Cover Page	
Study Title	EASiVENT *Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU subjects*.
Study NCT number	NCT04400643
Document	Statistical Analysis Plan
Document version and Date	1.0 18 March 2022

IDDI

ADDING VALUE TO CLINICAL DATA

Confidential

Statistical Analysis Plan

Sponsor:	Hamilton Medical AG
Protocol Title:	Prospective, Multicentre, Randomized, Controlled Study Comparing Efficacy and Safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU Subjects.
Study Code:	EASiVENT
Version:	1.0 of 18 March 2022

The signatures on this form indicate approval of this document.

Signature and Date

VERSION HISTORY

Version	Date	Effective Date	Changes
1.0	Draft version 05 Feb 2020	n/a	Initial version. Part of IDE submission
	DRAFT version 13 May 2020	Was not released and finalized, internal tracking.	Alignment with protocol version 1.1 13 May 2020. Patient word replaced in the document to subject. Secondary endpoint is updated with Fio2 level assessment in both study arms. VFD section is updated to clarify the 28D follow-up and definition of NIV is added. Clarification added how to calculate VFD and when study ventilation will end. Dropout definition is updated and expected number of % is added. O'Brien-Fleming-Type method is added instead of Wang-Tsiatis. Sample sizes and operational characteristics for the trial using O'Brien Fleming boundaries for futility and efficacy is added. Müller and Schäfer method is replaced by Following Mehta and Pocock (Mehta, 2011). Added to use the ITT population as the primary analysis population and the mITT for additional analyses. Intervention period (Day 1 – Day 27) is updated to be aligned with CIP version 1.1. Section 3.4 updated including changes in the sample size and enrolment cap added per site. Clarification when the subject will exit the study is added in section 4.1.2 Participant Duration. Section 4.2.2. DSMB is updated to be aligned with CIP version 1.1.

			Section 4.4 Subgroup Definitions is updated with forest plots analysis implementation. Section 4.8 Methods to be Used for Handling missing data is updated to reflect the method of imputation. Section 8.4. Sensitivity Analyses and 8.5 Subset Analysis sections are added. Section 9.4 Adverse Events and Serious Adverse Event section is updated to be aligned with CIP version 1.1. 9.6 Vital Signed, Physical Findings and Other Observations Related to Safety section is updated that the pivotal subjects' data during bedside training phase will not be taken into account for the study outcome and statistics. Appendix 1: updated to be in line with CIP version 1.1.
	DRAFT version 13 APRIL 2021	Was not released and finalized, internal tracking.	Section 4.4 Additional subgroup analyses for the six ventilation and oxygenation variables Section 9.2 Additional secondary safety variables added: • Severe Acute kidney injury (AKI) in need for CRRT/IHD • Severe critical illness neuro-myopathy signs of tetraplegia affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for

			limb movement, but not against gravity and score 3 for movement against gravity but not resistance. • Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points. • Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ failure affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation. • Extubation failure that is related to weaning process by itself or associated conditions based on the interpretation of the investigator. • Need for tracheostomy that is related to a difficult weaning process or associated conditions based on the interpretation of the investigator.
	DRAFT version 13 of 16th July 2021	Was not released and finalized, internal tracking.	Section 3.4 Inclusion CAP at each site changed to 15%. Section 4.4 Forest plots to report primary efficacy endpoints and some key secondary efficacy endpoints by regions.

			Section 6 Baseline characteristics by treatment and by region (EU and US)
	Draft 1st October 2021	Was not released and finalized, internal tracking	Section 4.9: Changes to protocol Section 7.4: Other sensitivity analysis on the primary efficacy variable using ANCOVA model and adjusting for region. Section 7.6: Individual patient profiles plots for FiO2 and PEEP.
	Draft 29th November 2021	Was not released and finalized, internal tracking	Section 4.2: Source of Tables, listings and figures to be presented during each DSMB meeting. Section 8.6: Normal ranges for vital signs parameters; systolic blood pressure, diastolic blood pressure, mean blood pressure and pulse rate.
1.0	Final version 1.0 18 March 2022		Individual patient profile plots was requested for the following additional parameters; VTe/IBW, Ftot, Fspont, mechanical power and Pmax minus PEEP Section 8.1: Extent of exposure to investigational device.

Table of Contents

1. List of Abbreviations and Definition of Terms

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
APRV	Airway Pressure Release Ventilation
ARDS	Acute Respiratory Distress Syndrome
ASADE	Anticipated Serious Adverse Effect
ASV	Adaptive Support Ventilation
ATC	Anatomical Therapeutic Chemical
CP	Conditional Power
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTC	Common Toxicity Criteria
DSMB	Data and Safety Monitoring Board
ECCO2R	Extracorporeal Carbon Dioxide Removal
ECMO	Extracorporeal Membrane Oxygenation
EU	European Union
FiO_2	Fraction of Inspiratory Oxygen
ICU	Intensive Care Unit
IMDRF	International Medical Device Regulators Forum
IMV	Invasive Mechanical Ventilation
ITT	Intention-To-Treat
MAR	Missing At Random
MNAR	Missing Not At Random
MV	Mechanical Ventilation
NCI	National Cancer Institute
NIV	Non-Invasive Ventilation
PaO_2	Partial Pressure of Oxygen
PEEP	Positive End-Expiratory Pressure
$PetCO_2$	End-tidal partial pressure of carbon dioxide
Pmax	Maximum Pressure
P_{PLAT}	Plateau Pressure
RR	Respiratory Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBT	Spontaneous Breathing Trial
SOFA	Sequential Organ Failure Assessment
SpO2	Oxygen Saturation Measured by Pulse Oximetry
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VFD	Ventilator Free Day(s)
VT	Tidal Volume
WHO-DD	World Health Organization Drug Dictionary

2. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for the clinical trial for Hamilton Medical AG with protocol number: EASiVENT_CIP_V2.0_clean_02OCT2020 (Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated ventilation in adult ICU subjects).

The ICH guideline E3 "Structure and Content of Clinical Study Reports" and E9 "Statistical Principles for Clinical Trials", as well as E9 (R1) "Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials" were used as guides to the writing of the plan.

This SAP is based on the following study document(s):

- Clinical Investigation Plan EASiVENT Version 2.0 of 02Oct2020
- Case Report Form, Version 6.0 of 07Jun2021

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Overall objective of the study

The study is designed to assess safety and efficacy of INTELLiVENT-ASV, a software accessory integrated in Hamilton ventilators that is designed to fully and automatically adjust both oxygenation and ventilation settings.

Efficacy and safety are primarily assessed to keep ventilation and oxygenation variables in optimal target ranges according to pertinent guidelines for Invasive Mechanical Ventilation.

3.1.2 Primary Objective

Efficacy: To assess the efficacy of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrolment.

Safety: To assess the safety of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrolment.

3.1.3 Secondary Objectives

The secondary objective is the assessment of ventilation safety and effectiveness by measuring physiologic parameters, clinical outcomes, associated interventions, workload, safety events and typical clinical complications up to day 28 after enrolment.

3.1.4 Tertiary Objectives

Efficacy: To assess the efficacy of INTELLiVENT-ASV in adult ICU subjects from day 8 up to day 28 after enrolment.

Safety: To assess the safety of INTELLiVENT-ASV in adult ICU subjects from day 8 up to day 28 after enrolment.

3.2 Study Endpoints

3.2.1 Primary endpoints

Primary endpoint will be measured continuously during the ventilation period up to 7 days after enrolment.

Efficacy

Efficacy of the investigational device will assess the ability to keep ventilation and oxygenation variables in optimal target ranges.

This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range during the 7 days after enrolment:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia. Please refer to Values for optimal, acceptable and sub-optimal ranges of the study protocol.

Safety:

The primary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range during the first seven (7) days of enrolment. For the values of sub-optimal ranges, please refer toValues for optimal, acceptable and sub-optimal ranges of the study protocol.

3.2.2 Secondary endpoints

Secondary endpoints will be recorded continuously until the end of intervention period (up to 28 days after enrolment).

Efficacy

Physiologic parameters:

- Respiratory mechanics (Compliance, resistance, expiratory time constant) will be assessed automatically breath-by-breath.
- Oxygenation (PaO_2/FiO_2, FiO_2, PEEP)
- Ventilation (VT, RR, mechanical power will be assessed automatically breath-by-breath, ΔP, P_{PLAT}, will be assessed twice a day).
- FiO_2 levels to be assessed in both study arms

Outcomes:

- Duration of invasive mechanical ventilation: time between intubation and last extubation or death. When a subject is re-intubated within 48 hours after extubation, the period between extubation and re-intubation is considered as invasive ventilation days.

- Duration of non-invasive mechanical ventilation: noninvasive ventilation refers to CPAP or pressure support NIV delivered before intubation or after extubation. High flow therapy is not considered in this calculation.
- Total duration of mechanical ventilation: sum of duration of invasive and noninvasive mechanical ventilation.
- Time from intubation to first successful Spontaneous Breathing Trial (SBT)
- Passive ventilation duration: passive ventilation is defined when the percentage of subject's triggered breath is lower than 25% of total respiratory rate.
- Weaning duration: time between the first sedation cessation to the last extubation or the last disconnection from the ventilator for tracheostomized subjects. Subjects re-intubated within 48h after extubation will be kept in the study. Subject re-intubated beyond 48h will be considered as weaned from the ventilation.
- VFD to day28 are defined as: the number of days from the time of initiating unassisted breathing to day 28 after start of ventilation, assuming survival for at least 48 hours and no re-intubation within 48 hours after initiating unassisted breathing and continued unassisted breathing to day 28.

  NIV will be considered as assisted breathing. CPAP will not be considered as assisted breathing. Ventilator free days will be calculated separately for invasive ventilation support and any other ventilation support (invasive and noninvasive).

  If a subject returns to assisted breathing (re-intubated within 48 hours) and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28.

  A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation.

  If a subject was receiving assisted invasive breathing on day 27 or dies prior to day 28, VFDs will be -1.

For subjects transferred to another hospital or other health care facility, study data collection will be stopped but subject will be contacted via a phone call on day 28 post enrolment to assess VFD endpoint if possible:

- ICU and hospital length of stay (discharge).
- ICU mortality (if the subjects is hospitalized in another hospital than the investigational site)
- Non-intensive ventilation (NIV) duration
- 28 days mortality
- Ventilation duration for study period (if re-intubated beyond 48h)
- Tracheostomy

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent. A maximum dropout rate of 5% of these cases is expected.

<u>Associated interventions:</u>

- Duration and doses of sedative infusion
- Duration and doses of analgesic infusion
- Duration and doses of vasopressors
- Duration and doses of myorelaxant
- Number of recruitment maneuvers
- Time spent in prone position
- Time spent with nitric oxide

Workload:

- Number of manual adjustments will be collected in both ventilation arms until considered as weaned from the ventilation.

Safety:

The secondary safety endpoint will be determined by evaluating the number of Serious Adverse Events (all SAEs included) within 28 days of the enrolment and the rescue therapy requirement (APRV, high frequency ventilation, ECCO2R and ECMO).

In addition, to better characterise the risk profile of the study population the following non-mechanical ventilation related adverse events will be recorded on study day 7 and 28.

- Severe Acute kidney injury (AKI) in need for CRRT/IHD
- Severe critical illness neuro-myopathy signs of tetraplegia affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for limb movement but not against gravity and score 3 for movement against gravity but not resistance.
- Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points.
- Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ failure affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation.
- Extubation failure that is related to weaning process by itself or associated conditions based on the interpretation of the investigator.
- Need for tracheostomy that is related to a difficult weaning process or associated conditions based on the interpretation of the investigator.

3.2.3 Tertiary endpoints

Tertiary endpoints will be measured continuously during ventilation period from day 8 up to day 28 after enrolment.

Efficacy

Efficacy of the investigational device will assess the ability to keep ventilation and oxygenation variables in optimal target ranges.

This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range during day 8 through day 28:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia.

Tertiary endpoints will be measured continuously during ventilation period from day 8 up to day 28 after enrolment.

Safety:

The tertiary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range from day 8 up to day 28 after enrolment.

3.3 Study Design

EASiVENT is a Pivotal, two-arm, controlled, single-blind, multicenter, randomized trial of INTELLiVENT-ASV versus non automated Ventilation in adult ICU subjects.

3.3.1 Randomization

The subjects will be randomized to either INTELLiVENT-ASV or Non-automated Ventilation using in a 1:1 ratio by a computerized central randomization system.

The two study arms will be stratified by subject condition at inclusion (normal lungs, ARDS, chronic hypercapnia, or brain injury) and by site to ensure balanced assignment for interventions at each site. The randomization scheme will be generated and maintained by the randomization module part of the electronic case report form (eCRF).

3.3.2 Blinding

Study subjects will be blinded to the random intervention assignment of all study participants. Therefore, this study is considered single blind since study staff will know each subject's intervention assignment.

3.3.3 Justification for the design of the clinical investigation

The reference treatment used for comparison is a combination of controlled modes for passive subjects (volume control or pressure control) and assisted/spontaneous modes for active subjects (synchronized intermittent mechanical ventilation or pressure support).

Sample size has been adjusted with an adaptive design to be able to fulfill the targeted endpoints (see section 3.4).

3.4 Sample Size Determination

A minimum of 254 and maximum of 508 subjects will be included in this study, based on adaptive sample size assessments at scheduled 2nd interim analysis. Subjects will be selected for this study according to Section 7 (Study population) of the protocol.

Requirements related to participant withdrawal from the study are described in Section 7.6 (Study Withdrawal) of the protocol. All sites will have a minimum number of enrolment targets in order to meet overall cross-site enrolment and protocol goals.

Inclusion will be halted at sites that reach the 15% inclusion cap of total enrolment and a 50%-50% geographic distribution (EU vs US) in terms of patients is expected.

3.4.1 Group sequential design with 2 interim analyses

The planned sample size is a minimum of 254 and a maximum of 508 subjects.

The sample sizes for this trial are calculated using the following assumptions:

- significance level equal to 0.025 (1-sided)
- power of 0.8 (at final analysis)
- allocation ratio of 1:1
- Two interim analyses at half and three-quarter information time (i.e. when half and three-quarter of the subjects are evaluable for response), using spending functions with O'Brien-Fleming-Type boundaries for efficacy and futility.
- Efficacy endpoint (%All in optimal, more is better) on logit-scale:
  - Mean conventional = -1.86
  - Mean INTELLiVENT-ASV = -1.28
  - Sd = 1.5 for both devices
- Safety endpoint (%Any in sub-optimal, less is better) on logit-scale:
  - Mean conventional = -0.09
  - Mean INTELLiVENT-ASV = -0.74
  - Sd = 1.6 for both devices
- Correlation between endpoints = -0.85
- Dropout could occur when subjects are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU or withdrawal of informed consent. A maximum dropout rate of 5% of these cases is expected. Given the large uncertainty on the assumed performance differences and the inclusion of a sample size reassessment, the initial sample size is not increased to deal with this dropout rate. At the second interim the sample size will be re-estimated, taking this observed dropout rate into account.

The table below shows the sample sizes and characteristics of a study with 2 interim analyses, with O'Brien-Flemming boundaries for efficacy and futility. The final sample size for this group sequential design is 254. 254 stands for the number of subjects with evaluable endpoints and means more subjects might have to be enrolled to reach this number. The p-values for significance are increasing at each analysis while the p-value to stop for futility decreases from the first interim analysis to the final analysis. The study has a high probability to stop at the first interim analysis if both ventilation modes have an equal performance.

Sample sizes and operational characteristics for the trial using O'Brien Fleming boundaries for futility and efficacy.

Analysis	SS	Z Efficacy	Nominal p Efficacy	α Spend	Power (Prob stop H_A)
1 (IA1)	128	2.96	0.0015	0.0015	0.25

2 (IA2)	192	2.36	0.0093	0.0097	0.43
3 (final)	254	2.02	0.0220	0.0250	0.19

Analysis	SS	Z Futility	Nominal p Futility	Prob Futility Stop (Prob stop under H_0)
1 (IA1)	128	0.44	0.3315	0.67
2 (IA2)	192	1.34	0.0904	0.25
3 (final)	254	2.02	0.0220	0.06

Recorded data has to be 24 hours at minimum, and 80% of the invasive ventilation duration have to be recorded in the Memory box. Note that subjects for which less than 80% of mechanical ventilation time could be recorded due to documented technical reasons, the recorded data (with 'percent spent' calculated per the recorded time) will be used for the primary analysis of the co-primary endpoints.

3.4.2 Adaptive sample size increase

An adaptive sample size reassessment is foreseen at the second interim analysis. In case promising results are obtained at this interim analysis, additional resources will be committed to the trial. Following Mehta and Pocock (Mehta, 2011), sample sizes will only be increased in case the interim results are promising, in which case the overall type-I error is not inflated by use of the conventional Wald Statistic. The maximum number of additional subjects will be capped at 254 (above the pre-planned 254 subjects) or a maximal total sample size of 508. More specifically, this 'promising zone' is defined in terms of the conditional probability of rejecting the null hypothesis at final analysis, given the estimated performance difference at interim ('conditional power') and assuming that this estimated performance difference is the true underlying difference. Depending on the conditional power (CP) for each of the two endpoints at the second interim analysis, three different zones and anticipated actions are to be considered:

1) **Unfavourable zone**: At least one endpoint with CP <0.33.

The interim results are so disappointing that it is not worth to increase the sample size to retrieve CP and the original sample size is retained. This zone is defined as 0 to 0.33, for a sample size reassessment at 0.75 information fraction. If the CP for either of endpoints is below 0.33, this is considered unfavourable, and no sample size increase will be performed.

2) **Promising zone**: Both endpoints with CP >0.33, at least one endpoint with CP <0.80

If the CP is above 0.33 but below the originally planned 0.80 for at least one primary endpoint, the sample size will be increased by just the right amount to recover the targeted power of 0.80, while not exceeding the pre-specified maximal sample size of 508 subjects. As stated above, both endpoints would need to have a CP above 0.33 and one endpoint a CP below 0.80 to embark on a sample size increase. The sample size increase will be set to the highest of two recalculated sample sizes if both endpoints have a CP between 0.33 and 0.80.

3) **Favourable zone**: Both endpoints CP >0.80

The conditional power at second interim analysis is 0.80 or larger for both endpoints. In this zone, the interim results are sufficiently favourable that the trial continues to the original sample size without the need to adaptively increase the trial size.

4. General Analysis Definitions

Data will be expressed by mean±SD or median (interquartile range) depending on the normality of the distribution assessed with Kolmogorov-Smirnov test. Comparisons will use the two sample Z-test on log-transformed primary endpoint variables. P values <0.025 (one-sided) will be considered significant. Bonferroni adjustment will be applied when applicable. Data will be analyzed using SAS (Version 9.4 or higher).

The tables will be created by treatment arm. Listings with individual values will be provided for all data presented in the tables.

4.1 Study Period and Participant Duration

4.1.1 Study Periods

Screening period: Starting the day of signature of informed consent up to and including the day before randomization. For subjects who are not randomized, the screening period will end on the day the subject is determined to be a screen failure.

Randomization (Day 0): After screening assessments are completed and subject's eligibility confirmed, the subject will be randomly assigned (1:1) to the automated ventilation with INTELLiVENT-ASV or to the non-automated ventilation. Randomization will be stratified according to the clinical condition at inclusion (normal lungs, ARDS, chronic hypercapnia, brain injury).

Intervention period (Day 1 – Day 27): From inclusion up to day of extubation (and not re-intubated within 48h after extubation), even if subjects remain on mechanical ventilation. During this period, subjects re-intubated within 48h after extubation will be kept in the study. Subject re-intubated beyond 48h will be considered as weaned from the ventilation.

The INTELLiVENT-ASV or control arm ventilator protocols will be continued until subjects are able to breathe unassisted for 48 hours, death, ICU discharge, study withdrawal, or day 28, whichever comes first.

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent. We expect a maximum of 5% of these cases.

Note a maximum of 5% of subjects are anticipated for which not 80% of mechanical ventilation time within the allocated randomized ventilation mode could be recorded due to documented technical reason. The recorded data will be used (with 'percent spent' calculated per the recorded time) for the primary analysis of the co-primary endpoints. As a sensitivity analysis, these values will be treated as missing data.

End of Study and participation duration (Day 1- Day 28):

Each enrolled subject will be followed for a maximum of 28 days. Prior to completion of study close out, all subject data must be captured and monitored in the eCRF.

The end of study visit should be completed at the time a subject completes the study.
A subject will be considered to have completed the study for the following reasons:

- Subject completes follow-up visits as until day 28 as per investigational plan.
- Subject dies.
- Subject or legally authorized representative requests to be withdrawn from the study.
- Investigator requests to be withdrawn from the study to protect the welfare of the subject.

Subject re-intubated within 48h after extubation will continue to be followed up until day 28. Subject re-intubated beyond 48h will be considered as weaned for the ventilation procedure. They remain in the study but only a phone call will be done at Day 28.

See Appendix 1 in the SAP for a detailed schedule of assessments.

There is no replacement of subjects. Dropout could occur when patients have less than 80% of the invasive ventilation duration recorded or when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent.

4.2 Planned analyses

4.2.1 Interim analyses for Adaptive sample size reassessment

4.2.2 Two interim analyses at half and three-quarter information time (i.e. when half and three-quarter of the subjects are evaluable for response), using O'Brien-Fleming boundaries for efficacy and futility.

A Data Safety Monitoring Board will be settled by the sponsor and will be composed of experts in mechanical ventilation independent from the study coordinators and investigators.
The responsibility of the DSMB is to evaluate safety data during the trial and to advise Hamilton Medical about the continuing safety of the Study. Tables, listings and figures to be presented during each DSMB meeting are listed in the DSMB Charter. However, additional items can be added upon request from DSMB members.

Listings of all Adverse Events and Device Deficiencies will be provided by Hamilton Medical to the Independent Medical Monitor to evaluate safety of the study device. All events, including any device related events will be reviewed case by case by the Independent Medical Monitor. A safety concern raised by the Independent Medical Monitor triggers a DSMB meeting. Trial data will be reviewed on a periodic basis as defined in the DSMB Charter.

Based on the available safety data, the DSMB may recommend that Hamilton Medical modify or terminate the trial. DSMB composition, duties, procedures, deliberation rules are detailed and documented in the DSMB Charter.

4.2.3 Final Analysis

The final analysis will be performed when the last subject has been followed at the end of the study. Accrual is expected to be completed in approximately 24 months.

4.3 Definition of Populations

This study will enrol adult ICU subjects, 21 years and older, requiring invasive mechanical ventilation and meeting the inclusion and exclusion criteria. Inclusion and exclusion criteria are detailed in Sections 7.2 and 7.3 of the protocol respectively.

4.3.1 Intention-To-Treat (ITT) Population

The Intention-To-Treat population (ITT) will consist of all randomized subjects. Subjects who receive the wrong ventilation support will be analysed in the arm to which they were randomized. The ITT population will be used for primary, secondary, and tertiary efficacy analyses.

4.3.2 Modified Intention-To-Treat (MITT) Population

The MITT population consists of all ITT subjects whose recorded data are at least 24h and at least 80% of the invasive ventilation duration within the allocated randomized ventilation mode is recorded in the eCRF. The sensitivity analyses for efficacy endpoints will be conducted using the MITT population. Subjects will be analyzed in the group to which they were randomized.

4.3.3 Safety Analysis Population

The Safety population will include all subjects who once received invasive mechanical ventilation. Subjects will be analyzed according to the ventilation mode that they received. The safety population will be used for safety analyses.

4.4 Subgroup Definitions

Forest plots will be used to display results of primary endpoints and total duration of MV within the following subgroups listed below:

- Regions (US vs Europe)
- Study centers
- Gender

All efficacy tables and forest plots displaying primary and tertiary efficacy results will also be presented by treatment arm and for four groups based on subject condition at inclusion:

- Normal lungs
- ARDS
- Chronic Hypercapnia
- Brain injury

Additionally, forest plots to display primary and tertiary efficacy results by spontaneous and passive breathing subjects for the six ventilation and oxygenation variables will be reported:

1) Tidal volume (VT)

2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

Study centers will be pooled from largest to smallest until the pooled center had more than 5 subjects in each treatment group.

4.5 Treatment Assignment and Treatment Arms

The two ventilation arms are:

- Automated ventilation arm: INTELLiVENT-ASV software accessory will be activated, utilizing a Hamilton-Medical Ventilator
- Non automated ventilation arm: INTELLiVENT-ASV software accessory won't be activated

4.6 Calculated Variables

- Study day 0 is defined as the first day when study ventilation period starts.
- Baseline assessments done on the date of ventilation are assumed to take place before the study ventilation period starts, unless specified otherwise.
- Event durations in days (e.g., AE duration) are calculated as follows: [end date – start date +1]. When applicable, Time durations in hours are calculated as follows: [end time – start time]

4.7 Partial Dates

If part of the starting or ending dates of an adverse event (AE) is missing, the following convention will be used:

- For a missing day in an AE 'start date', the missing day is replaced by the first day of the month (e.g., UKMAY2020 -> 01MAY2020)
- For a missing day in an AE 'end date', the missing day is replaced by the last day of the month (e.g., UKMAR2020 -> 31MAR2020)

4.8 Methods to be used for handling Missing Data

The subject dataset is considered complete if both of the following conditions are met:

1. Minimum of 24h of recorded data available
2. Minimum of 80% of the total invasive ventilation time within the allocated randomized ventilation mode has been recorded.

An incomplete dataset leading to a dropout in the study is a dataset that misses at least one of the above-mentioned variables. Subjects for which less than 80% of mechanical ventilation time within the allocated randomized ventilation mode could be recorded due to documented technical reasons, the recorded data (with 'percent spent' calculated per

the recorded time) will be used for the primary analysis of the co-primary endpoints. A maximum of 5% of subjects with less than 80% recorded time is expected. As a sensitivity analysis, these values will be treated as missing data and imputed as described below.

Method that takes into account the presence of missing data and that yield valid estimates under the assumption of data missing at random (MAR) will be used. For the primary analysis, multiple imputation of the missing primary outcome data in both arms will be performed under a missing at random model for the control arm, hence leading to a conservative imputation. The 'percent spent' variables that need to be imputed are continuous-type variables. Those variables will be imputed sequentially using covariates constructed from the corresponding sets of preceding variables, in this case. In addition, should there be any issues with the estimation of the model, the covariates will be prioritized based on the order in which they are listed below.

- Study arm
- Demographic data: Age and gender at Baseline (visit 2)
- Pulmonary condition at visit 1
- History: Cause of ICU admission and patient medical history at baseline (visit 2)
- Intubation status at Visit 5
- ICU severity scores: SAPS II, APACHE and SOFA at visit 5
- Concomitant rescue therapies: Proning, Nitric Oxide at visit 5
- Weaning Information: Active/Passive, NIV, CPAP, weaning process and sedation status at visit 5

Multiple imputation will be used in secondary, tertiary or sensitivity analyses, whenever necessary, to impute the missing data under the MAR assumption.

Missing AE intensities will not be imputed. Such AEs will be included in summaries by including a category of "missing" in the tables. If the assessment of the relationship of the AE to investigational device is missing, we will assume that the AE is possibly related to investigational device.

4.9 Changes to Protocol

The protocol indicates that inclusion will be halted at sites that reach the 30% inclusion cap of total enrolment. This cap was changed to 15% in this SAP following request from the FDA.

5. Study Subjects

5.1 Disposition of Subjects

The number of subjects in each population will be tabulated by treatment arms as defined in section 4.5 and overall.

The study disposition of all randomized subjects will be summarized by randomized ventilation group and overall, with descriptive statistics for the ITT population. It will include the number of subjects who discontinued study treatment prematurely, or

withdrawn from the study completely, or stopped the follow-up for any reason upon investigator decision and patients who have completed study treatment or replaced due to technical failure in recording. The summary will also include reasons for discontinuing study treatment and termination of the study as recorded on the eCRF. The details of the 'other reason' will be included in the listing.

5.2 Protocol Deviations

The major protocol deviations will be summarized for each ventilation arm and overall, for the ITT population. The details will be listed by subject and ventilation arm.

Violations of inclusion and/or exclusion criteria, allocating patient to incorrect ventilation mode and deviations of other restrictions will be considered in the determination of the major deviations.

Protocol deviations will be defined as major or minor by the Sponsor during data review meetings before the interim and final database locks.

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed for the ITT population(s). All subjects' characteristics at baseline will be described overall and by treatment group:

- Age
- BMI
- Race
- Ethnicity
- Height and weight
- Comorbidities and medical history
- Concomitant Treatment
- Reason for hospitalization (Cause of ICU admission)
- Smoking status

Physiology admission scores SAPS II, APACHE II and SOFA, Mechanical ventilation characteristics (INTELLiVENT-ASV, VC, PAC, VAC, SIMV, BiPaP, APRV, PS, ASV, Others) and Arterial Blood Gas analysis (PH, PaO_2, $PaCO_2$, HCO_3^-, SaO_2, FiO_2, End-Tidal CO_2) at baseline will be summarized by treatment arms. Similarly, stratification information based on subject condition at inclusion will be tabulated by treatment arm if applicable. In addition, baseline characteristics will be presented by region (US vs EU). For categorical baseline variables, Fisher exact test will be used to test if there's a significant difference between US and EU whereas for continuous variables Mann-Whitney U test will be used to test for differences between the two populations. Results for these statistical tests will be mainly for informative purpose and no inference is intended to be made on these results.

7. Efficacy Evaluation

Efficacy evaluation will be performed on the ITT population. Values for optimal, acceptable, and sub-optimal ranges (maybe different for passive and spontaneous breathing ventilation periods) are listed in Values for optimal, acceptable and sub-optimal ranges of the study protocol.

7.1 Primary Efficacy Variable

The primary efficacy endpoint is a composite endpoint to assess the ability to keep the ventilation and oxygenation variables in optimal target ranges. The primary efficacy variable will be calculated as the percentage of time spent with **ALL** six variables in the optimal target ranges during the **7 days** after randomization:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia.

The primary efficacy variable will be expressed by median (interquartile range). Log transformation will be performed on the data before performing the 2 sample Z-test. Comparisons will use the 2 sample Z-test for log transformed variables. The P values <0.025 (one-sided, the hypothesis is that INTELLiVENT-ASV is better than "non-automated ventilation" on the Hamilton Medical Ventilators, in terms of efficacy) will be considered significant.

7.2 Secondary Efficacy Variable

Secondary efficacy variables covering physiologic parameters, clinical outcomes, workload, safety events, typical clinical complications up to day 28 after enrolment and associated interventions will be assessed.

Please refer to section 3.2.2 of SAP for the complete list for the secondary efficacy endpoints.

Data will be expressed by median (interquartile range) or mean±SD and 95% confidence interval depending on the normality of the distribution assessed with Kolmogorov-Smirnov test. Between group differences will be performed using the 2 sample Z-test for normal variables or Mann-Whitney test for variables with a non-normal distribution. If applicable, a Bonferroni correction will be applied for pairwise comparisons corresponding to the sponsor's variable of interest.

7.3 Tertiary Efficacy Variable

The tertiary efficacy endpoint is a composite endpoint and will be used to assess the ability to keep ventilation and oxygenation variables in optimal target ranges. The tertiary efficacy variable will be calculated as the percentage of time spent with **ALL** six variables in the optimal target ranges during the ventilation period **from day 8 up to day 28** after randomization:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)

5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia.

The tertiary efficacy variable will be expressed by median (interquartile range). Log transformation will be performed on the data before performing the 2 sample Z-test. Comparisons will use the 2 sample Z-test for log transformed variables. The P values <0.025 (one-sided, the hypothesis is that INTELLiVENT-ASV is better than conventional non-automated ventilation in terms of efficacy) will be considered significant.

7.4 Sensitivity Analyses

The Primary efficacy analysis will be repeated for the MITT population as sensitivity analysis. Other sensitivity analyses may be performed as appropriate. The Sensitivity analysis will be performed under MAR (Missing at Random) assumption. The Tipping point approach will be implemented to test the MAR assumption.

To check the sensitivity of the results of the primary efficacy analysis to the MAR assumption, MI based on models compatible with Missing Not At Random (MNAR) missingness mechanisms will be used. The approach below, using SAS PROC MI, will be considered:

The "shift imputation" approach: for missing values at a particular visit, it will be assumed that their expected value is smaller (shifted) by a specified amount than for the observed responses (implying that the missing values are more likely corresponding to smaller differences between arms than the observed ones). Different values of the shift will be explored to investigate the sensitivity of the results. This approach can be applied to data with arbitrary missing data patterns.

As other sensitivity analysis, the primary efficacy variable will be analyzed using an ANCOVA model, adjusting for region. All sensitivity analyses will be done at final analysis.

7.5 Subset Analyses

The trial is not sized to test for the presence of treatment by subset interactions. Thus, true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone.

With these caveats in mind, exploratory subset analyses on the primary efficacy endpoint will be performed to identify any major effect. The subgroups have been defined in Section 4.4.

If applicable, the homogeneity testing of the treatment effect across subgroups with the significance level of 0.15 will be performed.

These analyses will be considered as supportive efficacy analyses and conducted without any alpha-level adjustment.

7.6 Individual patient profiles

An individual patient profile plot showing average FiO2, VTe/IBW, Ftot, Fspont, mechanical power and Pmax minus PEEP over all breaths for each 24hours period from day 0 to day 7 will be presented by treatment arms.

8. Safety Evaluation

8.1 Extent of Exposure to Investigational Device

The number of subjects randomized to INTELLIVENT-ASV who switched to non-INTELLiVENT ASV mode will be shown. In addition, for those patients, the total time spent in both modes will be described. Details of all subjects randomized to ASV but transiently ventilated in another mode will be provided in a listing.

8.2 Primary Safety Variable

The primary safety variable will be calculated as the percentage of time spent with **at least one** of the six variables in the sub-optimal target ranges during the **7 days** after randomization:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The primary safety variable will be expressed by median (interquartile range). Log transformation will be performed on the data before performing the 2 sample Z-test. Comparisons will use the 2 sample Z-test for log transformed variables. The P values <0.025 (one-sided, the hypothesis is that INTELLiVENT-ASV is better than conventional non-automated ventilation in terms of efficacy) will be considered significant.

Primary safety variable will be performed on the safety population.

8.3 Secondary Safety Variable

The secondary safety endpoint will be determined by evaluating the number of Serious Adverse Events (all SAEs included) within 28 days of the enrolment and the rescue therapy requirement (APRV, high frequency ventilation, ECCO2R and ECMO).

Tabulations of the number of subjects who experienced AEs as well as severity of the events will be presented overall and by system organ class and preferred term. SOCs will be ordered by frequency (highest frequency first). PTs will be ordered alphabetically per SOC. Subjects will only be counted once for each preferred term. In case a subject experienced the same event more than once, the worst severity will be presented.

The following non-mechanical ventilation related adverse events recorded on study day 7 and 28 will also be considered as additional secondary safety variables.

- Severe Acute kidney injury (AKI) in need for CRRT/IHD

- Severe critical illness neuro-myopathy signs of tetraplegia affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for limb movement, but not against gravity and score 3 for movement against gravity but not resistance.
- Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy, and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points.
- Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ failure affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation.
- Extubation failure that is related to weaning process by itself, or associated conditions based on the interpretation of the investigator.
- Need for tracheostomy that is related to a difficult weaning process or associated conditions based on the interpretation of the investigator.

Secondary safety variables will be performed on the safety population.

8.4 Tertiary Safety Variable

The tertiary safety variable will be calculated as the percentage of time spent with **at least one** of the six variables in the sub-optimal target ranges during ventilation period **from day 8 up to day 28** after randomization:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The tertiary safety variable will be expressed by median (interquartile range). Log transformation will be performed on the data before performing the 2 sample Z-test. Comparisons will use the 2 sample Z-test for log transformed variables. The P values <0.025 (one-sided, the hypothesis is that INTELLiVENT-ASV is better than conventional non-automated ventilation in terms of efficacy) will be considered significant.

Tertiary safety variable will be performed on the safety population.

8.5 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded using the IMDRF terminologies for categorized Adverse Event Reporting (Version 5.0) and will be graded according to the National Center Institute Common Terminology Criteria for AEs (NCI-CTCAE criteria [v5.0]). Adverse events will be analyzed in terms of their type, incidence, severity, and relationship to the study treatment.

Related AEs are defined as events with a relationship to mechanical ventilation, study procedure and INTELLiVENT-ASV equal to 'Not related', 'Related'.

A summary table will present by treatment arm the number and percentage of subjects with at least one of the adverse events, adverse device effects or observed device deficiencies.

The following tabulations will be presented:

Non-Device-Related:

- Adverse Event (AE)
- Serious Adverse Event (SAE)

Device/Procedure-Related:

- Adverse Device Effect (ADE)
- Serious Adverse Effect (SADE)
- Anticipated SADE (ASADE)
- Unanticipated Serious Adverse Device Effect (USADE)

For detailed categorization of Adverse Events, refer to protocol section 9 safety and ANNEX A in the protocol.

Listings of all adverse events by treatment arms will be provided, flagging the ones that are Device/Procedure-Related.

The relationship between the use of the medical device (including the medical - procedure, i.e., invasive mechanical ventilation) and the occurrence of each adverse event will be assessed and categorized.

Each SAE will be classified according to four different levels of causality.

1. Not related to the device in question
2. Possible
3. Probable
4. Causal relationship

A frequency table will be provided to assess the relationship of the serious adverse event to INTELLiVENT-ASV.

8.6 Deaths

The number of deaths will be tabulated with the primary cause of death respectively of device/procedure related or non-device related.

In addition, listing of deaths will be provided.

8.7 Vital Signs, Physical Findings and Other Observations Related to Safety

Data from vital signs (blood pressure, pulse rate and temperature) will be summarized by treatment arms. In addition, box plots of vital sign (Systolic Blood Pressure, Diastolic Blood Pressure, Mean Blood Pressure, Pulse Rate and Temperature) by visit (visit 1 to 5 and every 10^{th} visit) will be presented for each treatment arm to show the evolution of the different vital sign parameters over time. The following ranges will be used to classified subjects within normal range and will be displayed on the box plots.

- Systolic Blood Pressure Result between [80; 180] mmHg
- Diastolic Blood Pressure between [40; 110] mmHg
- Mean Blood Pressure Result between [50; 150] mmHg
- Pulse Rate Result between [50; 150] Beats/min
- Temperature Result between [36; 38] °C / [96.8; 100.4] °F

The Acute pulmonary conditions will be displayed by treatment arm.

8.8 (Prior and) Concomitant Treatment

(Prior and) Concomitant medications including sedation (and the drugs used to treat adverse events or chronic diseases) will be classified according to World Health Organization Drug Dictionary (WHO-DD Version March 1, 2019).

The number and percentage of participants receiving a (prior or) concomitant medication will be displayed by anatomical main group (1st level of the Anatomical Therapeutic Chemical (ATC) classification) and chemical subgroup (4th level of the ATC classification) for the safety population.

Medications will be reported as prior when they start before the first day of ventilation.

Medications will be reported as concomitant when they start before, on or after first day of ventilation and continue afterwards.

Medications started before the first day of ventilation and continuing afterwards will be reported both as prior and concomitant.

(Prior and) Concomitant medication summaries will be sorted alphabetically by generic term within ATC class.

A listing of all medications recorded on the concomitant medications CRF page will provide details including indication, dose, route, frequency, and start and stop dates.

The type and cumulative dose of concomitant sedation and vasopressor used before and after randomization will be displayed by treatment arm.

Subjects ventilated during the practical training phase (Bedside training) will be monitored for safety events but will not be taken into consideration for the study outcome and statistics.

9. References

Mehta CR and Pocock SJ. *Adaptive increase in sample size when interim results are promising: A practical guide with examples.* Statistics in Medicine. 2011; 30(28): 3267–84.

10. List of Tables/Graphs/Listings

10.1 List of Tables

N°	Table	Title	Population	IA1& IA2*
1	Table 14.01.01	Patient Disposition	ITT population	
2	Table 14.01.02	Protocol Deviations	ITT population	
3	Table 14.01.03	Stratification Information based on subject condition at inclusion	ITT population	
4	Table 14.01.04.01	Demographic and Other Baseline Characteristics	ITT population	
5	Table 14.01.04.02	Demographic and Other Baseline Characteristics by region	ITT population	
6	Table 14.01.05.01	Physiology Admission Scores SAPS II, APACHE II and SOFA and Other Baseline Characteristics	ITT population	
7	Table 14.01.05.02	Physiology Admission Scores SAPS II, APACHE II and SOFA and Other Baseline Characteristics by Region	ITT population	
8	Table 14.01.06	Patient Medical History Including Pulmonary and Cardiovascular Medical History by System Organ Class and Preferred Term	ITT population	
9	Table 14.02.01.01	Primary Efficacy Assessment Based on ITT Population	ITT population	X
10	Table 14.02.01.02	Primary Efficacy Assessment Based on MITT Population	mITT population	X
11	Table 14.02.01.03	Sensitivity Analysis on Primary Efficacy Assessment Based on Shift Imputation Approach	ITT population	
12	Table 14.02.01.04	Sensitivity Analysis on Primary Efficacy Assessment Based on Multiple Imputation Approach	ITT population	
13	Table 14.02.01.05	Sensitivity Analysis on Primary Efficacy Assessment Based on Multiple Imputation Approach on Missing and Partially Missing Data	ITT population	
14	Table 14.02.01.06	Sensitivity Analysis on Primary Efficacy Assessment – ANCOVA Model Adjusting for Region	ITT population	
15	Table 14.02.01.07	Primary Efficacy Assessment (Percentage of time#) by Patient Condition at Baseline	ITT population	X
16	Table 14.02.02.01	Secondary Efficacy Assessment (Physiologic Parameters)	ITT population	X
17	Table 14.02.02.02	Secondary Efficacy Assessment (Physiologic Parameters)	mITT population	X
18	Table 14.02.02.03	Secondary Efficacy Assessment (Outcomes)	ITT population	X
19	Table 14.02.02.04	Secondary Efficacy Assessment (Outcomes)	mITT population	X

20	Table 14.02.02.05	Secondary Efficacy Assessment (Associated Intervention)	ITT population	X
21	Table 14.02.02.06	Secondary Efficacy Assessment (Associated Intervention)	mITT population	X
22	Table 14.02.02.07	Secondary Efficacy Assessment (Workload**) Based on ITT Population	ITT population	X
23	Table 14.02.02.08	Secondary Efficacy Assessment (Workload**) Based on mITT population	mITT population	X
24	Table 14.02.03.01	Tertiary Efficacy Assessment	ITT population	X
25	Table 14.02.03.02	Tertiary Efficacy Assessment	mITT population	X
26	Table 14.02.03.03	Tertiary Efficacy Assessment (Percentage of time#) by Patient Condition at Baseline	ITT Population	X
27	Table 14.03.01	Duration of Exposure to Ventilation	SAF population	
28	Table 14.03.02	Duration of Exposure to INTELLiVENT ASV	SAF population	
29	Table 14.03.03	Primary Safety Endpoint, day 0 to day 7	SAF population	
30	Table 14.03.04	Secondary Safety Endpoints	SAF population	
31	Table 14.03.05	Tertiary Safety Endpoint	SAF population	
32	Table 14.03.06	Overall Summary of Adverse Events	SAF population	
33	Table 14.03.07	Adverse Events by Level 1 and Level 2	SAF population	
34	Table 14.03.08	Serious Adverse Events by Level 1 and Level 2	SAF population	
35	Table 14.03.09	Serious Adverse Events by Level 1 and Causality Level	SAF population	
36	Table 14.03.10	Number of Deaths	SAF population	
37	Table 14.03.11	Vital Signs Over Time	SAF population	
38	Table 14.03.12	Acute Pulmonary Condition	SAF population	
39	Table 14.03.11.01	(Prior and) Concomitant Medications by ATC Level 1 and Level 4.	SAF population	
40	Table 14.03.11.02	Type of Concomitant Sedation and Vasopressor used Before Randomization	SAF population	
41	Table 14.03.11.03	Dose of Concomitant Sedation and Vasopressor used Before Randomization	SAF population	
42	Table 14.03.11.04	Type of Concomitant Sedation and Vasopressor used After Randomization	SAF population	

43	Table 14.03.11.05	Cumulative Dose of Concomitant Sedation and Vasopressor After Randomization	SAF population	

***Outputs marked with X will be produced in addition to outputs for safety reviews**

10.2 List of Figures

N°	Figures	Title	Population	IA1& IA2*
1	Figure 14.01.01	Forest plot of Primary Efficacy Results (Overall)	ITT	X
2	Figure 14.01.02	Forest plot of Results of key Secondary Efficacy Endpoint (Overall)	ITT	X
3	Figure 14.01.03	Forest plot of Tertiary Efficacy Results (Overall)	ITT	X
4	Figure 14.01.04	Forest plot of Primary Efficacy Results by Ventilation and Oxygenation Parameters for Passive and Spontaneous Breathing Subjects	ITT	X
5	Figure 14.01.05	Forest plot of Tertiary Efficacy Results by Ventilation and Oxygenation Parameters for Passive and Spontaneous Breathing Subjects	ITT	X
6	Figure 14.02.01	Hourly FiO2 Time plot (with individual patient profile)	ITT	
7	Figure 14.02.02	Hourly PEEP Time plot (with individual patient profile)	ITT	
8	Figure 14.02.03	Daily VTe/IBW Time plot (with individual patient profile)	Safety population	
9	Figure 14.02.04	Daily Ftot Time plot (with individual patient profile)	Safety population	
10	Figure 14.02.05	Daily Mechanical Power Time plot (with individual patient profile)	Safety population	
11	Figure 14.02.06	Daily Pmax minus PEEP Time plot (with individual patient profile)	Safety population	
12	Figure 14.03.01	Forest plot of Primary Safety Variables	Safety population	
13	Figure 14.03.02	Boxplot of vital sign (SBP, DBP and PR) by visit	ITT	

***Outputs marked with X will be produced in addition to outputs for safety review**

10.3 List of Listings

N°	Listings	Title	Population	IA1& IA2*
1	Listing 16.02.01	Listing of Study or Treatment Discontinuation (with reason for discontinuation)	Safety population	
2	Listing 16.02.02	Protocol Deviation	All randomized subjects.	
3	Listing 16.02.03	Subjects Excluded from Efficacy Analysis	ITT Population	
4	Listing 16.02.04.01	Demographic and Baseline Characteristics	ITT Population	
5	Listing 16.02.04.02	Physiology Admission Scores SAPS II, APACHE II and SOFA and Other Baseline Characteristics	ITT Population	
6	Listing 16.02.04.03	Patient Medical History Including Pulmonary and Cardiovascular Medical History (Prior or Ongoing).	ITT Population	
7	Listing 16.02.07.01	Listings of subjects randomized to INTELLiVENT ASV but transiently ventilated in a non-INTELLiVENT ASV mode.	Safety Population	
8	Listing 16.02.07.02	Listings of all Adverse Events (indicating relatedness to device or procedure)	Safety Population	
9	Listing 16.02.07.03	Listing of Serious Adverse Events	Safety Population	
10	Listing 16.02.07.04	Listings of Death and AEs Terms link to Death	Safety population	
11	Listing 16.02.09.01	Listings of Vital Signs (SBP, DBP and heart rate) with Abnormal Values	Safety Population	
12	Listing 16.02.09.02	Listing of all Medications Recorded on the Concomitant Medications CRF (including dose, route, frequency, and start and stop dates)	Safety Population	
13	Listing 16.02.09.03	Type and Dose of Concomitant Sedation and Vasopressor used Before Randomization	Safety Population	
14	Listing 16.02.09.04	Type and Dose of Concomitant Sedation and Vasopressor used After Randomization	Safety Population	

***Outputs marked with X will be produced in addition to outputs for safety review**

IDDI
ADDING VALUE TO CLINICAL DATA

Appendix

Appendix 1 Summary of subject evaluation tests: schedule of assessments for both Study Arms

The following clinical and research tests will be conducted with the following sequence during the study to assess eligibility, efficacy, and safety:

Study Period	Screening	Baseline	Intervention Period											End of Study	Study Exit
Time	Day 0	Day 0	Day 0	Day 0	Day 1	Day 1	Day 2-3	Day 4	Day 4	Day 5-6	Day 7	Day 7	Day 8-27	Day XX	Day 28
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-11	Visit 12	Visit 13	Visit 14-17	Visit 18	Visit 19	Visit 20-60	Visit 61	Visit 62
Inclusion/exclusion criteria	X														
Pregnancy Test	X														
Informed Consent	X														
Randomization	X														
Demographic Data	-	X													
Intubation/reintubation status	X	X			X	X	X	X	X	X	X	X	X	X	X
Acute Pulmonary Condition	X			-	X	X	X	X	X	X	X	X	X	X	X
Medical history & comorbidity factors		X													
Current INTELLIVENT-ASV settings			X	X	X	X	X	X	X	X	X	X	X	X	
INTELLIVENT-ASV randomisation violation status			X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	-	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ventilatory parameters manual assessment	-	X	X	X	X	X	X	X	X	X	X	X	X	X	
24h Recording of ventilation parameters *(Memory Box)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood gas analysis (If available visit ± 2h)	X	X#	X	X	X	X	X	X	X	X	X	X	X	X	
ICU severity Scores (SAPS II, APACHE II)					X										
SOFA score					X			X			X			X	

Study Period	Screening	Baseline	Intervention Period											End of Study	Study Exit
Time	Day 0	Day 0	Day 0	Day 0	Day 1	Day 1	Day 2-3	Day 4	Day 4	Day 5-6	Day 7	Day 7	Day 8-27	Day XX	Day 28
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-11	Visit 12	Visit 13	Visit 14-17	Visit 18	Visit 19	Visit 20-60	Visit 61	Visit 62
ICU and hospital length of stay														X	X**
ICU/Hospital death														X	X**
Adverse Event collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X**

Legend

* 24H recording of ventilation parameters include: Ventilator settings, Alarm settings and Breath-by-breath monitoring of: Tidal volume (VT), total Respiratory rate (RR), spontaneous RR, inspiratory time, expiratory time, Maximum pressure (Pmax), Oxygen saturation measured by pulse oximetry (SpO_2), End-tidal partial pressure of carbon dioxide ($PetCO_2$), PEEP, inspiratory flow, expiratory flow, static compliance for passive subjects, inspiratory resistance for passive subjects, expiratory time constant.

ƒ to be assesst only in the morning visit.

If ventilator settings have changed since visit 1

** For subjects transferred to another hospital or other health care facility, subject will be contacted via a phone call on day 28 post enrollment to assess the followings if possible.

* Ventilation parameters include

- Ventilator settings
- Alarm settings

Breath-by-breath monitoring of: Tidal volume (VT), total Respiratory rate (RR), spontaneous RR, inspiratory time, expiratory time, Maximum pressure (Pmax), Oxygen saturation measured by pulse oximetry (SpO_2), End-tidal partial pressure of carbon dioxide ($PetCO_2$), PEEP, inspiratory flow, expiratory flow, static compliance for passive subjects, inspiratory resistance for passive subjects, expiratory time constant.

Study Period	Screening	Baseline	Intervention Period											End of Study	Study Exit
Time	Day 0	Day 0	Day 0	Day 0	Day 1	Day 1	Day 2-3	Day 4	Day 4	Day 5-6	Day 7	Day 7	Day 8-27	Day XX	Day 28
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-11	Visit 12	Visit 13	Visit 14-17	Visit 18	Visit 19	Visit 20-60	Visit 61	Visit 62
Concomitant sedation, analgesia and myorelaxants use		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant vasopressors and inotropics use		X		X	X	X	X	X	X	X	X	X	X	X	
Number of recruitment maneuvers within the last observation period				X	X	X	X	X	X	X	X	X	X	X	
Concomitant rescue therapies (proning, Nitric oxyde, ...)		X		X	X	X	X	X	X	X	X	X	X	X	
Weaning information NIV, CPAP, High Flow.)				X	X	X	X	X	X	X	X	X	X	X	
Screening of readiness to extubate criteria (SBT)						X	X	X	X	X	X	X	X	X	
Assessment of re-intubation status							X	X	X	X	X	X	X	X	
Extubation failure (yes/no)							X	X	X	X	X	X	X	X	X
Acute Kidney Injury (AKI) status and need vor RRT (yes/no)	X	X						X		Xf	X		Xf	X	X
Criticall illness polyneuro- myopathy status (yes/no)	X	X						X		Xf	X		Xf	X	X
Critcial illness encepahlopathy status (yes/no)	X	X						X		Xf	X		Xf	X	X
Tracheostomy status (yes/no)											X		Xf	X	X**
Resuscitted cardiac arrest status (yes/no)								X			X			X	
Other imminently life-threatening experience								X			X			X	
Barotrauma status (yes/no)								X			X			X	
Rescue therapy requirement (APRV, HFO, ECCO2R and ECMO).														X	
Patient status incl. Withhold of weaning and/or withdrawald of MV														X	X**
Ventilation duration for study period *(if reintubated beyond 48h)*														X	