 months post-training, and 1 year post-training. Sedation teams will be assessed on several dimensions of device utilization and each team will receive a final

"pass" or "fail" grade. A McNemar's test (unconditional) will be conducted to determine training effectiveness.

- Patients that received a pharmacologic interventions for hemodynamic events will be summarized descriptively, (n, mean, standard deviation, minimum, median, maximum)

Other safety outcomes:
Product failures, product failures leading to meaningful injury, AEs, and SAEs (n, percent), level of sedation and oxygen saturation during the procedure will be summarized descriptively

A complete statistical analysis plan will be generated prospectively prior to database lock.

J. Quality assurance and control

The study will be monitored according to FDA regulations and ICH/GCP guidelines.

K. Study Timeline

- Expected date of study initiation: January 2010
- Expected monthly number of study sites with IRB approvals: 4 sites estimated with IRB approval per month, up to 20 sites
- Expected number of subjects enrolled per month: on average 50 subjects expected per month at each site
- Expected date of subject enrollment completion June 2010
- Expected date of study follow-up completion for subjects July 2010
- Expected date of training assessment completion May 2011
- Expected date for Final Report submission August 2011

L. Reporting requirements (interim and final reports)

Reports will be planned at 6 month intervals per CDRH Guidance. A report will be planned at the completion of analysis of subject data including the baseline and post training evaluations, a second report will be planned after analysis of 6-month training evaluation and a final report will be planned after the 12-month training data is analyzed.