SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Software option for anesthesia gas machine to achieve and maintain targeted end tidal oxygen and anesthetic agent concentrations

Device Trade Name: Et Control

Device Procode: QSF

Applicant's Name and Address: Datex-Ohmeda, Inc., 3030 Ohmeda Drive, PO Box 7550, Madison, WI 53707-7550 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P210018

Date of FDA Notice of Approval: 03/17/2022

II. INDICATIONS FOR USE

The optional Et Control feature is designed to interface with the Aisys CS2 Anesthesia System to support clinicians in maintaining the targeted end tidal oxygen and end tidal anesthetic agent concentrations that the clinician sets during an anesthetic procedure, by making multiple, limited adjustments to the fresh gas composition and total flow. The Et Control feature is indicated for patients, 18 years of age and older

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Et Control labeling.

V. DEVICE DESCRIPTION

The Et Control, or End Tidal Control, feature is used with the Aisys CS2 anesthesia system and the CARESCAPE Respiratory Gas Modules, E-sCAiOE or E-sCAiOVE that were cleared under K211171.

Et Control is an optional feature which allows the clinician to directly set the desired target End Tidal Oxygen (EtO2) and End Tidal Anesthetic Agent (EtAA) on the Aisys CS2 host

anesthesia machine. The Et Control software utilizes breath-by-breath measurements from the respiratory gas module and interfaces with the anesthesia machine to titrate the electronic gas mixer and electronic anesthetic agent vaporizer to help achieve and maintain the target end tidal concentrations set by the clinician.

Et Control requires the use of specific CARESCAPE Respiratory Gas Modules, E-sCAiOE or E-sCAiOVE, which were previously cleared under K211171. The "E" designation at the end of these product names indicates these are compatible with the Et Control feature. These Respiratory Gas Modules contain an additional fresh gas sampling connector on the module front panel which is required for the Fresh Gas Sample Check that runs on the Aisys CS2 with Et Control. The Aisys CS2 with Et Control software checks for the presence of these specific Respiratory Gas Modules during pre-use Checkout and when attempting to enter Et Control. If one of these Respiratory Gas Modules is not detected, the Aisys CS2 software does not allow Et Control to start.

The optional Et Control feature makes use of the current electronic vaporization and electronic gas mixing capabilities of the Aisys CS2 anesthesia machine. As shown in the following Figure 1, Et Control allows the clinician to set the target EtO2 and EtAA [see callout [1] in Figure 1 below] concentrations based on his or her clinical judgment, the patient's physiological response, and the appropriate drug labeling. The Et Control feature titrates the mixer and vaporizer to help achieve and maintain these target concentrations set by the clinician. The mixer and vaporizer output values are displayed on the screen of the anesthesia machine [see callout [2] in Figure 1 below], along with the targeted values selected by the clinician [see callout [1] in Figure 1 below] and the measured end tidal values [see callout [3] in Figure 1 below].

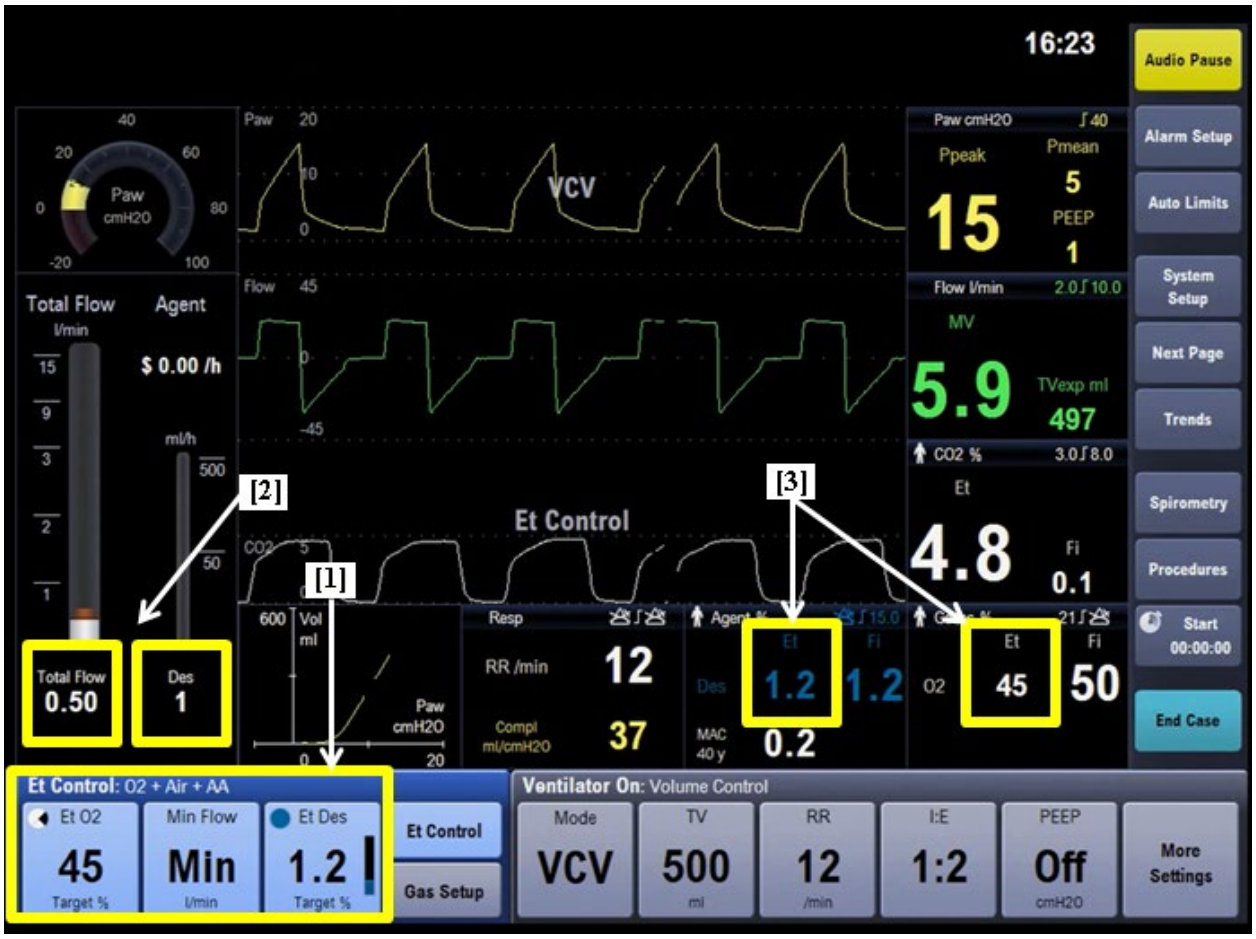

Figure 1 *Aisys CS2 Screen Display (User Interface) with Et Control Activated*

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative practice to the use of Et Control is the Fresh Gas Control method that is available on commercially available anesthesia machines, including the Aisys CS2 (K170872). Fresh Gas Control anesthesia delivery requires clinicians to manually adjust the vaporizer output and fresh gas flow rates and observe the resulting end tidal anesthetic agent (EtAA) and end tidal oxygen (EtO2) concentration throughout a case. This process is repeated with adjustments to the vaporizer and fresh gas flow rates as the blending of re-breathed gas is circulated to the patient and the ventilation, flow, and patient uptake continue to change the expired (end-tidal) agent and O2 concentrations. The clinician continuously monitors and adjusts these settings throughout the case to maintain desired target levels for the individual patient.

VII. MARKETING HISTORY

The Et Control feature on the Aisys and Aisys CS2 anesthesia machines is currently marketed in 101 countries world-wide, including markets such as the European Union, Argentina, Australia, Brazil, Costa Rica, Canada, Hong Kong, India, Indonesia, Japan,

Malaysia, Mexico, Morocco, Myanmar, Peru, Russia, Saudi Arabia, South Korea, Singapore, Turkey, United Arab Emirates, the United Kingdom, Venezuela, and Vietnam.

The Et Control option continues to be available for sale in these countries outside the United States, and has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The Et Control feature does not involve any new intended uses or clinical applications for the practice of anesthesia, or modifications to the practice of anesthesia. No new hazard categories or types of harms are associated with the use of the Et Control feature.

The potential adverse effects associated with the use of inhaled anesthesia, whether through conventional Fresh Gas Control or through anesthesia delivery using Et Control, remain unchanged. Adverse effects and toxicities of inhaled anesthetics include nephrotoxicity, hepatotoxicity, cardiac arrhythmias (including cardiac arrest), neurotoxicity, postoperative nausea and vomiting, respiratory depression and irritation, malignant hyperthermia, and post-anesthesia agitation (Stachnik, 2006).

Adverse effects associated with currently cleared Fresh Gas Control systems are also present with the use of Et Control. These events may include hemodynamic instability, hyperoxia, hypotension, hypoxia, increased probability of disease progression from temporary injury or from delays or deviations from standard of care, permanent or irreversible impairment or life-threatening changes in clinical status, post-traumatic stress disorder, and other reversible but non-life-threatening changes in clinical status.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

Non-clinical performance testing has been completed to demonstrate that the device performs as intended under anticipated conditions of use. This testing included the following:

a. Software verification, validation, and hazard analysis
b. Simulated-use testing in a clinically representative, patient model, assessing algorithm accuracy and response characteristics
c. Sensor accuracy verification of all sensors used in the feedback loop
d. Effectiveness of Safety Check(s) used to identify:
    i. Leaks in the system
    ii. Inaccuracy of the sensors used in the feedback loop
    iii. Inability to reach the set end-tidal target values
e. System transition in conditions of device software failure
f. System transition in conditions of device hardware failure/malfunction
g. Testing related to anesthesia machine performance

h. Electrical safety, thermal safety, mechanical safety, and electromagnetic compatibility testing
i. Biocompatibility testing of patient-contacting gas pathway components of the device

1. LABORATORY TESTING

Testing and evaluation of the Et Control feature included simulation, exploratory, and bench testing. Simulation and exploratory testing were completed to analyze the stability and sensitivity of the feature. Bench testing (formal verification testing) was conducted to evaluate the Et Control feature against the product requirements and design inputs, including product performance, hazard mitigation, and labeling requirements. The results of this testing demonstrate that the Et Control feature meets the product performance requirements. The laboratory testing conducted for verification of the Et Control feature is summarized in Table 1, below.

Table 1 *Summary of Et Control Laboratory/Bench Verification and Validation Testing*

Title of Report	Purpose	Acceptance Criteria	Result
Aisys CS2 Software Verification Report	Verification and validation, where applicable, of the software used on the host anesthesia machine, Aisys CS2, which is inclusive of Et Control requirements.	All requirements of the software have been met and all software design defects have been closed. The Aisys CS2 software has been verified in accordance with the test plan.	PASS
Aisys CS2 System and Standards Verification Report	Verification of the overall Aisys CS2 anesthesia machine specifications and performance and related standards compliance, which is inclusive of Et Control requirements.	All system level design requirements have been met and all design defects have been closed. The Aisys CS2 system has been verified in accordance with the test plan.	PASS
Et Control Mode	Verification of general entrance (starting) criteria for Et Control.	The anesthesia system will transition into Et Control mode only if the correct system qualification criteria are met.	PASS
Et Control Setting Ranges	Verification of Et Control settings and setting ranges.	The settings of the Et Control system perform in accordance with the requirements.	PASS
Et Control Performance	Verification of Et Control performance.	Et Control performs according to its design inputs, including: Agent settings, Oxygen settings, Patient profiles, machine configuration, anesthetic agent types and ventilation settings.	PASS
Auto Exit of Et Control	Verification of Et Control auto exit criteria.	The auto exit mechanism and criteria perform as specified in the design inputs.	PASS
Et Control Fallback	Verification of Et Control fallback (aka Increased Flow) criteria.	The “fallback” mechanism and criteria, performed as specified in the design inputs.	PASS
Et Control General	Verification of general criteria for Et Control, including the required hardware and interactions, as well as the content of the User's Reference Manual (URM).	The physical identification and hardware functionality/operation of the Aisys CS2 Fresh Gas Module performs according to the design inputs, and the User Manual contains labeling, descriptions of safety mechanisms, data logging and troubleshooting instructions as described in the design inputs.	PASS
Et Control Supervisor	Verification of Et Control Supervisor safety checks.	External system safety checks are performed by the Supervisor function as specified in the design inputs.	PASS

Title of Report	Purpose	Acceptance Criteria	Result
Et Control System Check and Leak Check	Verification of the System Check and for the System Leak Check Et Control safety checks.	The system check mechanism and the system leak check mechanism, performed as specified in the design inputs.	PASS
Et Control Fresh Gas Sample Check	Verification of the Fresh Gas Sample Check Et Control safety check.	Verification that the Fresh Gas Sample check mechanism meets the requirements described in the design inputs.	PASS
Respiratory Gas Module Accuracy	Verification of the accuracy of gas sampling on the Fresh Gas Sample.	Accuracy of gas reading shall be according to the specifications.	PASS
IEC 60601-1-10:2013	Verification of the requirements in IEC 60601-1-10: Medical electrical equipment — Part 1-10: General requirements for basic safety and essential performance — Collateral standard: Requirements for the development of physiologic closed-loop controllers	The performance requirements were met as called out in the IEC 60601-1-10:2013 Closed Loop Controllers Standard.	PASS
Biocompatibility	Verification that the materials in the new components associated with the use of Et Control do not introduce biocompatibility risk to the patient.	The biocompatibility of the materials in the system shall comply with the acceptance criteria specified in ISO 10993 and ISO 18562 series of standards related to biocompatibility of breathing gas pathways.	PASS

The testing described above includes verification of all requirements related to Et Control. These requirements are driven from the risk management/device hazard analysis, the product requirements, and applicable standards. All laboratory testing was successfully completed. All product requirements are met, and the specified product requirements are appropriate for the intended use of the Et Control feature.

2. ANIMAL STUDIES

Preliminary design concept and development animal testing was conducted to confirm the viability of the Et Control algorithm. Two animal studies were conducted during the final design phase of the algorithm development. These studies tested the performance of the algorithm, the usability of the system in various failure modes and misuse scenarios, and the overall function of the system during anesthesia delivery. A survey/questionnaire captured the subjective experiences of the clinicians. **Table 2** summarizes the animal studies and their results.

Table 2 *Summary of Animal Testing*

Title of Report	Purpose	Acceptance Criteria	Result
Initial Design Concept Testing	Test an early design concept to better understand the general behavior and performance of Et Control in use on a physiological subject in a clinical environment. One 50kg pig was used for the study.	The study provided support for the feasibility of the Et Control program. Responses to set changes in end-tidal sevoflurane and oxygen were recorded and found to be generally acceptable when compared against the deviation goal. A variety of test scenarios were conducted to provide further insights and qualitative checks to support continuing development and improvement of the algorithm.	PASS
Et Control Animal Testing Feasibility	Test Et Control performance capabilities in a real physiological situation. Two pigs were utilized for the study, as they are an appropriate respiratory model.	Et Control shall meet the performance criteria during set point changes in oxygen, anesthetic agent or combination concentration. In addition, anomalies/improvement opportunities were identified, tracked, analyzed, and corrected in future revisions.	PASS
Et Control Animal Verification Testing	Corroborate non-clinical laboratory testing of Et Control and verify performance of Et Control in a physiological situation. Five pigs were studied, ranging in weight from 10-80 kg.	Et Control shall meet the performance criteria during set point changes in oxygen, anesthetic agent or combination concentration. In addition, anomalies/improvement opportunities were identified, tracked, analyzed, and corrected in future revisions.	PASS

Overall, the Et Control feature performed as intended. Minor improvements were made during development based on feedback gathered during the animal testing.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed clinical studies in the United States to establish a reasonable assurance of safety and effectiveness of Et Control with the Aisys CS2 for delivery of inhaled anesthesia. A feasibility study was performed under IDE G120300 and a pivotal study was conducted under IDE G160132.

Randomized, controlled data comparing Et Control performance and safety to standard clinical practice using Fresh Gas Control in the United States was collected to demonstrate the safety and effectiveness of Et Control.

Clinical studies related to Et Control occurred throughout the development and evolution of the feature and were highlighted by the following major studies:

- Human Clinical Study (Non-USA)
- Human Clinical Studies (USA)
    - Feasibility Clinical Study
    - Pivotal Clinical Study

Data from the USA clinical studies were the basis for the PMA approval decision. A summary of the USA clinical studies is presented below.

1. ET CONTROL USA FEASIBILITY STUDY

A. STUDY DESIGN

A feasibility study was performed to evaluate the safety and performance of the investigational Et Control feature (called "Smartflow" in the feasibility study), titled "Single Site, Randomized, Controlled, Feasibility Study with and without Smartflow™ for Routine Anesthesia (Smartflow™ Feasibility)." Subjects were treated between February through September 2014. The final report for this study reflected the data collected in that timeframe and included 28 evaluable subjects.

The feasibility study was a single site feasibility, single-blinded (subject blinded), parallel comparator, prospective clinical trial. Subjects were randomized to either the Investigational Arm (Et Control Arm) or Control Arm with a 50% likelihood of being in either group. The clinicians and the investigators were not blinded because of the nature of Et Control's use by the clinician during each case.

Three investigators performed the study procedure. Subjects in the Et Control Arm were induced and airway secured based on the investigator's Fresh Gas Control intravenous induction and intubation practice. Et Control and mechanical ventilation were initiated after intubation. Et Control data collection started after the feature was turned on by the clinician. Adjustments to the anesthesia machine settings, discontinuation of use of Et Control, and changes to treatment were made according to the clinician's judgment for the well-being of the subject.

The Control Arm used the legally-marketed anesthesia machine without the investigational Et Control feature. Subjects in the Control Arm were induced and airway secured based on the investigator's Fresh Gas Control intravenous induction and intubation practice. The investigator used Fresh Gas Control /manual means to adjust the electronic vaporizer and electronic gas mixer on the anesthesia machine without Et Control and monitored the subject's gas concentrations with the anesthesia machine.

Volunteer subjects were randomly assigned anesthetic administration using commercial anesthesia machines with or without the investigational Et Control feature according to a pre-established randomization schema provided to the investigators. Prior to each procedure, subject demographic data, medical history, physical examination, and laboratory assessment data were collected. During each study procedure, safety endpoints and adverse events were recorded. Data was also collected during post-anesthesia care, and a 24-hour follow-up was conducted after Post-Anesthesia Care Unit ((PACU) discharge.

A Data Safety Monitoring Board (DSMB) was utilized for the study and their reviews were conducted independent of the applicant. The members of the DSMB included two physicians with expertise in anesthesia and one biostatistician.

Data analysis for this feasibility study was exploratory. Descriptive statistics were used to summarize study endpoints and parameters. Continuous variables were tested using Student's t-test or non-parametric methods depending on variable distribution. Descriptive statistics for continuous variables include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size. Categorical variables were tested using appropriate contingency table analysis (exact or chi-square approximations), and are described with counts, percentages, and sample size. P-values are presented with three decimal places, and p-values less than 0.001 are presented as "<.001." Subjects administered with different anesthetic agents were pooled for analysis according to their randomized arm. Performance comparison analysis was completed using a data processing algorithm developed to objectively analyze the occurrence of desired end tidal concentration and the time the new desired concentration change was initiated. No separate analysis was performed for each anesthetic agent, except in cases when pooling anesthetic agent data is not appropriate (e.g., pooling agent concentration as the concentration varies among different agents). No separate analysis was performed on concomitant medications administered for sedation and/or analgesia.

Clinical Inclusion and Exclusion Criteria: Male and female subjects, who were 18 years or older and were scheduled to undergo general inhaled anesthesia during surgery, were screened for enrollment into this clinical study. The following criteria were used during the screening/enrollment phase.

Inclusion criteria (subjects who met the following criteria were included in the study):

1. Male or female 18 years old or older;
2. Scheduled to undergo general inhaled anesthesia and could be safely exposed to 100% oxygen for up to 2 minutes during general anesthesia;

3. Expected to have airway secured with laryngeal mask airway (LMA) or endotracheal tube;
4. Scheduled for a surgical procedure that was anticipated by the investigator to last greater than or equal to 1 hour (operative time measured from induction to cessation of general inhalation anesthetic);
5. American Society of Anesthesiologists (ASA) physical status classification system I through II;
6. Undergoing intravenous induction; and
7. Able to provide written informed consent.

Exclusion criteria (subjects who met any of the following criteria were excluded from the study):

1. Have an emergency medical condition requiring surgery; or
2. Female subjects who were pregnant or lactating.

Clinical Follow-Up Schedule: During each study procedure, safety endpoints and adverse events were recorded. Data was also collected during post-anesthesia care, and a 24-hour follow-up was conducted post-PACU discharge.

With regard to safety, the following endpoints were evaluated:

1. Primary safety endpoint: Adverse events

2. Secondary safety endpoints:
    1. Systolic and diastolic blood pressure and derived mean blood pressure
    2. Heart rate
    3. SpO_2 (blood oxygen saturation)
    4. Post-anesthesia time

With regard to clinical use/effectiveness, the following endpoints were evaluated:

1. Steady state mean concentrations of EtAA and EtO2 (deviations from the mean steady status concentration for sample size estimation)
2. Time to steady state mean end tidal concentration after each user desired step change
3. Under- and overshooting the steady state mean concentration after each user desired step change
4. Total and average usage per minute of anesthesia agent, O2, and fresh gas rate per minute for the first 10 minutes after intubation and for the entire duration after intubation
5. Number of user setting interactions per step change for the first 10 minutes following induction phase and for the entire case
6. Assessment of incidence of user setting interactions stratified by time following a step change

B. ACCOUNTABILITY OF FEASIBILITY PATIENT COHORT:

At the time of database lock, of the 31 subjects (16 Et Control (Smartflow) and 15 control) originally enrolled in the feasibility PMA study, 28 (90.3%; 28/31) subjects were available

for analysis at the completion of the study, and all post-operative data collection was completed.

Subjects could withdraw consent at any time without prejudice. The reason for withdrawal was recorded. Early termination was defined as any situation in which the clinician determined they no longer wanted to continue the case, or they chose to discontinue the use of Et Control during a case.

A summary of patient accountability is provided in Table 3, which identifies the subjects which were assigned to the control and test cohorts and subjects who did not complete the study.

Table 3 *Feasibility Patient Accountability Summary*

	Et Control (Smartflow)	**Control**
Enrolled Subjects (N)	16	15
Randomized Subjects (N)	16	15
	n (%)	n (%)
Evaluable Population	15 (93.8%)	13 (86.7%)
Safety Population	15 (93.8%)	13 (86.7%)
Completed Study	15 (93.8%)	13 (86.7%)
Early Termination	1 (6.3%)	2 (13.3%)
Reason for Early Termination		
Other	1 (6.3%)	0 (0.0%)
Physician Decision	0 (0.0%)	1 (6.7%)
Protocol non-compliance	0 (0.0%)	1 (6.7%)

Percent (%) = (n/N)100

C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS:

The demographics of the study were recorded as part of the data collection. The study population demographics for the feasibility trial are provided as Table 4.

Table 4 *Demographics of the Et Control Feasibility Study Population*

	Et Control (Smartflow) (N=15) %(n/N)	**Control (N=13) % (n/N)**
Gender		
Female	40.0% (6/15)	69.2% (9/13)
Male	60.0% (9/15)	30.8% (4/13)
Race		
Black or African American	6.7% (1/15)	0.0% (0/13)
Other	6.7% (1/15)	0.0% (0/13)
White	86.7% (13/15)	100.0% (13/13)

Table 4 *Demographics of the Et Control Feasibility Study Population*		
	Et Control (Smartflow) (N=15) %(n/N)	**Control (N=13) % (n/N)**
Ethnic Group		
Hispanic Or Latino	13.3% (2/15)	0.0% (0/13)
Not Hispanic Or Latin	86.7% (13/15)	100.0% (13/13)
ASA Status		
I	26.7% (4/15)	0.0% (0/13)
II	73.3% (11/15)	100.0% (13/13)
Age at Screening (yrs)		
Mean±SD (N)	49 ± 17.4 (15)	44 ± 13.3 (13)
Median	45	50
Range (min,max)	(19,82)	(19,66)
Height (cm)		
Mean±SD (N)	170.5 ± 12.88 (15)	168.4 ± 10.54 (13)
Median	172.7	169.5
Range (min,max)	(147.3,193.0)	(152.4,190.5)
Weight (kg)		
Mean±SD (N)	82.6 ± 22.92 (15)	93.3 ± 35.62 (13)
Median	78.9	85.7
Range (min,max)	(46.7,127.4)	(54.3,199.6)
BMI		
Mean±SD (N)	28.30 ± 6.946 (15)	32.61 ± 10.399 (13)
Median	25.81	29.11
Range (min,max)	(20.09,46.59)	(21.92,61.40)

Percent (%) = (n/N)100; SD – standard deviation

D. SAFETY AND EFFECTIVENESS RESULTS

The analysis of safety during the feasibility study was based on the Et Control cohort of 15 subjects and the Control cohort of 13 subjects available for evaluation.

The purpose of this feasibility study was to collect and analyze safety and effectiveness data on the investigational Et Control (Smartflow) feature. There were 28 subjects in the evaluable/safety population. There were no serious/severe adverse events (SAEs), deaths, or unanticipated adverse device effects (UADEs) reported. There were 9 adverse events (AEs) that occurred. Of the 9 reported AEs, 6 were in the Smartflow Arm and 3 were in the Control Arm. None were considered serious or unanticipated. These 9 AEs were all hypotension events, and none were attributed by the clinician to the Et Control feature.

In summary, Et Control did not change the way the clinicians practiced anesthesia. In both the treatment and control groups, the clinicians were able to adjust the anesthetic agent to maintain the subject's blood pressure and depth of anesthesia based on normal clinical practice. There was no significant difference apparent between the Et Control (treatment) Arm and the Control Arm with regard to the clinician's practice of maintaining the subject's vital sign status during surgery. The study results are further discussed below:

1. **Safety Results:** The safety evaluation was performed according to whether any adverse events were reported; and any measurements that exceeded a pre-determined range for blood pressure, heart rate, oxygen saturation via pulse oximetry (SpO_2), and post anesthesia time, which were the secondary safety endpoints. Nine adverse events (AEs) were reported. Of the AEs reported, 0 were considered serious/severe adverse events (SAEs) and 0 were unanticipated adverse device effects (UADEs). None of the AEs were related to the investigational Et Control (Smartflow) feature or the anesthesia device. Eight AEs occurred after induction, and of these eight AEs, five occurred 15 minutes after induction. One subject experienced an AE that was reported to have occurred before induction and thus, was not included in the summary table below, as it was not related to the use of the investigational device.

   Table 5 summarizes the adverse events by safety population. All AEs resolved with medication (treated with vasoactive medication) and without sequelae. No serious adverse events or deaths were reported when using Et Control (Smartflow).

Table 5 *Adverse Events by Safety Population*

	Et Control (Smartflow) (N=15) %(n/N)	**Control (N=13)% (n/N)**	**p-value**
Subjects with any AE	40.0% (6/15)	15.4% (2/13)	0.221
Subjects with any SAE	0.0% (0/15)	0.0% (0/13)	--
Subjects with any Unanticipated AE	0.0% (0/15)	0.0% (0/13)	--
Subjects with any Device Related AE	0.0% (0/15)	0.0% (0/13)	--
Subjects with any Anesthetic Related AE	40.0% (6/15)	15.4% (2/13)	0.221
Subjects with any Surgery Related AE	0.0% (0/15)	0.0% (0/13)	--
Subjects with any Severe AE	0.0% (0/15)	0.0% (0/13)	--
Subjects with Procedure Stopped due to AE	0.0% (0/15)	0.0% (0/13)	--
Subjects Withdrawn from Study due to AE	0.0% (0/15)	0.0% (0/13)	--

% = (n/N)100

   All adverse events were determined by the clinician to likely be related to the anesthetic agents or the delivery of anesthesia, and not related to the device. During surgery and after the start of anesthesia administration, some subjects did become hypotensive because of the subject's response to induction drugs, and as part of normal practice, a vasoactive drug was administered to address the hypotension. Anesthesiologists adjusted the anesthetic agent or administered vasoactive medication to the subjects to maintain the blood pressure during surgery.

2. **Effectiveness Results:**

Performance Endpoint: To make a comparison between the Et Control (Smartflow) Arm and the Control Arm, a method was developed to objectively analyze and determine the "desired" end tidal concentration level for both Et Control and Control. A desired end tidal concentration was defined as attaining a stable concentration following a significant setting change (i.e., a significant change in EtO2 or EtAA measured 2 minutes after the setting change). Using the time of the identified significant setting change as the start time of a desired setting event, and the mean concentration after the stable concentration as the desired end-tidal target value, effectiveness performance statistics (i.e., response time, settling time, overshoot amount and deviation) were computed and compared between the two arms (Smartflow and Control). These results are summarized in Table 6, below.

The results indicate that Et Control (Smartflow) performed as expected, delivering consistent and accurate EtAA (results summarized in Table 7) and EtO2 (results summarized in Table 8) levels as set by the clinician. On average, Et Control tended to exhibit a quicker response with a faster settling time, while also achieving a comparable overshoot amount. Additionally, Et Control was able to maintain the desired steady state concentration better than observed with the Control Arm. This is particularly evident in the calculation of "Percent Duration of Large Deviation" for EtAA. This percentage reflects the average percentage of time during steady state in which the concentration deviated significantly from the intended target. Et Control exhibited a percent duration of large deviation of 3.4% ± 7.56 (59) versus the Control result of 11.3% ± 18.02.(40) This parameter is considered a reasonable representation of the overall stability, and a measure of the ability of Et Control to avoid large deviations from the clinician's intended maintenance levels.

Although there are examples of similar control/management of end-tidal concentrations in the Control group, on average, because Et Control adjusts delivery on a breath-by-breath basis, Et Control performance appears to be more consistent. The breath-to-breath adjustment enables Et Control to be more immune to inadvertent concentration changes.

Table 6 *Summary of Et Control (Smartflow) Setting Accuracy*

	Desflurane (N=3)	Isoflurane (N=5)	Sevoflurane (N=7)	Smartflow (N=15)
Absolute Difference between Steady State and Set EtAA Concentration (%)				
Mean±SD (N)	0.06 ± 0.081 (15)	0.03 ± 0.049 (28)	0.03 ± 0.032 (47)	0.03 ± 0.050 (90)
Median	0.05	0.01	0.01	0.02
Range (min,max)	(0.00,0.34)	(0.00,0.22)	(0.00,0.14)	(0.00,0.34)
95% CI	[0.019,0.109]	[0.010,0.048]	[0.019,0.038]	[0.024,0.045]
Percent Difference between Steady State and Set EtAA Concentration				
Mean±SD (N)	1.5 ± 2.80 (15)	3.4 ± 5.94 (28)	2.2 ± 3.65 (47)	2.4 ± 4.40 (90)

Median	0.7	0.9	0.9	0.8
Range (min,max)	(0.0,11.2)	(0.0,27.0)	(0.0,21.8)	(0.0,27.0)
95% CI	[0,3.04]	[1.13,5.74]	[1.09,3.23]	[1.52,3.37]
Percent Duration with Difference > 5% of EtAA				
Mean±SD (N)	7.2 ± 17.59 (15)	24.7 ± 29.71 (28)	18.6 ± 23.27 (47)	18.6 ± 25.10 (90)
Median	0.0	14.6	6.9	5.7
Range (min,max)	(0.0,66.8)	(0.0,98.0)	(0.0,79.2)	(0.0,98.0)
Percent Duration with Difference > 10% of EtAA				
Mean±SD (N)	3.4 ± 11.44 (15)	17.6 ± 24.15 (28)	5.8 ± 13.18 (47)	9.1 ± 17.94 (90)
Median	0.0	4.0	0.0	0.0
Range (min,max)	(0.0,44.5)	(0.0,84.4)	(0.0,51.8)	(0.0,84.4)
Percent Duration with Difference > 15% of EtAA				
Mean±SD (N)	3.1 ± 10.99 (15)	8.4 ± 19.14 (28)	3.1 ± 11.07 (47)	4.8 ± 14.12 (90)
Median	0.0	0.0	0.0	0.0
Range (min,max)	(0.0,42.8)	(0.0,84.4)	(0.0,50.2)	(0.0,84.4)
Absolute Difference between Steady State and Set EtO2 Concentration (%)				
Mean±SD (N)	5.79 ± 9.982 (3)	4.78 ± 11.879 (8)	0.39 ± 0.372 (9)	2.95 ± 8.265 (20)
Median	0.04	0.48	0.20	0.27
Range (min,max)	(0.01,17.31)	(0.05,34.15)	(0.06,1.04)	(0.01,34.15)
95% CI	[0,30.583]	[0,14.707]	[0.104,0.676]	[0,6.822]
Percent Difference between Steady State and Set EtO2 Concentration				
Mean±SD (N)	5.8 ± 9.96 (3)	5.4 ± 11.69 (8)	0.8 ± 0.84 (9)	3.4 ± 8.17 (20)
Median	0.1	0.9	0.4	0.6
Range (min,max)	(0.0,17.3)	(0.1,34.1)	(0.1,2.3)	(0.0,34.1)
95% CI	[0,30.56]	[0,15.15]	[0.17,1.47]	[0,7.22]
Percent Duration with Difference > 5% of EtO2				
Mean±SD (N)	30.8 ± 52.01 (3)	17.8 ± 33.33 (8)	2.3 ± 2.91 (9)	12.8 ± 28.48 (20)
Median	1.0	5.2	0.2	3.5
Range (min,max)	(0.5,90.8)	(0.0,99.3)	(0.0,7.0)	(0.0,99.3)
Percent Duration with Difference > 10% of EtO2				
Mean±SD (N)	27.2 ± 47.10 (3)	15.3 ± 34.17 (8)	0.7 ± 1.13 (9)	10.5 ± 27.63 (20)
Median	0.0	2.9	0.0	0.1
Range (min,max)	(0.0,81.6)	(0.0,99.3)	(0.0,2.8)	(0.0,99.3)
Percent Duration with Difference > 15% of EtO2				
Mean±SD (N)	17.0 ± 29.48 (3)	14.4 ± 34.47 (8)	0.5 ± 0.95 (9)	8.5 ± 24.21 (20)
Median	0.0	0.6	0.0	0.0
Range (min,max)	(0.0,51.1)	(0.0,99.3)	(0.0,2.7)	(0.0,99.3)

CI – confidence interval; SD – standard deviation

Table 7 *Comparison of Performance Endpoints of End Tidal Anesthetic Agent*			
Performance Measurement	Control (N=13)	Smartflow (N=15)	p-value
Response Time (sec)			
Mean±SD (N)	111 ± 205.3 (40)	52 ± 129.8 (59)	0.116
Median	42	15	
Range (min,max)	(1,907)	(1,916)	
Settling Time (sec)			
Mean±SD (N)	566 ± 884.2 (40)	278 ± 207.0 (59)	0.050
Median	236	221	
Range (min,max)	(27,5320)	(3,1112)	
Overshoot Amount (%)			
Mean±SD (N)	0.26 ± 0.521 (40)	0.27 ± 0.411 (59)	0.933
Median	0.01	0.10	
Range (min,max)	(0.00,2.30)	(0.00,1.66)	
>10%	30.0% (12/40)	33.9% (20/59)	0.827
>20%	20.0% (8/40)	15.3% (9/59)	0.593
>30%	10.0% (4/40)	10.2% (6/59)	1.000
Average Deviation (vol%)			
Mean±SD (N)	0.08 ± 0.080 (40)	0.06 ± 0.078 (59)	0.292
Median	0.05	0.04	
Range (min,max)	(0.00,0.38)	(0.00,0.48)	
Maximum Deviation (vol%)			
Mean±SD (N)	0.32 ± 0.350 (40)	0.30 ± 0.498 (59)	0.774
Median	0.19	0.16	
Range (min,max)	(0.00,1.47)	(0.00,3.36)	
Half Width of 95% CI of Deviation (vol%)			
Mean±SD (N)	0.12 ± 0.127 (40)	0.11 ± 0.184 (59)	0.720
Median	0.08	0.06	
Range (min,max)	(0.00,0.47)	(0.00,1.29)	
Average Deviation (% to mean)			
Mean±SD (N)	4.89 ± 4.534 (40)	3.94 ± 6.411 (59)	0.390
Median	4.23	2.31	
Range (min,max)	(0.00,19.70)	(0.00,40.00)	
Maximum Deviation (% to mean)			
Mean±SD (N)	20.14 ± 22.051 (40)	15.62 ± 20.412 (59)	0.298
Median	16.37	9.64	
Range (min,max)	(0.00,100.00)	(0.00,100.00)	
Half Width of 95% CI of Deviation (% to mean)			
Mean±SD (N)	7.65 ± 8.625 (40)	6.61 ± 14.471 (59)	0.656

Table 7 *Comparison of Performance Endpoints of End Tidal Anesthetic Agent*			
Performance Measurement	Control (N=13)	Smartflow (N=15)	p-value
Median	7.00	3.74	
Range (min,max)	(0.00,46.57)	(0.00,107.35)	
Percent Duration of Large Deviation (%)*			
Mean±SD (N)	11.3 ± 18.02 (40)	3.4 ± 7.56 (59)	0.011
Median	4.5	0.0	
Range (min,max)	(0.0,79.7)	(0.0,33.7)	

SD – standard deviation;
* Large deviation is defined as: when the difference between the measured end tidal concentration and the steady state concentration is > 5%

Table 8 *Comparison of Performance Endpoints of End Tidal O2*			
Performance Measurement	Control (N=13)	Smartflow (N=15)	p-value
Response Time (sec)			
Mean±SD (N)	299 ± 490.9 (37)	60 ± 81.0 (62)	0.006
Median	70	7	
Range (min,max)	(1,2728)	(1,357)	
Settling Time (sec)			
Mean±SD (N)	392 ± 316.5 (37)	188 ± 135.2 (62)	<.001
Median	407	126	
Range (min,max)	(26,1449)	(46,592)	
Overshoot Amount (%)			
Mean±SD (N)	3.60 ± 6.318 (37)	2.78 ± 7.226 (62)	0.565
Median	0.45	0.27	
Range (min,max)	(0.00,21.75)	(0.00,38.00)	
>10%	21.6% (8/37)	9.7% (6/62)	0.136
>20%	10.8% (4/37)	8.1% (5/62)	0.724
>30%	0.0% (0/37)	4.8% (3/62)	0.291
Average Deviation (%)			
Mean±SD (N)	4.02 ± 6.150 (37)	1.27 ± 1.551 (62)	0.011
Median	2.16	0.60	
Range (min,max)	(0.00,33.92)	(0.00,7.41)	
Maximum Deviation (%)			
Mean±SD (N)	17.72 ± 18.406 (37)	5.68 ± 9.121 (62)	<.001
Median	10.39	1.96	
Range (min,max)	(0.00,71.21)	(0.00,51.38)	
Half Width of 95% CI of Deviation (%)			
Mean±SD (N)	6.75 ± 10.120 (37)	2.22 ± 3.250 (62)	0.012
Median	3.99	1.11	
Range (min,max)	(0.00,59.02)	(0.00,20.21)	

Table 8 *Comparison of Performance Endpoints of End Tidal O2*			
Performance Measurement	Control (N=13)	Smartflow (N=15)	p-value
Percent Duration of Large Deviation (%)*			
Mean±SD (N)	16.4 ± 20.52 (37)	3.2 ± 10.75 (62)	<.001
Median	8.6	0.0	
Range (min,max)	(0.0,66.9)	(0.0,66.7)	

* Large deviation is defined as: when the difference between the measured end tidal concentration and the steady state concentration is > 5%

Agent Usage Endpoint: Overall, the results show that there tends to be a reduction in anesthetic agent usage when using Et Control; in particular, when evaluating the usage rate over the entire case. From the results, the average agent usage rate savings for Et Control was 22% (46% for Desflurane cases (3), 6% for Isoflurane cases (3), and 14% for Sevoflurane cases (6)). This correlates directly with the average Fresh Gas Flow rate for the Et Control (Smartflow) Arm, which was approximately 29% lower than the Control Arm (1.78 ± 0.704 (12) l/min and 2.51 ± 0.795 (12) l/min, respectively). The summary results are shown in Table 9.

Table 9 *Summary of Anesthetic Agent (AA), O2 and Fresh Gas Usage*

Agent Usage	Desflurane Control (N=3)	Desflurane Smartflow (N=3)	Isoflurane Control (N=4)	Isoflurane Smartflow (N=3)	Sevoflurane Control (N=6)	Sevoflurane Smartflow (N=6)	All Subjects Control (N=13)	All Subjects Smartflow (N=12)
Anesthetic Agent								
AA Usage 10 Minutes Following Induction (ml)								
Mean±SD (N)	10.57 ± 7.996 (3)	5.63 ± 1.860 (3)	2.47 ± 1.018 (4)	3.50 ± 0.214 (3)	3.24 ± 0.401 (5)	4.01 ± 1.457 (6)		
Median	6.87	5.62	2.31	3.41	2.98	3.67		
Range (min,max)	(5.10,19.75)	(3.77,7.49)	(1.49,3.78)	(3.34,3.74)	(2.93,3.78)	(1.96,6.02)		
AA Usage from Induction to Case End (ml)								
Mean±SD (N)	76.87 ± 49.171 (3)	75.20 ± 31.262 (3)	37.13 ± 19.559 (4)	22.14 ± 9.910 (3)	36.23 ± 13.092 (5)	47.09 ± 30.758 (6)		
Median	56.25	78.87	34.44	18.75	33.18	35.31		
Range (min,max)	(41.36,132.99)	(42.26,104.46)	(16.44,63.21)	(14.37,33.30)	(22.22,50.40)	(16.98,87.16)		
AA Usage Rate 10 Minutes Following Induction (ml/hr)								
Mean±SD (N)	63.45 ± 47.991 (3)	33.76 ± 11.160 (3)	14.81 ± 6.117 (4)	20.97 ± 1.306 (3)	19.45 ± 2.393 (5)	24.05 ± 8.746 (6)		
Median	41.23	33.71	13.81	20.45	17.86	22.01		
Range (min,max)	(30.59,118.52)	(22.62,44.94)	(8.92,22.68)	(20.01,22.46)	(17.60,22.66)	(11.77,36.14)		
AA Usage Rate From Induction to Case End (ml/hr)								
Mean±SD (N)	38.86 ± 18.234 (3)	20.95 ± 3.067 (3)	9.89 ± 3.379 (4)	9.29 ± 1.566 (3)	16.33 ± 2.290 (5)	14.02 ± 4.456 (6)		
Median	30.93	22.07	9.53	9.07	15.00	15.09		
Range (min,max)	(25.94,59.72)	(17.48,23.30)	(6.38,14.11)	(7.84,10.95)	(14.38,18.96)	(7.39,18.85)		
Oxygen								
O2 Usage 10 Minutes Following Induction (l)								
Mean±SD (N)	31.51 ± 40.020 (3)	12.53 ± 16.273 (3)	11.97 ± 9.844 (4)	13.24 ± 9.431 (3)	19.15 ± 4.726 (5)	18.29 ± 15.068 (6)	19.85 ± 19.637 (12)	15.59 ± 13.250 (12)
Median	11.89	3.77	10.02	14.47	19.52	13.11	15.59	13.11
Range (min,max)	(5.08,77.55)	(2.52,31.31)	(2.23,25.62)	(3.25,21.99)	(11.97,25.25)	(6.15,46.59)	(2.23,77.55)	(2.52,46.59)
O2 Usage From Induction to Case End (l)								
Mean±SD (N)	251.80 ± 128.950 (3)	178.53 ± 62.072 (3)	209.00 ± 62.103 (4)	134.58 ± 35.007 (3)	188.13 ± 50.328 (5)	188.13 ± 62.524 (6)	211.00 ± 75.428 (12)	172.34 ± 56.882 (12)

Table 9 *Summary of Anesthetic Agent (AA), O2 and Fresh Gas Usage*

	Desflurane		Isoflurane		Sevoflurane		All Subjects	
Agent Usage	Control (N=3)	Smartflow (N=3)	Control (N=4)	Smartflow (N=3)	Control (N=6)	Smartflow (N=6)	Control (N=13)	Smartflow (N=12)
Median	212.64	213.99	189.95	152.61	193.79	170.61	192.11	163.52
Range (min,max)	(146.97,395.79)	(106.86,214.75)	(156.93,299.18)	(94.23,156.89)	(137.87,260.85)	(137.22,306.71)	(137.87,395.79)	(94.23,306.71)
O2 Usage Rate 10 Minutes Following Induction (l/min)								
Mean±SD (N)	3.15 ± 3.998 (3)	1.25 ± 1.627 (3)	1.20 ± 0.985 (4)	1.33 ± 0.941 (3)	1.92 ± 0.473 (5)	1.83 ± 1.508 (6)	1.98 ± 1.963 (12)	1.56 ± 1.325 (12)
Median	1.19	0.38	1.00	1.45	1.95	1.31	1.56	1.31
Range (min,max)	(0.51,7.75)	(0.25,3.13)	(0.22,2.56)	(0.33,2.20)	(1.20,2.53)	(0.61,4.66)	(0.22,7.75)	(0.25,4.66)
O2 Usage Rate From Induction to Case End (l/min)								
Mean±SD (N)	2.15 ± 0.731 (3)	0.93 ± 0.502 (3)	0.98 ± 0.189 (4)	1.03 ± 0.444 (3)	1.45 ± 0.190 (5)	1.09 ± 0.360 (6)	1.47 ± 0.579 (12)	1.04 ± 0.382 (12)
Median	1.95	0.80	1.04	0.86	1.42	1.16	1.36	1.08
Range (min,max)	(1.54,2.96)	(0.50,1.48)	(0.70,1.12)	(0.69,1.53)	(1.29,1.75)	(0.46,1.55)	(0.70,2.96)	(0.46,1.55)
Fresh Gas								
Fresh Gas Usage Rate 10 Minutes Following Induction (l/min)								
Mean±SD (N)	3.62 ± 3.824 (3)	1.45 ± 1.490 (3)	1.78 ± 0.888 (4)	1.99 ± 0.937 (3)	2.41 ± 0.576 (5)	2.70 ± 1.672 (6)	2.50 ± 1.878 (12)	2.21 ± 1.461 (12)
Median	1.96	0.63	1.95	1.91	2.00	2.33	2.00	1.86
Range (min,max)	(0.90,7.99)	(0.55,3.17)	(0.55,2.67)	(1.09,2.96)	(1.97,3.12)	(1.17,5.78)	(0.55,7.99)	(0.55,5.78)
Fresh Gas Usage Rate From Induction to Case End (l/min)								
Mean±SD (N)	3.27 ± 1.018 (3)	1.61 ± 1.159 (3)	1.80 ± 0.451 (4)	1.73 ± 0.403 (3)	2.62 ± 0.348 (5)	1.89 ± 0.675 (6)	2.51 ± 0.795 (12)	1.78 ± 0.704 (12)
Median	2.97	1.10	1.88	1.64	2.47	1.95	2.42	1.81
Range (min,max)	(2.43,4.40)	(0.80,2.94)	(1.19,2.26)	(1.38,2.17)	(2.23,2.99)	(0.70,2.74)	(1.19,4.40)	(0.70,2.94)

SD – Standard deviation

Usability Endpoint: The number of setting interactions over the entire case between the Et Control (Smartflow) Arm and the Control Arm was comparable (26 ± 8.7 and 26 ± 12.6, respectively). In Et Control, the minimum number of setting interactions made was 12 and the maximum 47. With the Control device, the range of setting interactions was from 12 to 61.

In addition to determining the number of setting interactions, the users' feedback regarding their interaction with Et Control was collected in a questionnaire. Results show that the investigators favored Et Control because, as a whole, it was easier to use. Clinicians also indicated they could start and stop Et Control and adjust settings without assistance or additional knowledge. This feedback is summarized in Table 10, below.

Table 10 *User feedback summary*

Questionnaire	Et Control (Smartflow)(N=15) **%(n/N)**
Rate Smartflow feature compared to the Fresh Gas Control practice to achieve and maintain target concentrations	
Same	20.0% (3/15)
Smartflow is easier	73.3% (11/15)
Smartflow is more difficult	6.7% (1/15)
Start Smartflow without assistance	100.0% (15/15)
Stop Smartflow without assistance	100.0% (15/15)
Adjust Smartflow user settings without assistance	100.0% (15/15)
React to and understand Smartflow related alarms	86.7% (13/15)
The time from cessation of inhaled anesthetic to discharge from the operating room was typical of similar patients undergoing similar procedures	
Agree	73.3% (11/15)
Neutral	6.7% (1/15)
Strongly agree	20.0% (3/15)
Use the same target end tidal anesthetic concentrations	93.3% (14/15)
Use the same target end tidal oxygen concentrations	100.0% (15/15)

Please note that the Usability Endpoint and the information in Table 10 were not considered as part of the device use-safety assessment during the human factors review. Nonetheless, the information can be used as part of the device usability metrics.

3. **Subgroup Analysis:** No preoperative characteristics were evaluated for potential association with outcomes.

4. **Pediatric Extrapolation:** In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The feasibility clinical study included one principal investigator, and the pivotal clinical study included four principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

2. ET CONTROL USA MASTER PIVOTAL STUDY

A. STUDY DESIGN

A USA pivotal study titled "Multi-site Anesthesia randomized controlled STudy of End-tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)" (MASTER) was performed to evaluate the safety and performance of the investigational Et Control feature. Subjects were treated between June 2017 through July 2018. The final report for this PMA reflected the data collected in that timeframe and included 208 evaluable subjects. There were four investigational sites.

This was a prospective, multi-site, single-blinded (subject blinded), randomized, parallel comparator, confirmatory IDE (G160132) study of the investigational Et Control option of the Aisys CS2 anesthesia device. This pivotal clinical study was designed based on the feasibility clinical study described above.

Subjects enrolled into the study were randomized at a 1:1 ratio to either the Investigational Arm (Et Control Arm) or the Control Arm. Randomization was stratified based on the investigator, subject's pre-existing hypertension status, and subject's ASA status classification (I through III). Randomization sequences were administered through the Interactive Response Technology (IRT) – IXRS®3 System by Almac. Prior to each procedure, subject demographic data, medical history, physical examination, and laboratory assessment data were collected. During each study procedure, safety endpoints and adverse events were recorded. Data was also collected during post-anesthesia care, and a 24-hour follow-up was conducted post-PACU discharge.

The Control Arm used a legally-marketed anesthesia machine without the investigational Et Control option. The investigator used Fresh Gas Control/manual means to adjust the electronic vaporizer and electronic gas mixer on the anesthesia machine without Et Control and monitored the subject's gas concentrations with the anesthesia machine. The Et Control Arm used the anesthesia machine with the investigational Et Control option. The investigator continuously assessed individual response and used Et Control to monitor inspired and End-Tidal Oxygen (EtO2) and anesthesia agent concentration (EtAA) and compared these to the target concentrations. The investigator maintained adequate ventilation to deliver appropriate oxygen and anesthetic agent to the subject. A Data Safety Monitoring Board (DSMB) was

utilized for the study and their reviews were conducted independent of the applicant. The members of the DSMB included two physicians with expertise in anesthesia and one biostatistician.

DSMB meetings were based on the enrollment timeline. Each site was informed to pause enrollment at each enrollment milestone. During each enrollment pause, the safety data were reviewed during scheduled open and closed DSMB sessions.

Table 11 *DSMB Meetings*

Enrollment Milestone	**DSMB Meeting Date**	**Date of DSMB Recommendation**	**DSMB's Recommendation**
Minimum of 20 Et Control subjects enrolled and at least 2 sites initiated and enrolling	30-Aug-2017	13-Sep-2017	No safety issues were identified. The DSMB unanimously recommended that the MASTER-Anesthesia Trial continue without modification.
50% enrollment	19-Dec-2017	19-Dec-2017	No safety issues were identified. The DSMB unanimously recommended that the MASTER-Anesthesia Trial continue without modification.
80% enrollment	17-Apr-2018	18-Apr-2018	No safety issues were identified. The DSMB unanimously recommended that the MASTER-Anesthesia Trial continue without modification.
100% enrollment	15-Aug-2018	15-Aug-2018	At the last DSMB meeting, 100% of the data were reviewed, general updates were discussed, Tables, Listings and Figures reviewed, and data discussed. The DSMB had no additional comments or questions. The DSMB identified no safety issues.

Clinical Inclusion and Exclusion Criteria: Male and female subjects, who were 18 years or older and were scheduled to undergo general inhaled anesthesia during surgery, were screened for enrollment into this clinical study.

Inclusion criteria (subjects who met the following criteria were included in the study):

1. Male or female 18 years old or older;
2. Scheduled to undergo general inhaled anesthesia and could be safely exposed to 100% oxygen for up to 2 minutes during general anesthesia;
3. Expected to have airway secured with laryngeal mask airway (LMA) or endotracheal tube;
4. Scheduled for a surgical procedure that was anticipated by the investigator to last greater than or equal to 1 hour (operative time measured from induction to cessation of general inhalation anesthetic);
5. Met one of the ASA physical status classification system I through III:
    5. ASA Physical Status I = a normal healthy patient
    6. ASA Physical Status II = a patient with mild systemic disease
    7. ASA Physical Status III = a patient with severe systemic disease;
6. Undergoing intravenous induction; and
7. Able to provide written informed consent.

Exclusion criteria (subjects who met any of the following criteria were excluded from the study):

1. Have an emergency medical condition requiring surgery;
2. Are female subjects who were pregnant or lactating;
3. Any subject undergoing cardiac bypass surgery; or
4. Any subject undergoing open chest surgery.

Clinical Follow-Up Schedule: Study procedures for preparation and administration of anesthetic agent were defined in the protocol as three distinct phases: Induction and Intubation, Maintenance, and Emergence. Following surgery, the subject was transferred to the post-anesthesia care unit (PACU). The investigator or designee assessed adverse events (AEs), collected vital signs, and other pertinent information according to the protocol. When the subject met the criteria to discharge from PACU, the last vital signs were collected, and the subject was discharged from PACU.

At the completion of each subject case, the clinician or investigator completed a User Survey Questionnaire. The survey captured responses regarding the usability of Et Control.

Twenty-four hours (±8 hours) post PACU discharge, the investigator or designee collected assessments of intraoperative awareness from the subject (from induction to emergence) and assessed AEs, if any.

Clinical Endpoints:

With regard to safety, the Adverse events (AEs)were observed and recorded, the number of events were counted, and comparison between groups performed.

With regard to effectiveness, the primary objective of the study was to demonstrate that Et Control achieves and maintains the concentration of EtAA and the concentration of EtO2 in a manner that is non-inferior to conventional anesthesia practice, by a margin of 5%, in a surgery population of 18 years or older. To demonstrate this, the following endpoints were evaluated:

The primary endpoints of the Et Control MASTER pivotal trial were:

1. Percent duration without large deviation of EtAA
2. Percent duration without large deviation of EtO_2

The secondary effectivness endpoints were:

1. Response time: time to reach 90% of the desired change in EtAA and EtO2 steady state mean concentration;
2. Settling time: time to achieve the desired EtAA and EtO2 steady state mean concentration;
3. Overshoot amount of the desired EtAA and EtO2 from steady state mean concentration;
4. Accuracy of Et Control in maintaining EtAA and EtO2 control between user set target and steady state end-tidal concentrations – For Et Control only.

B. ACCOUNTABILITY OF PIVOTAL MASTER PATIENT COHORT:

Of the 248 subjects originally enrolled in the pivotal study, 208 (83.9%; 208/248) subjects were available for analysis at the completion of the study, and all post-operative data collection was completed.

Subjects could withdraw consent at any time without prejudice. The reason for withdrawal was recorded. Early termination was defined as any situation in which the clinician determined they no longer want to continue the case, or they chose to discontinue the use of Et Control during a case.

A patient accountability summary table is provided below (Table 12) to identify which subjects were assigned to the control and test cohorts and identify subjects who did not complete the study.

Table 12 *MASTER Patient Accountability Summary*

	Control	Et Control	Screen Failed	Total
Enrolled (N)	118	110	20	248
Intent-To-Treat Population (Randomized) (N)	118	110		228
Completed the Study*, n(%)	116(98.3%)	101(91.8%)		217
Withdrawal*, n (%)	2(1.7%)	9(8.2%)		11
Withdrawal before Surgery Procedure	2	6		8
Withdrawal from the Active Study	0	3		3
Safety Population (Procedure Performed)	116	104		220
Evaluable Population	108	100		208
Per-Protocol Population	104	95		199

* The number in parantheses is showing the percentage of randomized subjects. % = (n/N)100

C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS:

The demographics of the study were recorded as part of the data collection. The study population demographics for the MASTER pivotal trial are provided as Table 13.

Table 13 *Demographics - Intent-to-Treat Population*

	Control (N=118) % (n/N)	Et Control (N=110) % (n/N)
Gender		
Female	53.4% (63/118)	46.4% (51/110)
Male	46.6% (55/118)	53.6% (59/110)
Race		
American Indian or Alaskan Native	1.7% (2/118)	1.8% (2/110)
Asian	2.5% (3/118)	0.9% (1/110)
Black or African American	16.9% (20/118)	19.1% (21/110)
Native Hawaiian or Pacific Islander	0.8% (1/118)	0.0% (0/110)
Other	9.3% (11/118)	8.2% (9/110)
White	68.6% (81/118)	70.0% (77/110)
Ethnicity		
Hispanic or Latino	11.0% (13/118)	10.9% (12/110)
Not Hispanic or Latino	89.0% (105/118)	89.1% (98/110)
ASA Status		
1	14.4% (17/118)	18.2% (20/110)
2	48.3% (57/118)	50.9% (56/110)
3	37.3% (44/118)	30.9% (34/110)

Table 13 *Demographics - Intent-to-Treat Population*		
	Control (N=118) % (n/N)	Et Control (N=110) % (n/N)
History of Hypertension		
Yes	39.0% (46/118)	34.5% (38/110)
No	61.0% (72/118)	65.5% (72/110)
Age (yr)		
Mean±SD (N)	50.5 ± 17.21 (118)	49.3 ± 16.41 (110)
Median	51.0	53.0
Range (min,max)	(18.0,88.0)	(18.0,85.0)
Q1, Q3	(39.0,63.0)	(37.0,61.0)
Height (cm)		
Mean±SD (N)	170.5 ± 10.27 (118)	171.4 ± 11.33 (109)
Median	169.8	171.5
Range (min,max)	(149.9,193.0)	(142.2,195.6)
Q1, Q3	(162.6,177.8)	(162.6,180.0)
Weight (kg)		
Mean±SD (N)	86.8 ± 21.77 (118)	88.4 ± 23.59 (110)
Median	86.6	83.8
Range (min,max)	(39.9,134.4)	(33.0,179.8)
Q1, Q3	(72.6,101.3)	(72.5,101.0)
BMI		
Mean±SD (N)	29.8 ± 6.93 (118)	30.0 ± 7.58 (109)
Median	29.2	28.5
Range (min,max)	(13.8,54.2)	(15.4,56.1)
Q1, Q3	(24.6,34.7)	(24.8,33.3)
Cardiovascular exam		
Abnormal	3.4% (4/118)	2.8% (3/109)
Normal	96.6% (114/118)	97.2% (106/109)
Pulmonary exam		
Abnormal	2.5% (3/118)	3.7% (4/109)
Normal	97.5% (115/118)	96.3% (105/109)
Neurological exam		
Abnormal	8.5% (10/118)	3.7% (4/109)
Normal	91.5% (108/118)	96.3% (105/109)

SD – standard deviation; percent (%) = (n/N)100

D. SAFETY AND EFFECTIVENESS RESULTS:

The purpose of this pivotal clinical study was to demonstrate that the Et Control performance is non-inferior to Fresh Gas Control anesthesia practice in achieving and maintaining the concentration of End-Tidal Anesthetic agent (EtAA) and the concentration of End-Tidal Oxygen (EtO2) in the surgery population of 18 years of age and older.

1. **Safety Results**

Safety risks and AEs were evaluated throughout the study. To ensure an appropriate assessment of the potential risks that the device may pose, randomization was stratified based

on the Investigator, subject's ASA status, and pre-existing hypertension status. While interim effectiveness analyses were not performed for this study, a continuous safety evaluation was conducted. A DSMB was utilized and met at several points (per the DSMB Charter) during the study to review AEs, assess the safety of study subjects and any concerns related to the Et Control feature. No safety issues were identified during any of the DSMB meetings. The DSMB unanimously recommended, after each safety review, that MASTER-Anesthesia Trial continue without modification.

With regards to safety, the endpoint of Adverse Events was evaluated. Adverse Events (AEs) were observed and recorded, the number of events were counted, and comparison between groups was performed. This data is summarized in Table 14.

Overall, there was no statistically significant difference between the number of subjects with AEs in the Et Control Arm (34/104) and the Control Arm (41/116). There was also no statistically significant difference between the number of subjects with SAEs, unanticipated AEs, device related AEs, anesthetic agent related AEs, procedure related AEs, or Severe AEs between the 2 study arms. Based on the randomization scheme, which took into account ASA classification and pre-existing hypertension, there was a similar distribution of subjects with potential risk factors associated with subject ASA classification (1-3) and pre-existing hypertension status in the Et Control Arm and Control Arm. The number of subjects with an AE does not appear to be influenced by ASA status in either study arm. There was no statistically significant difference in the number of subjects with AEs between the 2 arms in subjects with or without pre-existing hypertension. There were no AEs or SAEs related to the Et Control feature.

There were 51.0% (53/104) subjects in the Et Control Arm that received vasoactive medication and 54.3% (63/116) subjects in the Control Arm that received vasoactive medication, a non-statistically significant difference between the two arms (p-value 0.685).

Table 14 *Overall Summary of Adverse Events – Safety Population*

	Control (N=116)	Et Control (N=104) **%(n/N)**	p-value
Subjects with any AE	35.3% (41/116)	32.7% (34/104)	0.776
Subjects with any SAE or UADE	0.9% (1/116)	1.0% (1/104)	1.000
Subjects with any Unanticipated AE	16.4% (19/116)	12.5% (13/104)	0.449
Subjects with any Device Related AE	0.9% (1/116)	0.0% (0/104)	1.000
Subjects with any Anesthetic Agent Related AE	6.9% (8/116)	3.8% (4/104)	0.383
Subjects with any Procedure Related AE	24.1% (28/116)	23.1% (24/104)	0.875

Table 14 *Overall Summary of Adverse Events – Safety Population*			
	Control (N=116)	Et Control (N=104) **%(n/N)**	p-value
Subjects with any Severe AE	6.0% (7/116)	5.8% (6/104)	1.000
Subjects with Procedure Stopped due to AE	0.0% (0/116)	0.0% (0/104)	--
Subjects Withdrawn from Study due to AE	0.0% (0/116)	0.0% (0/104)	--
Subjects with any AE due to Device Failure	0.0% (0/116)	0.0% (0/104)	--

Percent(%) = (n/N)100

The results demonstrate that the patient population was comparable across both arms and that there was no difference in the rate of AEs or vasoactive medication use seen in either arm of the study. There were no safety issues identified related to Et Control and the device performed as intended.

2. Effectiveness Results

The analysis of effectiveness was based on the 208 evaluable subjects at the conclusion of the study. Key effectiveness outcomes are presented in Tables 15-18. Separate analyses were performed for the primary endpoints based on the following scenarios:

- using the algorithm (ALG) to determine the desired end-tidal concentration of anesthetic agent and oxygen for both arm, and
- using the clinicians' or investigators' recorded target (TGT) values of anesthetic agent and oxygen for the Control Arm and using the set target values for the Et Control Arm.

The primary endpoints for this study were:

1. EtAA: The percent duration of EtAA concentration during steady state was to be maintained within the acceptable limit, which was defined as the greater of 5% of the steady state inhaled anesthetic agent concentration and 0.6% v/v for Desflurane (DES), 0.2% v/v for Sevoflurane (SEV), or 0.1% v/v for Isoflurane (ISO). The percent duration is the weighted average of all steady states for a subject using the duration of steady state as the weight.
2. EtO2: Percent duration of EtO2 concentration during steady state maintained within the acceptable limit, which was defined as 5% v/v.

The primary effectiveness was calculated as percent duration for EtAA and EtO2 maintained within the acceptable ranges for each steady state for subjects in the Et Control (Investigational) and Control Arms using both ALG and TGT. The EtAA was within the acceptable range 91.7% ± 10.82 (98) and 98.0% ± 2.05 (98) in the Et Control Arm and 80.8 % ± 17.93 (106) and 45.9 % ± 31.45 (114) in the Control Arm using ALG and TGT,

respectively. The EtO2 was within the acceptable range 98.1% ± 2.76 (100) and 98.8% ± 1.49 (100) in the Et Control Arm and 92.8 % ± 14.38 (116) and 41.0% ± 40.65 (113) in the Control Arm using ALG and TGT, respectively. The results of both analyses scenarios show the lower limit of the 95% Confidence Interval (CI) ≥ 5%. The results indicate that steady states for EtAA and EtO2 were maintained (within the +/- 5% range defined in the protocol) for a greater percentage of time with the Et Control Arm, than with the Control Arm.

The performance of the Et Control feature is considered non-inferior to Fresh Gas Control anesthesia practice.

Table 15 *Comparison of Primary Endpoint of End Tidal Anesthetic Agent – ALG – Intent-to-Treat Population*

	Control (N=118)	Et Control (N=110)	p-value	Difference	Lower Limit of 95% CI	Upper Limit of 95% CI
Percent Duration*						
Mean±SD	80.8 ± 17.93	91.7 ± 10.82	<.001	10.9	6.89	15.01
(N)	(106)	(98)				
Median	86.6	95.7				
Range (min,max)	(11.9,99.8)	(24.5,99.8)				
Q1, Q3	(72.9,93.0)	(88.3,97.8)				

* Percent duration of EtAA concentration during steady state maintained within the acceptable limit is defined as: the difference between the measured end tidal concentration and the steady state concentration (target concentration) is < the greater of 5% of the steady state concentration or 0.1% for ISO, 0.2% for SeEV, 0.6% for DES.

Table 16 *Comparison of Primary Endpoint of End Tidal Anesthetic Agent – TGT – Intent-to-Treat Population*

	Control (N=118)	Et Control (N=110)	p-value	Difference	Lower Limit of 95% CI	Upper Limit of 95% CI
Percent Duration*						
Mean±SD	45.9 ± 31.45	98.0 ± 2.05	<.001	52.1	46.25	57.95
(N)	(114)	(98)				
Median	48.7	98.5				
Range (min,max)	(0.0,99.4)	(87.3,100.0)				
Q1, Q3	(13.2,71.4)	(97.8,99.2)				

* Percent duration of EtAA concentration during steady state maintained within the acceptable limit is defined as: the difference between the measured end tidal

Table 17 *Comparison of Primary Endpoint of End Tidal Oxygen – ALG – Intent-to-Treat Population*

	Control (N=118)	Et Control (N=110)	p-value	Difference	Lower Limit of 95% CI	Upper Limit of 95% CI
Percent Duration*						
Mean±SD	92.8 ± 14.38	98.1 ± 2.76	<.001	5.3	2.64	8.04
(N)	(116)	(100)				
Median	98.3	98.8				
Range (min,max)	(14.7,100.0)	(82.1,100.0)				
Q1, Q3	(93.7,99.6)	(97.8,99.7)				

SD – deviation; percent (%) = (n/N)100; CI – confidence Interval; * Percent duration of EtO2 concentration during steady state maintained within the acceptable limit is defined as: the difference between the measured end tidal concentration and the steady state concentration (target concentration) is < 5% v/v.

Table 18 *Comparison of Primary Endpoint of End Tidal Oxygen – TGT – Intent-to-Treat Population*

	Control (N=118)	Et Control (N=110)	p-value	Difference	Lower Limit of 95% CI	Upper Limit of 95% CI
Percent Duration*						
Mean±SD	41.0 ± 40.65	98.8 ± 1.49	<.001	57.8	50.23	65.39
(N)	(113)	(100)				
Median	29.0	99.5				
Range (min,max)	(0.0,100.0)	(92.9,100.0)				
Q1, Q3	(0.0,89.8)	(98.3,99.9)				

SD – deviation; percent (%) = (n/N)100; CI – confidence Interval; * * Percent duration of EtO2 concentration during steady state maintained within the acceptable limit is defined as: the difference between the measured end tidal concentration and the steady state concentration (target concentration) is < 5% v/v.

The performance of the Et Control feature is considered non-inferior to Fresh Gas Control anesthesia practice.

With regards to effectiveness, the following Secondary Endpoints were evaluated. These results are summarized in Tables 19-22, below.

1. Response time: time to reach 90% of the desired change in EtAA and EtO2 steady state mean concentration:

Results: EtAA response time was statistically significantly faster in the Et Control Arm (73 sec ± 174.1 (283) and 23 sec ± 40.9 (520)) than in the Control Arm (196 sec ± 378.3 (184) and 196 sec ± 455.0 (281)) using ALG and TGT. EtO2 response time was statistically significantly faster in the Et Control Arm (93 sec ± 77.3 (238) and 129 sec ± 451.7 (240)) than in the Control Arm (246 sec ± 346.8 (318) and 406 sec ± 727.8 (209)) using ALG and TGT. The significantly faster response time (p value <.001) in the Et Control Arm is intended and expected, because with Et Control there is a direct end tidal target being driven towards by actively controlling gas flows and concentrations to achieve those end target values.

2. Settling time: time to achieve the desired EtAA and EtO2 steady state mean concentration:

   Results: EtAA settling time was statistically significantly faster in the Et Control Arm (105 sec ± 181.9 (283) and 31 sec ± 74.9 (520)) than in the Control Arm (165 sec ± 186.4 (184) and 371 sec ± 633.7 (281)) using ALG and TGT. EtO2 settling time was statistically significantly faster (p-value <.001) in the Et Control Arm (123 sec ± 117.5 (238) and 167 sec ± 121.1 (240)) than in the Control Arm (235 sec ± 213.2 (318) and 815 sec ± 1327.2 (209)) using ALG and TGT.

3. Overshoot amount of the desired EtAA and EtO2 from steady state mean concentration:

   Results: There was no statistically significant difference (p-value = 0.055) between EtAA overshoot amount in the Et Control Arm (8.85% ± 12.026 (283)) compared to the Control Arm (6.54% ± 13.576 (184)) using ALG. EtAA overshoot amount was significantly lower (p-value <.001) in the Et Control Arm (5.28% ± 6.953 (519)) than in the Control Arm (12.09% ± 27.085 (278)) using TGT. There was no statistically significant difference (p-value = 0.423) between EtO2 overshoot amount in the Et Control Arm (3.47% ± 8.238 (238)) compared to the Control Arm (2.80% ± 11.373 (318)) using ALG. EtO2 overshoot amount was significantly lower (p-value <.001) in the Et Control Arm (2.14% ± 6.277 (240)) than in the Control Arm (11.13% ± 20.2662 (209)) using TGT.

4. Accuracy of Et Control in maintaining EtAA and EtO2 control between user set target and steady state end-tidal concentrations (for Et Control only). The accuracy measures include percent difference relative to the user set target and percent duration over the steady state with percent difference greater than 5%, 10%, and 15% of the user set target.

   Results: For all agent types, the absolute difference between Steady State and Set EtAA Concentrations was within the acceptable limits defined by the primary endpoint using ALG and TGT. The acceptable limits defined by the primary endpoint were: 0.1% of Isoflurane, 0.2% for Sevoflurane, 0.6% for Desflurane. The data shows that Et Control accuracy is maintained across the full spectrum of Minimum Alveolar Concentration (MAC) settings.

The absolute difference between Steady State and Set EtO2 Concentrations was within the acceptable limit defined by the primary endpoint using ALG and TGT. The acceptable limit defined by the primary endpoint was < 5% v/v. The data shows that Et Control accuracy is maintained across the full spectrum of EtO2 settings.

Table 19 *Comparison of Performance Endpoint of End Tidal Anesthetic Agent – ALG – Intent-to-Treat Population*

	Control (N=118) % (n/N)	Et Control (N=110) % (n/N)	p-value
Response Time (sec)			
Mean±SD (N)	196 ± 378.3 (184)	73 ± 174.1 (283)	<.001
Median	48	36	
Range (min,max)	(0,2512)	(0,2339)	
Settling Time (sec)			
Mean±SD (N)	165 ± 186.4 (184)	105 ± 181.9 (283)	<.001
Median	82	39	
Range (min,max)	(0,860)	(0,1207)	
Overshoot Amount (% to mean)			
Mean±SD (N)	6.54 ± 13.576 (184)	8.85 ± 12.026 (283)	0.055
Median	0.00	5.01	
Range (min,max)	(0.00,78.33)	(0.00,100.00)	
>10%	21.7% (40/184)	27.6% (78/283)	0.191
>20%	10.9% (20/184)	11.0% (31/283)	1.000
>30%	6.5% (12/184)	5.7% (16/283)	0.695
Average Deviation (% to mean)			
Mean±SD (N)	7.19 ± 3.711 (184)	4.44 ± 2.690 (283)	<.001
Median	6.48	3.81	
Range (min,max)	(2.76,27.76)	(0.63,16.89)	
Maximum Deviation (% to mean)			
Mean±SD (N)	37.51 ± 20.875 (184)	42.22 ± 36.864 (283)	0.772
Median	33.06	33.33	
Range (min,max)	(13.61,187.24)	(13.13,274.46)	
Half Width of 95% CI of Deviation (% to mean)			

Table 19 *Comparison of Performance Endpoint of End Tidal Anesthetic Agent – ALG – Intent-to-Treat Population*

	Control (N=118) % (n/N)	Et Control (N=110) % (n/N)	p-value
Mean±SD (N)	10.58 ± 4.568 (184)	7.57 ± 3.811 (283)	<.001
Median	9.31	6.58	
Range (min,max)	(4.13,28.72)	(2.06,24.72)	

Table 20 *Comparison of Performance Endpoints of End Tidal Anesthetic Agent – TGT – Intent-to-Treat Population*

	Control (N=118) % (n/N)	Et Control (N=110), % (n/N)	p-value
Response Time (sec)			
Mean±SD (N)	196 ± 455.0 (281)	23 ± 40.9 (520)	<.001
Median	24	4	
Range (min,max)	(0,4407)	(0,317)	
Settling Time (sec)			
Mean±SD (N)	371 ± 633.7 (281)	31 ± 74.9 (520)	<.001
Median	140	0	
Range (min,max)	(0,4407)	(0,705)	
Overshoot Amount (% to mean)			
Mean±SD (N)	12.09 ± 27.085 (278)	5.28 ± 6.953(519)	<.001
Median	0.00	3.81	
Range (min,max)	(0.00,169.60)	(0.00,100.00)	
>10%	23.5% (66/281)	9.2% (48/520)	<.001
>20%	16.7% (47/281)	3.1% (16/520)	<.001
>30%	12.5% (35/281)	1.2% (6/520)	<.001
Average Deviation (% to mean)			
Mean±SD (N)	20.27 ± 13.360 (281)	1.96 ± 0.877(520)	<.001
Median	16.06	1.69	
Range (min,max)	(2.81,73.71)	(0.63,5.04)	
Maximum Deviation (% to mean)			
Mean±SD (N)	85.92 ± 27.773 (281)	33.74 ± 26.887 (520)	<.001
Median	100.00	27.14	
Range (min,max)	(16.00,124.29)	(8.00,265.00)	
Half Width of 95% CI of Deviation (% to mean)			

Table 20 *Comparison of Performance Endpoints of End Tidal Anesthetic Agent – TGT – Intent-to-Treat Population*

	Control (N=118) % (n/N)	Et Control (N=110), % (n/N)	p-value
Mean±SD (N)	22.29 ± 16.240 (281)	4.57 ± 1.950 (520)	<.001
Median	18.20	4.14	
Range (min,max)	(1.83,71.75)	(1.53,16.78)	

Table 21 *Comparison of Performance Endpoints of End Tidal Oxygen – ALG – Intent-to-Treat Population*

	Control (N=118) %(n/N)	Et Control (N=110) %(n/N)	p-value
Response Time (sec)			
Mean±SD (N)	246 ± 346.8 (318)	93 ± 77.3 (238)	<.001
Median	154	83	
Range (min,max)	(0,3600)	(0,341)	
Settling Time (sec)			
Mean±SD (N)	235 ± 213.2 (318)	123 ± 117.5 (238)	<.001
Median	213	125	
Range (min,max)	(0,930)	(0,720)	
Overshoot Amount (% to mean)			
Mean±SD (N)	2.80 ± 11.373 (318)	3.47 ± 8.238 (238)	0.423
Median	0.00	0.48	
Range (min,max)	(0.00,126.93)	(0.00,73.36)	
>10%	6.9% (22/318)	9.2% (22/238)	0.343
>20%	3.5% (11/318)	5.0% (12/238)	0.393
>30%	1.9% (6/318)	2.1% (5/238)	1.000
Average Deviation (% to mean)			
Mean±SD (N)	4.26 ± 5.111 (318)	1.35 ± 0.958 (238)	<.001
Median	2.43	1.11	
Range (min,max)	(0.62,32.79)	(0.42,5.89)	
Maximum Deviation (% to mean)			
Mean±SD (N)	34.22 ± 24.837 (318)	32.65 ± 23.080 (238)	0.423
Median	29.19	27.51	

Table 21 *Comparison of Performance Endpoints of End Tidal Oxygen – ALG – Intent-to-Treat Population*

	Control (N=118) %(n/N)	Et Control (N=110) %(n/N)	p-value
Range (min,max)	(6.58,128.91)	(5.37,134.00)	
Half Width of 95% CI of Deviation (% to mean)			
Mean±SD (N)	7.49 ± 7.643 (318)	3.71 ± 2.489 (238)	<.001
Median	4.84	2.84	
Range (min,max)	(1.25,52.91)	(0.85,20.43)	

Table 22 *Comparison of Performance Endpoints of End Tidal Oxygen – TGT – Intent-to-Treat Population*

	Control (N=118) %(n/N)	Et Control (N=110) %(n/N)	p-value
Response Time (sec)			
Mean±SD (N)	406 ± 727.8 (209)	129 ± 451.7 (240)	<.001
Median	224	73	
Range (min,max)	(0,6801)	(0,6723)	
Settling Time (sec)			
Mean±SD (N)	815 ± 1327.2 (209)	167 ± 121.1 (240)	<.001
Median	432	155	
Range (min,max)	(0,8331)	(0,873)	
Overshoot Amount (% to mean)			
Mean±SD (N)	11.13 ± 20.662 (209)	2.14 ± 6.277 (240)	<.001
Median	1.64	0.00	
Range (min,max)	(0.00,215.53)	(0.00,52.68)	
>10%	34.9% (73/209)	6.3% (15/240)	<.001
>20%	19.6% (41/209)	3.3% (8/240)	<.001
>30%	11.5% (24/209)	1.3% (3/240)	<.001
Average Deviation (% to mean)			
Mean±SD (N)	18.10 ± 14.745 (209)	2.62 ± 2.247 (240)	<.001
Median	13.36	1.92	
Range (min,max)	(0.73,81.34)	(0.45,14.86)	
Maximum Deviation (% to mean)			
Mean±SD (N)	61.86 ± 58.845 (209)	35.12 ± 22.938 (240)	<.001

Table 22 *Comparison of Performance Endpoints of End Tidal Oxygen – TGT – Intent-to-Treat Population*

	Control (N=118) %(n/N)	Et Control (N=110) %(n/N)	p-value
Median	44.13	31.54	
Range (min,max)	(0.73,385.80)	(5.12,134.50)	
Half Width of 95% CI of Deviation (% to mean)			
Mean±SD (N)	11.94 ± 18.176 (209)	3.82 ± 2.513 (240)	<.001
Median	5.01	2.95	
Range (min,max)	(0.00,124.28)	(0.81,20.70)	

Overall results: The primary endpoint for the study was achieved and demonstrated that Et Control achieves and maintains the concentration of EtAA and the concentration of EtO2 in a manner that is non-inferior to Fresh Gas Control anesthesia practice in the surgery population (18 years of age and older). The results of the pivotal study support the conclusion that the Et Control feature can be used to safely deliver the clinician set and controlled EtAA and EtO2 concentrations with non-inferior performance to Fresh Gas Control anesthesia practice. Et Control behaved in the manner expected and according to its design specifications, and satisfactorily achieved and maintained the set EtAA and EtO2 concentrations in clinical environments at 4 different U.S. hospital sites. The results from the study did not present any new evidence of risks related to the Et Control feature.

Pediatric Extrapolation: In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The feasibility clinical study included one principal investigator, and the pivotal clinical study included four principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

In addition to the clinical trials on the device as noted above, there has been use of Et Control in clinical research and in clinical use outside of the United States, as documented in peer

reviewed publications (refer to the References for literature citations). The feature has been used outside of the United States since its first release in 2010.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Anesthesiology and Respiratory Therapy Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

1. EFFECTIVENESS CONCLUSIONS

The primary effectiveness endpoint of the pivotal clinical trial is the non-inferiority of Et Control compared to Fresh Gas Control/conventional anesthesia. The clinical data indicate that steady states for EtAA and EtO2 were maintained (within the +/- 5% range defined in the protocol) for a greater percentage of time with the Et Control Arm than with the Control Arm. Et Control was able to achieve and maintain the clinician-set targets for EtAA and EtO2, and the maintenance of steady states with Et Control was considered more stable compared to the Control Arm. The results of the pivotal study support the conclusion that the Et Control feature can be used to safely deliver the clinician set and controlled EtAA and EtO2 concentrations with non-inferior performance to conventional anesthesia practice. The results of the study provided evidence that the Et Control design functioned as intended. The design mitigations built into the Et Control feature, including exiting Et Control or going to a temporary fallback state if there are issues detected, performed as intended and clinicians were able to safely and effectively use the feature and respond to on-screen information. Et Control accuracy was maintained across the full spectrum of EtO2 and EtAA settings.

The results indicate that Et Control behaved in the manner expected and according to its design specifications, and satisfactorily achieved and maintained the set EtAA and EtO2 concentrations in clinical environments at 4 different U.S. hospital sites.

Secondary effectiveness endpoints demonstrate that Et Control resulted in EtAA response time and EtO2 response time which was statistically significantly faster, EtAA settling time which was statistically significantly faster, and EtO2 settling time which was statistically significantly faster in the Et Control Arm than in the Control Arm. Additionally, the data shows that Et Control accuracy is maintained across the full spectrum of EtO2 settings.

2. SAFETY CONCLUSIONS

The results from the study did not present any new evidence of risks related to the Et Control feature. Overall, there was no statistically significant difference between the number of subjects with AEs in the Et Control Arm (34/104) and the Control Arm (41/116). There was

also no statistically significant difference between the number of subjects with SAEs, unanticipated AE, device related AE, anesthetic agent related AE, procedure related AE, or severe AE between the 2 study arms. Based on the randomization scheme which took into account ASA classification and pre-existing hypertension, there was a similar distribution of subjects with potential risk factors associated with subject ASA classification (1-3) and pre-existing hypertension status in the Control Arm and Et Control Arm. Analysis of the safety and effectiveness results based on numerous variables including agent type and ASA status did not identify any safety or performance differences between groups. The number of subjects with an AE does not appear to be influenced by ASA status in either study arm. There was no statistically significant difference in the number of subjects with AEs between the 2 arms in subjects with or without pre-existing hypertension. There are no AEs or SAEs related to Et Control.

There were no significant differences in the amount of vasoactive medications delivered between the two groups. 51.0% (53/104) of subjects in the Et Control Arm received vasoactive medication, and 54.3% (63/116) of subjects in the Control Arm received vasoactive medication.

No evidence of safety concerns related to the use of Et Control was identified. The evidence demonstrates Et Control performed as intended, met the specifications, and can be used to safely deliver EtO2 and EtAA across the range of agents and studied population (18 years or older)

3. BENEFIT-RISK DETERMINATION

The clinical studies demonstrated the benefits of Et Control and the ability of the feature to meet the defined study endpoints. The results of the pivotal study support the conclusion that the Et Control feature can be used to safely deliver anesthetic agent and oxygen to achieve the clinician set and controlled EtAA and EtO2 concentrations with non-inferior performance and safety to Fresh Gas Control anesthesia practice. Et Control behaved in the expected manner and satisfactorily achieved and maintained the set EtAA and EtO2 concentrations in clinical environments in a wide variety of surgical cases and a diverse patient population. There were no adverse events related to the Et Control feature during either the feasibility or pivotal clinical studies. The Et Control feature did not present any new evidence of risks or safety concerns related to the Et Control feature.

Given the information available from the design of the device including the risk mitigations incorporated, the verification and validation, as well as the clinical study results and experience in clinical use outside the United States as represented by the peer-reviewed journal articles, the data supports that the probable benefits of the Et Control feature outweigh its probable risks. Probable benefits include faster EtAA and EtO2 response time, faster EtAA and EtO2 settling time, fewer required interactions with the device, less anesthetic agent use and Et Control accuracy is maintained across the full spectrum of EtO2 settings.

i. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

4. OVERALL CONCLUSION

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on 03/17/2022.

The applicant's manufacturing facilities have been inspected and found to comply with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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