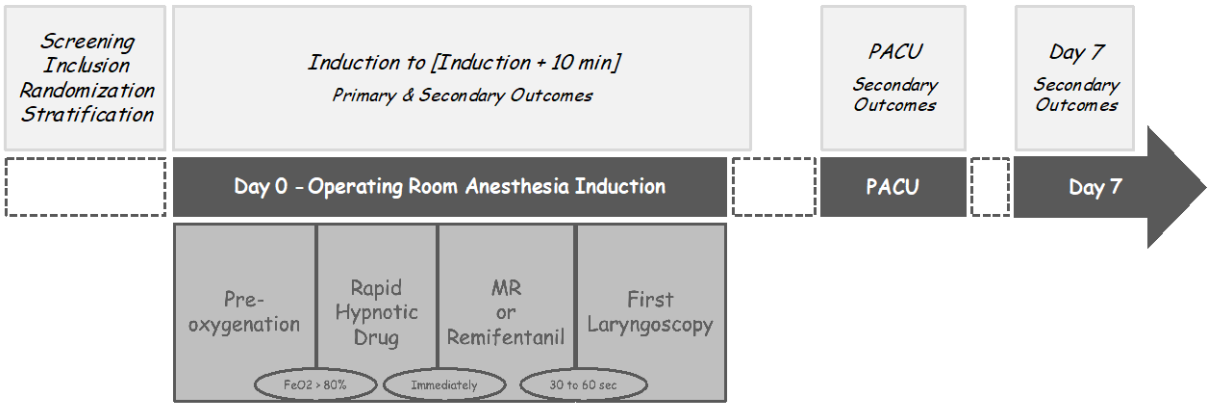
# Supplemental Online Content

Grillot N, Lebuffe G, Huet O, et al; Atlanrea Study Group; Société Française d'Anesthésie Réanimation (SFAR) Research Group. Effect of remifentanil vs neuromuscular blockers during rapid sequence intubation on successful intubation without major complications among patients at risk of aspiration: a randomized clinical trial. *JAMA*. Published January 3, 2023. doi:10.1001/jama.2022.23550



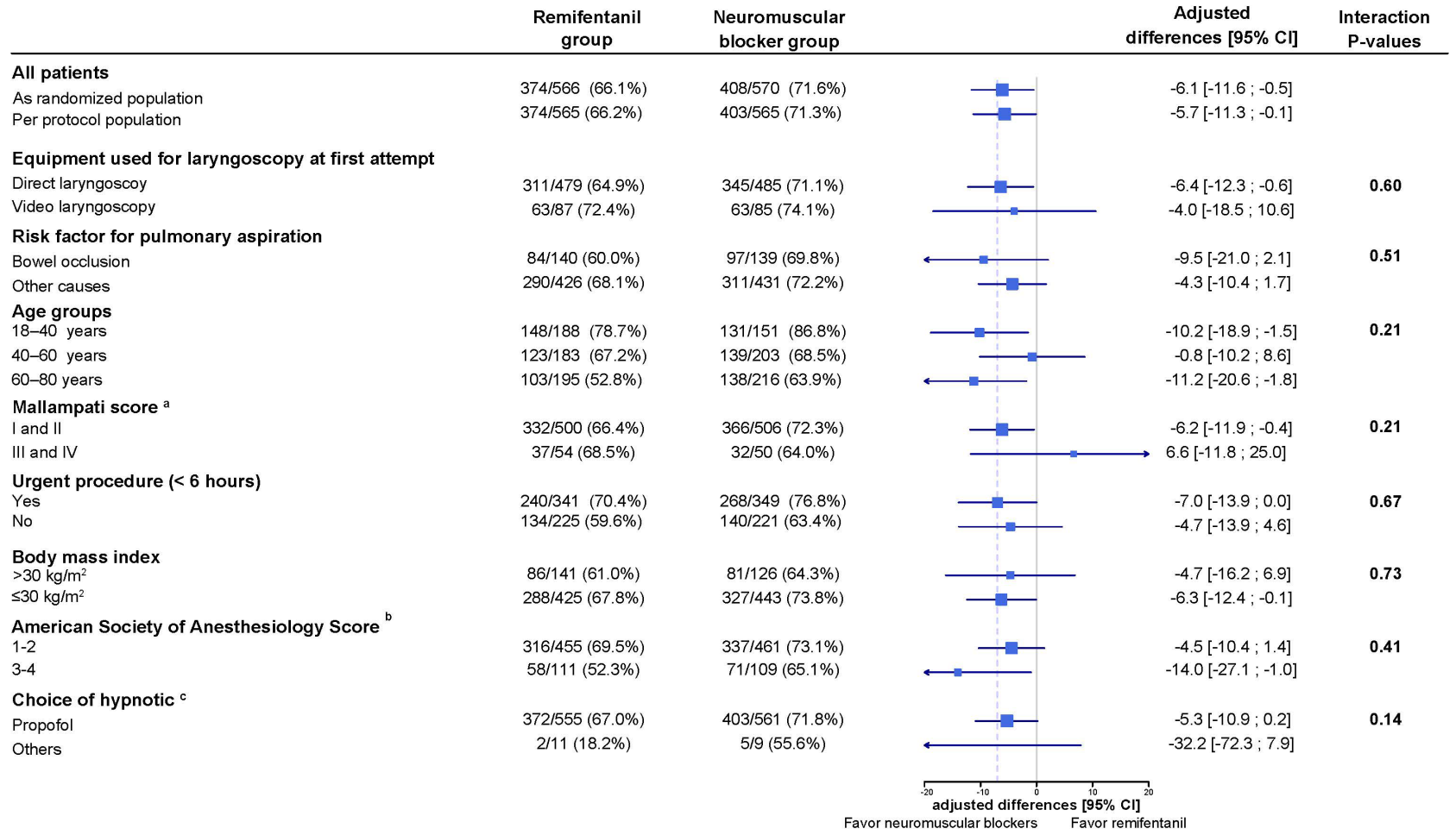
This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1. Study Intervention Timeline**




MR: Muscle relaxants. PACU: Post Anesthesia Care Unit

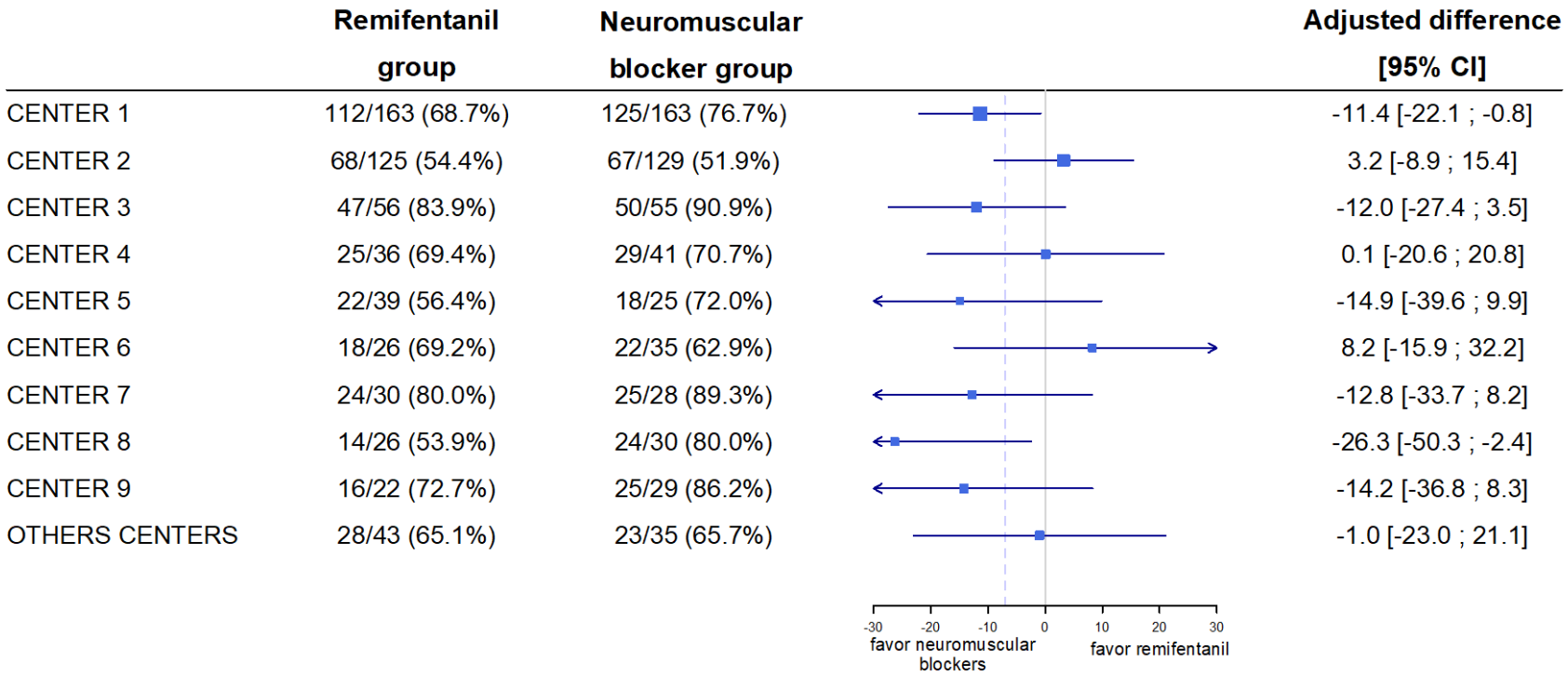
## eFigure 2. Pre-planned Subgroup Analyses in the Per-Protocol Population




Data are n/N (%) and adjusted risk difference with 95% CI in parentheses. Vertical dotted line indicates a noninferiority margin.

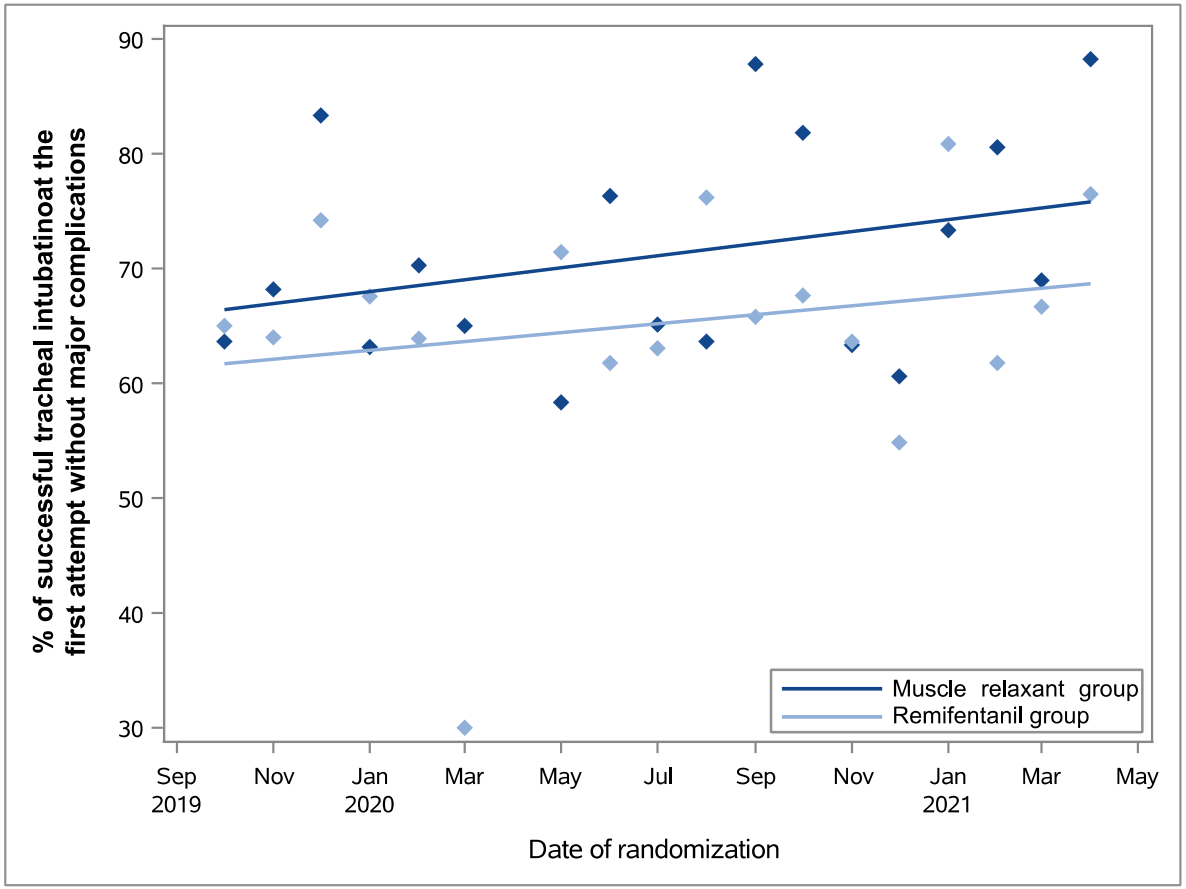
*PP: per protocol. BMI: Body Mass Index. ASA: American Society of Anesthesiology.*

**eFigure 3. Adjusted Difference of the Primary Outcome Across Participating Hospitals**




Data are n/N (%) and adjusted risk difference with 95% CI in parentheses. Vertical dotted line indicates a noninferiority margin. Square size representing the difference reflects the relative numbers in each subgroup, and horizontal bars represent 95% confidence intervals. P-value for heterogeneity of the effect of the trial regimen on the primary outcome across the center : $P < 0.001$.

**eFigure 4. Temporal Trends of the Rates of Successful Intubation Without Major Complication**




Time-series analysis of the percentages of the primary outcome (intubation without major complication) by month in the remifentanil and the neuromuscular blocker group. Using a linear regression model, the slopes were 0.017 for the intervention group (p=0.20) and 0.013 for the control group (p=0.41 ).

**eTable 1. Secondary Outcomes in the As-Randomized Population**

| | Remifentanil group N=575 | Neuromuscular blocker group N=575 | Adjusted Difference (95%CI) [g] |
|---|---|---|---|
| Number of laryngoscopy attempts – n/N (%) | | | |
| 1 | 503/567 (88.7) | 533/570 (93.5) | -4.8 (-8.1;-1.5) |
| 2 | 57/567 (10.1) | 32/570 (5.6) | / |
| 3 or more | 7/567 (1.2) | 5/570 (0.9) | / |
| Absence of esophageal intubation, no – n/N (%) | 558/567 (98.4) | 564/570 (98.9) | 0.0 (-0.02;0.02) |
| Second attempt with a different intubating device – n/N (%) | 34/567 (6.0) | 18/570 (3.2) | 2.7 (0.3;5.0) |
| Vocal cords in abduction - n/N (%) | 489/557 (87.8) | 548/560 (97.9) | -9.2 (-12.0;-6.3) |
| Severe hemodynamic instability [a] | 263/567 (46.4) | 286/570 (50.2) | -3.9 (-9.7;1.9) |
| Vasopressor after induction – n/N (%) | 360/568 (63.4) | 180/570 (31.6) | 35.7 (30.2;41.1) |
| Ephedrine, yes – n/N (%) | 329/568 (57.9) | 153/570 (26.8) | 34.3 (28.9;39.7) |
| Dose, mg – mean (SD) | 13.9 (7.0) | 11.1 (4.6) | 2.9 (1.7;4.1) |
| Neosynephrine, yes – n/N (%) | 9/568 (1.6) | 3/570 (0.5) | 0.0 (0.0;0.0) |
| Dose, µg – mean (SD) | 200.0 (70.7) | 133.3 (76.4) | 53.4 (-35.4;142.2) |
| Norepinephrine, yes – n/N (%) | 38/568 (6.7) | 32/570 (5.6) | 1.1 (-1.2;3.4) |
| Dose, mg – mean (SD) | 2.3 (13.1) | 12.2 (40.2) | -10.4 (-24.2;3.3) |
| Complications in the recovery room – n/N (%) | | | |
| Postoperative nausea and vomiting | 70/561 (12.5) | 57/565 (10.1) | 2.0 (-1.4;5.3) |
| Postoperative desaturation < 80% | 3/566 (0.5) | 10/567 (1.8) | -1.2 (-2.5;0.0) |
| Necessity of post-extubation respiratory support | 6/565 (1.1) | 4/565 (0.7) | 0.2 (-0.5 ;0.8) |
| Extubation failure | 1/567 (0.2) | 1/567 (0.2) | 0.0 (-0.5 ;0.5) |
| Necessity of postoperative emergency ICU admission | 3/567 (0.5) | 1/567 (0.2) | 0.4 (-0.3 ;1.1) |
| Neuromuscular blocker monitoring, yes – n/N (%) | 288/542 (53.1) | 339/541 (62.7) | -9.5 (-15.1 ;-3.8) |
| Neuromuscular blocker reversal, yes – n/N (%) | 162/540 (30.0) | 208/540 (38.5) | -9.5 (-15.0 ;-3.9) |
| Postoperative sore throat (POST) score – n/N (%) | | | |
| Absence to light pain | 486/520 (93.5) | 511/540 (94.6) | / |
| Moderate to severe pain | 34/520 (6.5) | 29/540 (5.4) | 0.9 (-1.6;3.3) |

[a] Defined as heart rate < 45 beats per minute (bpm) or > 110 bpm, Systolic blood pressure (SBP) < 80 mmHg or > 160 mmHg and/or a MAP < 55 mmHg or > 100mmHg

**eTable 2. Secondary Outcomes in the Per-Protocol Population**

| | Remifentanil group | Neuromuscular blocker group | Adjusted Difference (95%CI) [e] |
|---|---|---|---|
| Decomposed item of the primary outcome | | | |
| Intubation success at first attempt – n/N (%) | 501/565 (88.7) | 528/565 (93.5) | -4.7 (-8.0;-1.4) |
| No operator-reported aspiration – n/N (%) | 561/565 (99.3) | 563/565 (99.6) | -0.5 (-1.5;0.5) |
| No severe hypoxemia (Saturation < 95% requiring facial mask ventilation) – n/N (%) | 523/565 (92.6) | 527/565 (93.3) | -0.7 (-3.7;2.4) |
| Lowest Saturation if severe desaturation – mean (SD) | 87.0 (7.6) | 88.8 (5.7) | -0.7 (-3.6;2.2) |
| Episode of saturation < 80% | 8/565 (1.4) | 3/565 (0.5) | 0.6 (-0.3;1.6) |
| No episode of major hemodynamic instability [a] prolonged arrythmia (for > 30 sec.) and/or cardiac arrest | 448/565 (79.3) | 454/565 (80.4) | -0.9 (-5.7;4.0) |
| No severe anaphylactic reaction (grade III or IV) [b] | 564/565 (99.8) | 565/565 (100.0) | 0.0 (0.0;0.0) |
| No esophageal intubation – n/N (%) | 556/565 (98.4) | 559/565 (98.9) | -0.5 (-1.9;0.8) |
| Number of laryngoscopy attempts – n/N (%) | | | |
| 1 | 502/565 (88.9) | 528/565 (93.5) | -4.6 (-7.9;-1.3) |
| 2 | 56/565 (9.9) | 32/565 (5.7) | / |
| 3 or more | 7/565 (1.2) | 5/565 (0.9) | / |
| Time to successful intubation, min, [c] – mean (SD) | 2.5 (1.0) | 2.5 (1.2) | 0.0 (0.0;0.2) |
| Second attempt with different intubating device – n/N (%) | 34/565 (6.0) | 18/565 (3.2) | 2.7 (0.3;5.0) |
| Rescue therapy in case of difficult intubation | | | |
| Myorelaxant | 19/565 (3.4) | 7/565 (1.2) | 1.0 (-0.1;2.1) |
| Opioid | 6/565 (1.1) | 25/565 (4.4) | -3.7 (-5.6;-1.7) |
| Hypnotic | 29/565 (5.1) | 19/565 (3.4) | 1.8 (-0.4;4.0) |
| Cormack-Lehane view if direct laryngoscopy – n/N (%) | | | |
| Grade 1 | 385/475 (81.1) | 406/477 (85.1) | -4.2 (-9.0;0.7) |
| Grade 2 | 70/475 (14.7) | 53/477 (11.1) | / |
| Grade 3 | 19/475 (4.0) | 14/477 (2.9) | / |
| Grade 4 | 1/475 (0.2) | 4/477 (0.8) | / |
| POGO view if indirect laryngoscopy (%) – mean (SD) | 92.6 (19.7) | 91.8 (18.7) | 0.7 (-4.9;6.4) |
| Vocal cords in abduction - no (%) | 487/555 (87.8) | 543/555 (97.8) | -9.2 (-12.0;-6.3) |
| Sellick maneuver - no (%) | 19/565 (3.4) | 12/565 (2.1) | 1.5 (-0.6;3.5) |
| Intubation Difficulty Scale (IDS-3) – mean (SD) | 3.0 (1.6) | 2.7 (1.3) | 0.4 (0.2;0.6) |
| Mechanical complications – n/N (%) | | | |
| Dental injury | 0/565 (0.0) | 0/565 (0.0) | / |

| | Remifentanil group | Neuromuscular blocker group | Adjusted Difference (95%CI) [e] |
|---|---|---|---|
| Tracheal injuries | 1/565 (0.2) | 0/565 (0.0) | 0.0 (0.0;0.0) |
| Cough requiring sedation | 63/564 (11.2) | 41/565 (7.3) | 3.7 (0.4;7.0) |
| Severe hemodynamic instability d | 262/565 (46.4) | 284/565 (50.3) | -3.9 (-9.7;1.9) |
| Vasopressor after induction – n/N (%) | 359/565 (63.5) | 177/565 (31.3) | 36.0 (30.6;41.5) |
| Ephedrine, mg | 13.9 (7.0) | 11.0 (4.6) | 2.9 (1.7;4.1) |
| Neosynephrine, µg | 200.0 (70.7) | 133.3 (76.4) | 53.4 (-35.4;142.2) |
| Norepinephrine, mg | 2.3 (13.1) | 12.6 (40.8) | -9.0 (-22.7;4.8) |
| Complications in the recovery room – n/N (%) | | | |
| Postoperative nausea and vomiting | 70/558 (12.5) | 57/559 (10.2) | 1.9 (-1.4;5.3) |
| Post extubating laryngeal dyspnea | 6/558 (1.1) | 4/555 (0.7) | 0.3 (-0.7;1.2) |
| Postoperative desaturation ≤ 92% | 58/563 (10.3) | 56/561 (10.0) | 0.6 (-2.8;3.9) |
| Postoperative desaturation < 80% | 3/563 (0.5) | 10/561 (1.8) | -1.2 (-2.5;0.0) |
| Postoperative nurse reported aspiration | 2/559 (0.4) | 1/555 (0.2) | 0.3 (-0.5;1.0) |
| Necessity of post-extubating respiratory support | 6/562 (1.1) | 4/559 (0.7) | 0.2 (-0.5 ;0.8) |
| Necessity of reintubation | 1/564 (0.2) | 1/561 (0.2) | 0.0 (-0.5 ;0.5) |
| Necessity of postoperative emergency ICU admission | 3/564 (0.5) | 1/561 (0.2) | 0.4 (-0.3 ;1.1) |
| Monitoring of the curarization, yes – n/N (%) | 287/539 (53.3) | 335/535 (62.6) | -9.3 (-15.0 ;-3.7) |
| Antagonization of the myorelaxants, yes – n/N (%) | 161/537 (30.0) | 206/534 (38.6) | -9.5 (-15.0 ;-3.9) |
| Postoperative sore throat (POST) score – n/N (%) | | | |
| No pain or light | 483/517 (93.4) | 505/534 (94.6) | / |
| Moderate to severe | 34/517 (6.6) | 29/534 (5.4) | 0.8 (-1.6;3.3) |
| Analogical Visual Scale pain score – mean (SD) | 8.7 (17.1) | 7.2 (15.5) | 1.5 (-0.5;3.4) |
| Admission in intensive care unit at day 7 — n/N (%) | 35/565 (6.2) | 30/565 (5.3) | 0.4 (-2.2;3.0) |
| Postoperative pneumonia at day 7 — n/N (%) | 3/565 (0.5) | 2/565 (0.4) | 0.1 (-0.5;0.7) |
| Acute Respiratory Distress Syndrome at day 7 — n/N (%) | 5/565 (0.9) | 4/565 (0.7) | 0.2 (-0.9;1.3) |
| Death at day 7 — n/N (%) | 1/565 (0.2) | 1/565 (0.2) | 0.0 (-0.6;0.6) |

[a] Defined as Mean arterial pressure (MAP) ≤50mmHg or ≥110mmHg for more than 3 minutes

[b] Allergy severity Grade I: cutaneous rash, Grade II : moderate clinical signification requiring a medical intervention, grade III: Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm ; severity grade IV: Cardiac and/or respiratory arrest.

[c] Time between the administration of the hypnotic (start of anesthetic induction) and tracheal intubation (defined as the 6th capnography curve)

[d] Defined as heart rate < 45 beats per minute (bpm) or > 110 bpm, Systolic blood pressure (SBP) < 80 mmHg or > 160 mmHg and/or a MAP < 55 mmHg or > 100mmHg

[e] The confidence interval was calculated by a mixed-effects logistic regression adjusted on stratification factors and centres as random effect

**eTable 3. Successful Technique After Failed First Attempt**

| | Remifentanil group N=64 | Neuromuscular blocker group N=37 | Adjusted Difference |
|---|---|---|---|
| Alternative methods – no (%) | 34 (53.1) | 18 (48.6) | 5.0 (-15.1 ; 25.2 %] |
| New operator – no (%) | 4 (6.3) | 2 (5.4) | 0.4 (-7.2;8.0) |
| Laryngoscopy at 2nd attempt – no (%) | | | |
| Direct laryngoscopy | 27 (42.2) | 15 (40.5) | 2.2 (-17.9 ; 22.3) |
| Video laryngoscopy | 7 (10.9) | 6 (16.2) | -3.7 (-14.6;7.3 |
| Use of a stylet or bougie at second attempt – no (%) | 25 (39.1) | 18 (48.6) | -9.3 (-29.4;10.7) |
| Para-glossal straight blade laryngoscopy – no (%) | 6 (9.4) | 3 (8.1) | 0.0 (-0.1;0.1) |
| New blade size – no (%) | 6 (9.4) | 6 (16.2) | -2.4 (-11.1 ; 6.4) |
| Rescue technique for life-saving oxygenation — no. (%) | | | |
| Intubation through a laryngeal mask airway | 0 (0.0) | 0 (0.0) | / |
| Cricothyrotomy. | 0 (0.0) | 0 (0.0) | / |

**eTable 4. Safety**

| | Remifentanil group N=575 | Neuromuscular blocker group N=575 | Adjusted Difference (95%CI) |
|---|---|---|---|
| Side effects – no. (%) | 37 (6.5) | 13 (2.3) | 4.4 (1.9;6.8) |
| Severe side effects – no. (%) | 12 (2.1) | 3 (0.5) | 1.8 (0.4;3.2) |
| Allergy [a] | | | |
| Severe anaphylactic reaction(Grade III and IV) | 1 (0.2) | 0 (0.0) | / |
| Non severe anaphylactic reaction (grade I and II) | 1 (0.2) | 11 (1.9) | / |
| No Allergy | 565 (99.7) | 559 (98.1) | 1.0 (0.0;2.0) |
| Cardiac disorders | 6 (1.0) | 1 (0.2) | 0.9 (0.0;1.8) |
| Bradycardia | 5 (0.9) | 0 (0.0) | |
| Cardiac failure | 0 (0.0) | 1 (0.2) | |
| Extrasystoles | 1 (0.2) | 0 (0.0) | |
| Gastrointestinal disorders | 2 (0.3) | 0 (0.0) | 0.3 (-0.1;0.8) |
| Gastrointestinal necrosis | 1 (0.2) | 0 (0.0) | |
| Vomiting | 1 (0.2) | 0 (0.0) | |
| General disorders and administration site conditions | 0 (0.0) | 3 (0.5) | -0.5 (-1.1;0.1) |
| Immediate post-injection reaction | 0 (0.0) | 2 (0.3) | |
| Multiple organ dysfunction syndrome | 0 (0.0) | 1 (0.2) | |
| Immune system disorders | 1 (0.2) | 0 (0.0) | 0.2 (-0.2;0.5) |
| Anaphylactic reaction | 1 (0.2) | 0 (0.0) | |
| Infections and infestations | 4 (0.7) | 2 (0.3) | 0.3 (-0.5;1.2) |
| Peritonitis | 1 (0.2) | 1 (0.2) | |
| Pneumonia | 2 (0.3) | 1 (0.2) | |
| Infection | 1 (0.2) | 0 (0.0) | |
| Injury, poisoning and procedural complications | 2 (0.3) | 0 (0.0) | 0.3 (-0.1;0.8) |
| Endotracheal intubation complication | 1 (0.2) | 0 (0.0) | |
| Premature recovery from anaesthesia | 1 (0.2) | 0 (0.0) | |
| Musculoskeletal and connective tissue disorders | 1 (0.2) | 0 (0.0) | 0.2 (-0.2;0.5) |
| Trismus | 1 (0.2) | 0 (0.0) | |
| Respiratory, thoracic and mediastinal disorders | 2 (0.3) | 2 (0.3) | 0.0 (-0.7;0.7) |
| Bronchospasm | 0 (0.0) | 1 (0.2) | |
| Hypoxia | 1 (0.2) | 0 (0.0) | |
| Oxygen saturation decreased | 0 (0.0) | 1 (0.2) | |
| Pneumonia aspiration | 1 (0.2) | 0 (0.0) | |
| Skin and subcutaneous tissue disorders | 1 (0.2) | 2 (0.3) | -0.2 (-0.8;0.4) |
| Erythema | 0 (0.0) | 1 (0.2) | |
| Rash | 1 (0.2) | 1 (0.2) | |
| Vascular disorders | 19 (3.3) | 3 (0.5) | 2.8 (1.2;4.4) |
| Haemodynamic instability | 1 (0.2) | 0 (0.0) | |
| Hypotension | 18 (3.1) | 3 (0.5) | |

[a] Allergy severity Grade I: cutaneous rash, Grade II: moderate clinical signification requiring medical intervention, grade III: Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm; severity grade IV: Cardiac or respiratory arrest.

**eAppendix. Data Safety Report**

From the study: " "REMICrush

**Effect of Remifentanil vs. neuromuscular blockers during rapid sequence intubation on successful intubation without major complications among patients at risk for aspiration: a randomized clinical trial**

Protocol Reference RC19_0055

Study Drug: Remifentanil

Promoter: NANTES UNIVERSITY HOSPITAL
5 Gloriette Island Alley
44093 NANTES cedex 01
Phone: 02 53 48 28 35
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**Coordinating Investigator**: Dr. Nicolas GRILLOT

| | |
|---|---|
| **Alexandra JOBERT, Vigilance Officer, 02 44 76 67 81**<br>**Promotion Department** | **Date and signature:** |

As the University Hospital of Nantes does not hold the marketing authorization for the product under study, this safety report is written solely concerning the data from the clinical trial RC19_0055, which has been completed. This report contains open data.
This report is archived in the promoter's study file; a copy shall be sent to the coordinating investigator and pharmacist of the sponsoring PUI, the competent authority, the ethics committee and the independent supervisory committee.
This information is the exclusive property of the University Hospital of Nantes and is confidential.

## Summary of the key information contained in the report

| D.S.U.R for testing Final | |
|---|---|
| EudraCT number | 2019-000753-31 |
| Country | FRANCE |
| Name of Competent Authority | ANSM |
| Date of initial authorization of the ANSM | 25/06/2019 |
| Name of CPP | South-West Overseas II (Toulouse) |
| Favorable opinion of the CPP No. 2-19-052 | 04/07/2019 |
| Remifentanil<br>Therapeutic class: Opioid anesthetic (ATC: N01A H06)<br>Indication: Anesthetic induction<br>Dose and route of administration: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection<br>Total duration of treatment: single dose<br>MA: Yes for anesthetic induction in 1997<br>Country: France<br>Reference documents: RCP version of 02/08/2018 | |

The trial started on 09/10/2019 (1st inclusion date), and 1150 participants were included and randomized. The inclusions ended on 15/04/2021, and the last visit of the last patient took place on 22/04/2021. This is a study in, whose main objective is open, phase III to demonstrate the non-inferiority of an anesthetic induction in Neuromuscular blockers-free rapid sequence with Remifentanil on the prevention of major complications related to tracheal intubation compared to rapid sequence induction with short-acting Neuromuscular blockers and secondary objectives are:

1) Compare the effectiveness of rapid sequence intubation with or without rapid onset neuromuscular blockers
2) Compare the tolerance of rapid sequence induction with or without rapid onset neuromuscular blockers
3) Comparing the ability to prevent postoperative respiratory complications

At the time of the report, all patients have left the study (6 of them prematurely).

– Summary of Significant Risks :

The expected risks are detailed in the SPC and protocol; no new specific risk factors have been identified.

– Actions taken for security reasons :

No action was taken for security reasons.

– Summary of all security assessments over the period covered by this report :

*Due to the COVID-19 pandemic, the DSMB meeting scheduled for 400 patients could not be implemented; the 1st meeting was held on 15/09/2020 and the 2nd and last meeting is scheduled for 01/07/2021.*

– Conclusions:

Over the period covered by this second report, 10 reports of serious adverse events were transmitted, including 03 effects in the "Hypnotic + Remifentanil" arm; none in the "Hypnotic + Neuromuscular blockers" arm.

Over the duration of the study, there is a greater proportion of event and severe effect in the "Hypnotic + Remifentanil" arm, however the number of these AE/RA remains low and concerns known and usual AE/RA of the current management of these patients (effects of vascular SOC in particular).

The benefit-risk balance appears unchanged at the date of this second and last safety report. The trial ended without any change in the monitoring of the included patients.

## 1 Introduction

Remifentanil
Therapeutic class: Opioid anesthetic (ATC: N01A H06)
Indication: Anesthetic induction
Dose and route of administration: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection
Total duration of treatment: single dose
MA: Yes for anesthetic induction in 1997
Country: France
Reference documents: RCP version of 02/08/2018

As the Nantes University Hospital does not hold the marketing authorisation for the investigational medicinal product used in the study *REMICrush,* this safety report is drawn up solely in relation to the data from this clinical trial.

## 2 Statutes of Marketing Authorizations

The product under study has an MA in France and is indicated as an analgesic agent during induction and/or maintenance of general anesthesia or for analgesia of patients aged 18 years and over, ventilated in intensive care units at different dosages. As the product under study is generic, there are several marketing authorisation holders (B Braun, Mylan, Arrow, Hospira, Kabi, Pfizer, Teva, etc.). ).

## 3 Actions taken for security reasons during the reporting period

- Suspensive status of the clinical trial Yes No ☐☒
- Protocol change Yes No ☐☒
- Recommendation of a health authority and/or ethics committee: Yes No ☐☒
- Security developments Yes No ☐☒

No action on patient safety was taken during the reporting period.
No recommendations from the safety and scientific committees or authorities were brought to the attention of the sponsor during the period covered by this report.

## 4 Changes to reference documents

No reference documents were modified during the reporting period.

## 5 Descriptions of ongoing or completed clinical trials during the reporting period

This is an open-label Phase III study, whose primary objective is to demonstrate the non-inferiority of a Neuromuscular blockers-free rapid-sequence anesthetic induction with Remifentanil on the prevention of major complications related to tracheal intubation compared to rapid sequence induction with Neuromuscular blockers of short action time and secondary objectives are:
1) Compare the effectiveness of rapid sequence intubation with or without fast-acting Neuromuscular blockers
2) Compare the tolerance of rapid sequence induction with or without fast-acting Neuromuscular blockers
3) Comparing the ability to prevent postoperative respiratory complications

The trial started 09/10/2019 on (1st inclusion date) and 1154 participants were included and 1150 were randomised. The inclusions ended on 15/04/2021, the last visit of the last patient took place on 22/04/2021. Since the beginning of the study, 1150 patients have been treated since the beginning of the study. At the time of the report, all patients have left the study (6 of them prematurely).

## 6 Description of the subjects exposed to the product

### 6.1 Description of subjects included in the study

Since the beginning of the study 1150 patients have been enrolled and randomized (575 women and 575 men treated), 4 patients have been included but ultimately not randomized. The average age of treated patients is 51.4 years, the median is 54 years.

| | Nb of patients | Middle Ages | Age min. | Max age | Median Age |
|---|---|---|---|---|---|
| **Neuromuscular blockers** | **575** | **51,4** | **18** | **82** | **54** |
| Wife | 292 | 52,0 | 19 | 82 | 54,5 |
| Man | 283 | 50,9 | 18 | 81 | 53 |
| **Remifentanil** | **575** | **49,2** | **18** | **81** | **50** |
| Wife | 283 | 48,9 | 19 | 80 | 49 |
| Man | 292 | 49,5 | 18 | 81 | 51 |
| **Grand total** | **1150** | **50.3** | **18** | **82** | **52** |

**Demographic distribution of patients included and treated.**

### 6.2 Description of post-marketing topics

Not applicable.

## 7 Presentation of safety data

### 7.1 Origin and processing of security data

This report is based on data extracted from the eVe Report, as well as from the Ennov Clinical Clinical Clinical Database (eCRF). The coding of adverse events and events uses the MedDRA thesaurus (version 24.0). Accountability was defined using the standardized method.

The current version of the SPC serves as a reference for determining whether expected or unexpected. 02/08/2018

Over the period covered by this second report, 10 vigilance reports were transmitted, 01 a special situation/special interest, 07 serious adverse events and 03 serious adverse reactions. A total of 14 reports of serious adverse events since the study have been transmitted, including 05 effects, as well as 02 special/special situations of special interest.

Safety data are presented using Line Listings and Summary Tabulations in the Appendices. The 3 serious adverse reactions that occurred during the period covered by this report are detailed here.

### 7.2 Listings of Serious Adverse Reactions identified during the period covered by this report

The 3 SAR received over the period, for 3 patients included in the Hypnotic + Remifentail arm, 2 cases concern hypotension, and the 3rd a case of vomiting, the 3 cases were quickly resolved, and attributed to Remifentanil by the investigator and the sponsor.

Hypotension, as well as vomiting are expected effects of Remifentanil.

### 7.3 Cumulative Serious Adverse Events

| **SOC: Infections and infestations / 10021881 (1)** | | |
|---|---|---|
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Pneumonia | 1 | 1 |
| **Subtotal** | **1** | **1** |
| **SOC: Immune system disorders / 10021428 (1)** | | |

| MedDRA PT | Hypnotic + Remifentanil | Hypnotic + Neuromuscular blockers |
|---|---|---|
| Anaphylactic shock | 1 | |
| **Subtotal** | **1** | |
| **SOC : Respiratory, thoracic and mediastinal disorders / 10038738 (2)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Hypoxia | 1 | |
| Pneumonia aspiration | 1 | |
| **Subtotal** | **2** | |
| **SOC: Gastrointestinal disorders / 10017947 (1)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Gastrointestinal necrosis | 1 | |
| **Subtotal** | **1** | |
| **SOC: General disorders and administration site conditions / 10018065 (1)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Multiple organ dysfunction syndrome | | 1 |
| **Subtotal** | | **1** |
| **SOC: Investigations / 10022891 (1)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Oxygen saturation decreased | | 1 |
| **Subtotal** | | **1** |
| **SOC: Injury, poisoning and procedural complications / 10022117 (1)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| Premature recovery from anaesthesia | 1 | |
| **Subtotal** | **1** | |
| **SOC: / (1)** | | |
| **MedDRA PT** | **Hypnotic + Remifentanil** | **Hypnotic + Neuromuscular blockers** |
| | | 1 |
| **Subtotal** | | **1** |

| | | |
|---|---|---|
| **Total** | **6** | **4** |

## 7.4 Safety data from all clinical trials conducted by the sponsor

### *7.4.1* Completed clinical studies

Not applicable. The study is the only study covered by this report, all safety outcomes are described in detail in sections 7.2 and 7.3.REMICrush

### *7.4.2* Ongoing clinical studies

Not applicable. The study is the only study covered by this reportREMICrush and has been completed.

### *7.4.3* Long-term follow-up

Not applicable. At the date of the report, patients who complete are not subject to long-term follow-up.REMICrush

### *7.4.4* Data from other therapeutic uses (including therapeutic combination)

Not applicable. The University Hospital of Nantes does not hold the Marketing Authorization and has not initiated any other studies. To its knowledge, no safety data from other therapeutic uses, including combination therapies, are available.

## 8 Observational and post-marketing studies

Not applicable. The University Hospital of Nantes does not hold the Marketing Authorization and has not initiated observational or epidemiological studies. To its knowledge, no safety data from non-interventional studies.

## 9 Data from clinical studies conducted by a third party

Not applicable.

## 10 Non-clinical data (in vivo, in vitro)

Not applicable.

## 11 Bibliographic data

A search on the publication period from to au with the 25/06/202022/04/2021 keywords "Remifentanil" and "anesthesia", "side effects", "adverse reaction" and "safety" was performed on31/05/2021

Aucune publication evoking new risks has not been identified.

## 12 Other DSUR

Not applicable.

## 13 Lack of efficiency

No data regarding a lack of efficacy were brought to the attention of the proponent.

## 14 Information specific to national regulations

Not required by European or French regulations.

## 15 Last minute information

A serious adverse reaction identified in the eCRF is awaiting notification by the investigation centre on the date of the report; this is the case of "Trismus" of patient 12-0891, of moderate intensity and imputed by the investigator to Remifentanil.

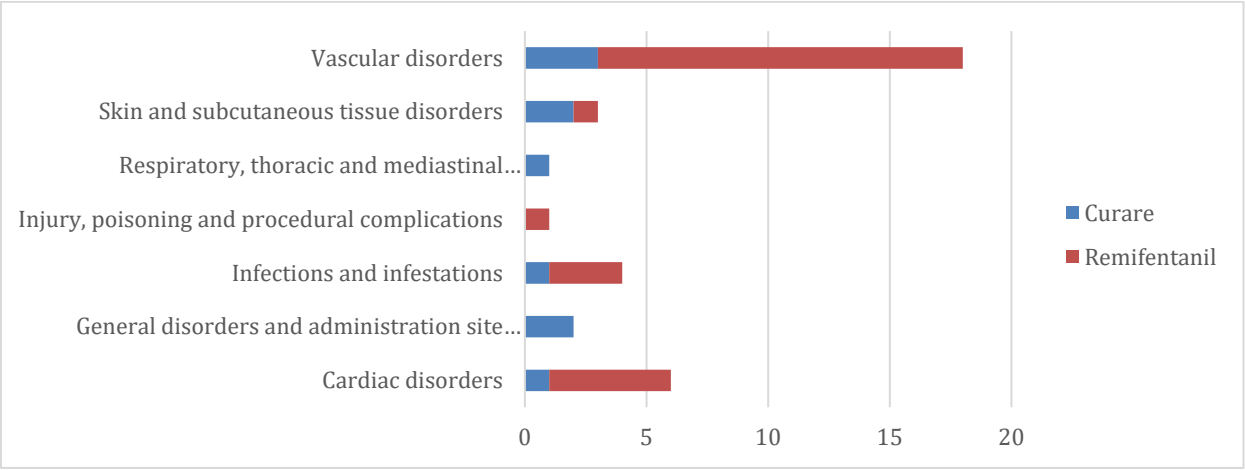
## 16 Overall Security Assessment

Since the beginning of the study, no security features have occurred.

### 16.1 Risk assessment

The analysis of non-serious RAs and AEs extracted from the CRF is carried out to detect a new fact or a variation in the overall safety profile but can only be indicative at this stage of the study, as the FIUs are not signed and the base is not frozen.

Since the beginning of the study, 35 non-serious independent events have been reported (11 in this second period), 10 in the "Hypnotic + Neuromuscular blockers" arm and 25 in the "Hypnotic + Remifentanil" arm, including 24 related to the treatment under study, including 6 in the "Hypnotic + Neuromuscular blockers" arm (corresponds to AE attributed to Neuromuscular blockers; the imputability of these EAs should be modified, as only Remifentanil is considered to be the treatment under study).




**Non-serious AE/AR by SOC and arm**

The vast majority of EAs attributed to the study treatment are of mild intensity. In addition, in the arm "Hypnotic + Remifentanil" there are more severe AE / AR than in the bras "Hypnotic + Neuromuscular blockers" where the AE / AR are of mild (5) or moderate intensity (5).

**Severity and evolution of non-serious EA/RA**

| Severity Evolution | In progress | Resolute | Total |
|---|---|---|---|
| **Neuromuscular blockers** | | | |
| ***Light*** | | 5 | 5 |
| Erythema | | 1 | 1 |
| Hypotension | | 2 | 2 |
| Immediate post-injection reaction | | 1 | 1 |
| Rash | | 1 | 1 |
| **Moderate** | | 5 | 5 |
| Bronchospasm | | 1 | 1 |
| Cardiac failure | | 1 | 1 |
| Hypotension | | 1 | 1 |
| Immediate post-injection reaction | | 1 | 1 |
| Peritonitis | | 1 | 1 |
| **Remifentanil** | | | |
| ***Light*** | | 14 | 14 |
| Bradycardia | | 1 | 1 |
| Endotracheal intubation complication | | 1 | 1 |
| Extrasystoles | | 1 | 1 |
| Hypotension | | 11 | 11 |
| ***Moderate*** | 1 | 5 | 6 |
| Bradycardia | | 3 | 3 |
| Hypotension | | 1 | 1 |
| Pneumonia | 1 | | 1 |
| Rash | | 1 | 1 |
| ***Severe*** | | 5 | 5 |
| Haemodynamic instability | | 1 | 1 |
| Hypotension | | 2 | 2 |
| Peritonitis | | 1 | 1 |
| Infection | | 1 | 1 |
| Total | 1 | 34 | 35 |

### 16.2 Updated assessment of the risk/benefit balance

Although there is a greater proportion of event and severe effect in the "Hypnotic + Remifentanil" arm, these AE/RAs remain known and usual from the current management of these patients.

The benefit-risk balance is unchanged at the date of this second and last safety report.

## 17 Summary of key risks

The most common risks with Reminfentanil are low blood pressure and bradycardia.
The most common expected AEs are: rigidity of the skeletal muscles, bradycardia, hypotension, postoperative hypertension, acute respiratory depression, apnea, nausea, vomiting.

## 18 Conclusion

Over the period covered by this second report, 10 reports of serious adverse events were transmitted, including 03 effects in the "Hypnotic + Remifentanil" arm; none in the "Hypnotic + Neuromuscular blockers" arm.

Over the duration of the study, there is a greater proportion of event and severe effect in the "Hypnotic + Remifentanil" arm, however the number of these EA/RA remains low and concerns known and usual EA/RA of the current management of these patients (effects of vascular SOC in particular).

The benefit-risk balance appears unchanged at the date of this second and last safety report. The trial ended without any change in the monitoring of the included patients.

**eAppendix 1A – Summary listing of Non-Serious Adverse Reactions and Events**
**eAppendix 1B – Cumulative Table of Serious and Non-Serious Adverse Events and Adverse Events**

## eAppendix 1A – Summary Listing of Non-Serious Adverse Reactions and Events

| Num. Pt | Arm | Nature | MedDRA SOC | MedDRA PT | Start date | End date | Severity | Causal link | Causal link, accuracy | Action taken | Support | Evolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01-0010 | Remifentanil | Stercoral peritonitis | Infections and infestations | Peritonitis | 19/10/2019 | 19/10/2019 | Severe | Other | Post operative | No | Surgical | Resolute |
| 01-0791 | Remifentanil | Reintubation on guide | Injury, poisoning and procedural complications | Endotracheal intubation complication | 09/11/2020 | 09/11/2020 | Light | Other | Balloon 1st porous intubation probe | No | Medical | Resolute |
| 01-0856 | Remifentanil | Rash cutaneous has induction | Skin and subcutaneous tissue disorders | Rash | 06/12/2020 | 06/12/2020 | Moderate | Concomitant treatments | Cefacidal | No | Medical | Resolute |
| 03-0437 | Neuromuscular blockers | Peritonitis | Infections and infestations | Peritonitis | 02/07/2020 | 03/07/2020 | Moderate | Disease justifying inclusion | | No | Surgical | Resolute |
| 04-0474 | Neuromuscular blockers | Cardiac compensation | Cardiac disorders | Cardiac failure | 09/07/2020 | 12/07/2020 | Moderate | Disease justifying inclusion | Hospitalization | Temporary shutdown | Medical | Resolute |
| 05-0211 | Neuromuscular blockers | Hypotension | Vascular disorders | Hypotension | 28/01/2020 | 28/01/2020 | Moderate | Disease justifying inclusion | | No | Medical | Resolute |
| 05-0314 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 04/03/2020 | 04/03/2020 | Severe | Treatment under study | Remifentanil | No | Medical | Resolute |
| 05-0573 | Remifentanil | Bigeminism | Cardiac disorders | Extrasystoles | 16/08/2020 | 16/08/2020 | Light | Treatment under study | Remifentanil | No | No | Resolute |
| 05-0771 | Remifentanil | Instabilitative hd | Vascular disorders | Haemodynamic instability | 30/10/2020 | 31/10/2020 | Severe | Treatment under study | Remifentanil | No | Medical | Resolute |
| 06-0035 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 30/10/2019 | 30/10/2019 | Light | Treatment under study | Remifentanil | No | No | Resolute |
| 06-0151 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 29/12/2019 | 29/12/2019 | Light | Treatment under study | | No | Medical | Resolute |
| 06-0553 | Neuromuscular blockers | Erythmus generalizes | Skin and subcutaneous tissue disorders | Erythema | 06/08/2020 | 06/08/2020 | Light | Treatment under study | | No | No | Resolute |
| 06-0628 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 01/09/2020 | 01/09/2020 | Light | Treatment under study | | No | Medical | Resolute |
| 06-0674 | Remifentanil | Hypotention | Vascular disorders | Hypotension | 18/09/2020 | 18/09/2020 | Light | Treatment under study | Remifentanil | No | Medical | Resolute |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 06-0684 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 21/09/2020 | 21/09/2020 | Light | Treatment under study | Remifentanil | No | Medical | Resolute |
| 06-0710 | Remifentanil | Hypotentio | Vascular disorders | Hypotension | 02/10/2020 | 02/10/2020 | Light | Treatment under study | Remifentanil | No | Medical | Resolute |
| 06-0738 | Neuromuscular blockers | Hypotension | Vascular disorders | Hypotension | 14/10/2020 | 14/10/2020 | Light | Treatment under study | Suxamethonium | No | Medical | Resolute |
| 06-0789 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 09/11/2020 | 09/11/2020 | Light | Treatment under study | Remifentanil | Temporary shutdown | No | Resolute |
| 06-0799 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 13/11/2020 | 13/11/2020 | Light | Treatment under study | Remifentanil | No | Medical | Resolute |
| 06-0826 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 26/11/2020 | 26/11/2020 | Light | Treatment under study | Remifentanil | No | Medical | Resolute |
| 06-1035 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 14/02/2021 | 14/02/2021 | Light | Treatment under study | | No | Medical | Resolute |
| 06-1137 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 06/04/2021 | 06/04/2021 | Light | Treatment under study | | No | Medical | Resolute |
| 06-1141 | Neuromuscular blockers | Hypotension | Vascular disorders | Hypotension | 08/04/2021 | 08/04/2021 | Light | Treatment under study | Suxamethonium | No | Medical | Resolute |
| 09-0434 | Remifentanil | Extended hospitalization | Infections and infestations | Infection | 26/06/2020 | 31/07/2020 | Severe | Concomitant disease | Peritontic superinfection | No | Medical | Resolute |
| 09-0622 | Remifentanil | Hypotension | Vascular disorders | Hypotension | 30/08/2020 | 30/08/2020 | Severe | Concomitant treatments | High dose propofol | No | Medical | Resolute |
| 11-0212 | Neuromuscular blockers | Rash cutaneous to the injection of Neuromuscular blockers | General disorders and administration site conditions | Immediate post-injection reaction | 29/01/2020 | 29/01/2020 | Moderate | Treatment under study | Suxamethonium | No | No | Resolute |
| 11-0229 | Neuromuscular blockers | Skin rash | Skin and subcutaneous tissue disorders | Rash | 03/02/2020 | 03/02/2020 | Light | Treatment under study | Neuromuscular blockers | No | Medical | Resolute |
| 11-0291 | Remifentanil | Pneumonia | Infections and infestations | Pneumonia | 29/02/2020 | 17/03/2020 | Moderate | Disease justifying inclusion | Evolution of the disease | No | Medical | In progress |
| 11-0308 | Remifentanil | Bradycardia | Cardiac disorders | Bradycardia | 02/03/2020 | 02/03/2020 | Moderate | Treatment under study | | No | No | Resolute |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11-0361 | Neuromuscular blockers | Rash has Neuromuscular blockers injection | General disorders and administration site conditions | Immediate post-injection reaction | 20/05/2020 | 20/05/2020 | Light | Treatment under study | Neuromuscular blockers | No | No | Resolute |
| 11-0563 | Remifentanil | Bradycardia at 42 bpm post induction, treated with atropine | Cardiac disorders | Bradycardia | 12/08/2020 | 12/08/2020 | Moderate | Treatment under study | Remifentanil | No | Medical | Resolute |
| 11-1042 | Remifentanil | Hypotension following anesthetic induction at 57/32 mmhg | Vascular disorders | Hypotension | 17/02/2021 | 17/02/2021 | Moderate | Concomitant treatments | Lie to propofol | No | Medical | Resolute |
| 12-0892 | Remifentanil | Bradycardia at induction | Cardiac disorders | Bradycardia | 25/12/2020 | 25/12/2020 | Light | Treatment under study | | No | Medical | Resolute |
| 12-0938 | Remifentanil | Bradycardia at 34 bpm minimum, resolutive after atropine injection | Cardiac disorders | Bradycardia | 12/01/2021 | 12/01/2021 | Moderate | Treatment under study | | No | Medical | Resolute |
| 15-0873 | Neuromuscular blockers | Bronchospasm | Respiratory, thoracic and mediastinal disorders | Bronchospasm | 16/12/2020 | 16/12/2020 | Moderate | Concomitant disease | Obesity | No | Medical | Resolute |

**eAppendix 1B – Cumulative Table of Serious and Non-Serious Adverse Events and Adverse Events**

| | Neuromuscular blockers | Remifentanil | Total |
|---|---|---|---|
| **Cardiac disorders** | **1** | **5** | **6** |
| Bradycardia | | 4 | 4 |
| Cardiac failure | 1 | | 1 |
| Extrasystoles | | 1 | 1 |
| **Gastrointestinal disorders** | | **2** | **2** |
| Gastrointestinal necrosis | | 1 | 1 |
| Vomiting | | 1 | 1 |
| **General disorders and administration site conditions** | **3** | | **3** |
| Immediate post-injection reaction | 2 | | 2 |
| Multiple organ dysfunction syndrome | 1 | | 1 |
| **Immune system disorders** | | **1** | **1** |
| Anaphylactic reaction | | 1 | 1 |
| **Infections and infestations** | **1** | **4** | **5** |
| Peritonitis | 1 | 1 | 2 |
| Pneumonia | | 2 | 2 |
| Infection | | 1 | 1 |
| **Injury, poisoning and procedural complications** | | **2** | **2** |
| Endotracheal intubation complication | | 1 | 1 |
| Premature recovery from anaesthesia | | 1 | 1 |
| **Musculoskeletal and connective tissue disorders** | | **1** | **1** |
| Trismus | | 1 | 1 |
| **Respiratory, thoracic and mediastinal disorders** | **3** | **2** | **5** |
| Bronchospasm | 1 | | 1 |
| Hypoxia | | 1 | 1 |
| Oxygen saturation decreased | 1 | | 1 |
| Pneumonia | 1 | | 1 |
| Pneumonia aspiration | | 1 | 1 |
| **Skin and subcutaneous tissue disorders** | **2** | **1** | **3** |
| Erythema | 1 | | 1 |
| Rash | 1 | 1 | 2 |
| **Vascular disorders** | **3** | **19** | **22** |
| Haemodynamic instability | | 1 | 1 |
| Hypotension | 3 | 18 | 21 |
| **Total** | **13** | **37** | **50** |