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Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial.

The iDIAPASON study

*Adrien Bouglé, M.D., Ph.D., Sophie Tuffet, M.D., Laura Federici, M.D., Marc Leone, M.D., Ph.D., Antoine Monsel, M.D., Ph.D., Thomas Dessalle, M.D., Julien Amour, M.D., Ph.D., Claire Dahyot-Fizelier M.D., Ph.D., François Barbier M.D., Ph.D., Charles-Edouard Luyt, M.D., Ph.D., Olivier Langeron, M.D., Ph.D., Bernard Cholley, M.D., Ph.D., Julien Pottecher, M.D., Ph.D., Tarik Hissem, M.D., Jean-Yves Lefrant, M.D., Ph.D., Benoit Veber, M.D., Ph.D., Matthieu Legrand, M.D., Ph.D., Alexandre Demoule, M.D., Ph.D., Pierre Kalfon, M.D., Jean-Michel Constantin, M.D., Ph.D., Alexandra Rousseau, M.D., Ph.D., Tabassome Simon, M.D., Ph.D., Arnaud Foucrier, M.D., et al., for the iDIAPASON Trial investigators**

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Bouglé at Anesthesiology and Critical Care Medicine, Cardiology Institute, University Hospital Pitié-Salpêtrière (AP-HP. Sorbonne Université), 47-83 Boulevard de l'Hôpital, 75013 Paris, France. *A complete list of iDIAPASON Trial Investigators is provided in the Supplementary Appendix.

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ABSTRACT

Purpose:

Compared to long duration of antibiotic therapy, a short duration has a comparable clinical efficacy for ventilator-associated pneumonia (VAP), with the exception of documented VAP of non-fermenting Gram negative bacilli (NF-GNB), including *Pseudomonas aeruginosa* (PA). We aimed to assess the non-inferiority of a short duration of antibiotics (8 days) vs. prolonged antibiotic therapy (15 days) in VAP due to PA (PA-VAP).

Methods:

We conduct a nationwide, randomized, open-labeled, multicenter, non-inferiority trial to evaluate optimal duration of antibiotic treatment in PA-VAP. Eligible patients were adults with diagnosis of PA-VAP and randomly assigned in 1:1 ratio to receive a short duration treatment (8 days) or a long duration treatment (15 days). A pre-specified analysis was used to assess a composite endpoint combining mortality and PA-VAP recurrence rate during hospitalization in the ICU within 90 days.

Results:

In intention-to-treat population (n=186), the percentage of patients who reached the composite endpoint was 25·5% (N=25/98) in the 15-day group versus 35·2% (N=31/88) in the 8-day group (difference 9·7%, 90% CI 0.0% to 21.2%). The percentage of recurrence of PA-VAP during the ICU stay was 9·2% in the 15-day group versus 17·0% in the 8-day group. The two groups had similar median days of mechanical ventilation, of ICU stay, number of extra pulmonary infections and acquisition of MDR pathogens during ICU stay.

Conclusions:

Our study showed no differences in the composite or separate outcomes (90-day mortality or VAP recurrence) between short and long duration treatment for PA-VAP. However, the lack of power limits the interpretation of this study.

Keywords:

Ventilator-associated pneumonia, *Pseudomonas aeruginosa*, antibiotic therapy, recurrence, survival

TAKE-HOME MESSAGE

The optimal duration of treatment for *Pseudomonas aeruginosa* ventilator-associated pneumonia remains unknown. In a prospective randomized trial, we showed no difference for mortality and PA-VAP recurrence between 8 days and 15 days durations of antibiotic therapy.

MANUSCRIPT

Introduction

Ventilator-associated pneumonia (VAP) remains a major cause of morbidity and mortality in intensive care units (ICUs), accounting for 25% of infections in the ICU patients. Despite guidelines frame the treatment of VAP[1–3], several uncertainties remain, particularly for treating *Pseudomonas aeruginosa* (PA-VAP)[4]. Hence, the optimal duration of antibiotic therapy for PA-VAP remains debated. Few studies have reported the recurrence rate according to the antibiotic therapy duration[5,6]. In the PneumA trial[5] comparing 8 days versus 15 days of antibiotic duration for VAP, if the mortality and recurrence rate of pneumonia 28 days after bronchoscopy did not differ among groups, the patients with VAP caused by non-fermenting Gram-negative bacilli (NF-GNB), mostly *Pseudomonas aeruginosa*, had a higher rate of pneumonia recurrence with short-duration therapy compared to a long-duration therapy group (40.6% vs. 25.4%). However, a secondary analysis of PneumA found no influence of antibiotic duration on recurrence or mortality[7]. Noteworthy, in the most recent meta-analysis[6], while a non-inferiority of short duration was found for mortality (OR 1·18; 95% CI 0·77 to 1·8) and recurrence rate of pneumonia (OR 1·41; 95% CI 0·94 to 2·12), the recurrence was more frequent after short-duration therapy for cases of VAP due to NF-GNB (OR 2·18; 95% CI 1·14 to 4·16), without a difference in the risk of mortality. The North American or European guidelines recommend a short duration even for NF-GNB VAP[1–3]. Therefore, there is still some doubt about the optimal duration of treatment for PA-VAP that need to be addressed in a prospective randomized study. The Impact of the Duration of Antibiotics on clinical events in Patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia (iDIAPASON) study was thus designed to assess the non-inferiority of a short duration of antibiotics (8 days) versus prolonged antibiotic therapy (15 days) in PA-VAP.

Methods

Study design

The design of this nationwide, randomized, open-labelled, multicentre, non-inferiority, controlled trial (NCT02634411) has been published previously[8]. Briefly, we consecutively screened adults (≥18 years of age), diagnosed with documented PA-VAP. The diagnosis of PA-VAP included a clinical suspicion[1] (≥ two criteria including fever > 38·5 °C, leucocytosis > 10^9/L or leukopenia < 4.10^8/L, purulent tracheobronchial secretions, and a new or persistent infiltrate on chest radiography) and confirmation by a *Pseudomonas aeruginosa* positive quantitative culture of a respiratory sample: broncho-alveolar lavage fluid (significant threshold ≥10^4 colony-forming units (CFU)/mL) or plugged telescopic catheter (significant threshold ≥10^3 CFU/mL) or quantitative endotracheal aspirate pulmonary secretion samples (significant threshold ≥10^6 CFU/mL), according to international definition. Patients were not eligible in case of the following conditions: pregnancy, immunosuppression (HIV, immunosuppressive therapy, corticosteroids > 0·5 mg/kg per day for more than a month), current antibiotic therapy active on *Pseudomonas aeruginosa* for extra-pulmonary infection, procedure of withdrawing life-sustaining treatment, chronic pulmonary colonization with *Pseudomonas aeruginosa* (chronic obstructive pulmonary disease (COPD) or bronchiectasis, with a positive respiratory sample below the threshold rate for *Pseudomonas aeruginosa* (i.e., <10^3 CFU/mL for protected specimen brush, <10^4 CFU/mL for broncho-alveolar lavage or <10^6 CFU/mL for tracheal aspirate), obtained in the absence of pneumonia or exacerbation during the 6 months before the ICU admission).The study was conducted in accordance with the Helsinki Declaration and French laws and regulations. The study has received its approval from the French ethical committee (Comité de Protection des Personnes Ile de France VI) as

well from the French Drug Safety Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé). Written informed consent was sought before inclusion or from a patient's relative or an emergency inclusion if their absence according to French law[9]. Additional details on the trial design, including investigator responsibilities, are described in the Supplementary Material.

Trial intervention

Antibiotic therapy was initiated just after bacteriological respiratory sampling, without waiting for the results of microbiological analysis (bacteria identification and/or results of antimicrobial susceptibility testing). The choice of initial antibiotic therapy was left to the discretion of the physician according to usual care based on the clinical context, previous antibiotic therapy, the presence or absence of risk factors[1] for multidrug-resistant (MDR) pathogen or hospitalization in the previous 90 days (current hospitalization ≥5 days, mechanical ventilation ≥5 days, support in a dialysis centre or residency in a nursing home), local epidemiological data, and finally knowledge that the patient is already known as being colonized by a MDR pathogen. In these situations, a broad-spectrum antibiotic was recommended immediately, with the association of a β-lactam/β-lactamase inhibitor or an antipseudomonal cephalosporin, and an aminoglycoside or an antipseudomonal fluoroquinolone for 3 to 5 days. Initial antibiotic therapy with a narrow spectrum was possible in case of early-onset pneumonia (mechanical ventilation <5 days) and in the absence of risk factors for MDR pathogens, as recommended[1–3]. Investigators were strongly encouraged to convert this initial regimen into a narrower spectrum therapy, based on culture results and antimicrobial susceptibility testing. Antibiotic therapy has to be interrupted, either at the end of day 8 or day 15, according to the randomization group, excluding antibiotic therapy for a documented pulmonary infection recurrence or a new extra-pulmonary infection before that day. Screening of MDR pathogens

was performed with a surveillance culture of swab samples from the rectum for extended-spectrum β-lactam-producing Enterobacteriaceae (ESBL) and of swab samples from the anterior nares for methicillin-resistant *Staphylococcus aureus* (MRSA) at the ICU admission, and then once weekly until the ICU discharge.

Randomization

After antibiotic susceptibility testing results, patients were randomized in a blocked-balanced 1:1 ratio and stratified on centre in the 8-day arm or the 15-day arm using the Internet (CleanWEB, Telemedicine Technologies, S.A.S). Investigators were blinded to the block size.

Primary and secondary outcomes

The primary outcome was a composite endpoint combining mortality and PA-VAP recurrence occurring during the ICU stay until day 90. Recurrence was defined with a *post hoc* diagnosis by two independent experts blinded to the treatment arms with predefined criteria: clinical suspicion of VAP after at least 48 hours without effective antibiotic therapy for *P. aeruginosa*, defined as the association of at least of one of the following signs (fever >38·5°C, leukocytosis $>10^9$/L or leukopenia $<4.10^8$/L) with purulent tracheobronchial secretions and a new or persistent infiltrate on chest radiography, then confirmed with a positive quantitative culture, as described above. In cases of disagreement between the two experts (C.-E. L., F.B.), a third expert (C. D.-F.) will reach a consensus.

Secondary outcomes, evaluated during the ICU stay until day 90, were mechanical invasive ventilation (MV) duration, ICU stay duration, antibiotic exposure duration, number and types of extra pulmonary infections, and acquisition of MDR pathogens (from swab sample of rectum and anterior nares).

Statistical analysis

The study was designed to demonstrate the non-inferiority for the composite endpoint of mortality and recurrence at 90 days of the 8-day strategy versus the 15-day strategy for PA-VAP, based on a 10% non-inferiority margin, in line with guidance from the European Medicines Agency[10]. Assuming a mortality and/or recurrence of PA-VAP rate of 35.7%[11] in the 15-day strategy, the 10% non-inferiority margin would achieve 80% power with a unilateral alpha risk of 5%, for which a target of 600 randomized patients was required, taking into account a drop-out rate of 5%.

Baseline characteristics were reported using frequencies and percentages for categorical data and using mean and standard deviation (sd) or median and interquartile range (IQR) for continuous data, according to their distribution.

The analysis of main endpoint was performed on the intention-to-treat (ITT) population, defined as "as randomized patients". Non-inferiority was assessed by a confidence interval (CI) approach (Exact two-sided 90% (1-2α) CI, equivalent to a one-sided test with an alpha value of 0.05). Non-inferiority of 8-day group to 15-day group could be claimed if the upper limit of the CI of the difference between groups is lower than 10%. Sensitivity analysis was performed in per-protocol (PP) population, defined as randomized patients excluding those wrongly included or with non-respect of the antibiotic duration allocated, except for medical reason. Event-free survival in the ITT population was represented using Kaplan-Meier survival curves, considering event as VAP recurrence or death from effective antibiotic therapy to 90 days, and Hazard Ratio (HR) was estimated with its 90% CI using Cox model. In *post hoc* analyses, adjusted proportion difference between groups and its 2-sided 90% CI was calculated in ITT and PP populations using a generalized linear mixed model with binomial distribution and logit link, considering the centre as random effect and adjusting for following baseline variables:

heart failure, hypertension, administration of catecholamines and PaO2/FiO2 ratio. Difference of VAP recurrence rate between groups and its exact 90% CI was performed. Time from effective antibiotic therapy to death in ICU or to censoring at day 90 was represented using Kaplan-Meier survival curves and HR and its 90% CI estimated using Cox Model. As *post hoc* analysis, VAP recurrence-free survival was performed, taking into account competing-risk of death with a Fine and Gray model. Results were expressed by sub-distribution Hazard Ratio (sHR) and its 90% CI and a cumulative incidence curve was performed. *Post hoc* sensitivity analysis was performed using Bayesian approach adopting a beta-binomial model[12].

Secondary outcomes were analysed under a superiority assumption. The acquisition of MDR pathogens rate during the ICU stay were compared using difference between groups with its Exact 95% CI. The durations of mechanical invasive ventilation, of ICU stay, of exposure to antibiotics and the number of extra-pulmonary infections during the ICU stay were compared using median differences between groups with their 95% CI (Mood method).

Missing data were not replaced for the primary outcome, because no data was missing. In *post hoc* analyses, missing data for PaO2/FiO2 ratio were replaced by median value of each group.

All analyses were performed with the SAS software version 9·4 (SAS Institute Inc. Cary, NC, USA), except for median differences CI estimated with the R Studio version 1.2.5019 (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org), for sensitivity adjusted analysis performed with STATA software version 17 (StataCorp, USA), Bayesian analysis using R version 4.1.1 (2021-08-10) -- "Kick Things", Copyright (C) 2021 The R Foundation for Statistical Computing, Platform: x86_64-apple-darwin17.0 (64-bit).

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Results

Patients

Between June 3rd 2016 and May 22 2018, 196 patients were enrolled in 30 centres between June 2016 and May 2018, of whom 190 underwent randomization. The study was stopped after 24 months due to the slow inclusion rate. Indeed, it was estimated that it would have taken 6 years to enrol the 600 patients needed to demonstrate the non-inferiority on the composite endpoint. Two patients refused their participation, and two patients were under guardianship, resulting in an ITT analysis of 186 patients. After excluding 34 patients with major deviation to the protocol (patients wrongly included (n=32) and randomization not respected (n=2), the PP population included 152 patients (Figure 1). Wrongly inclusions are detailed in the Supplementary file 1. In the overall population, the patients were mostly male (75·8%), aged of 59·4 ± 17·4 years-old and with a medical history of hypertension (25·3%). The first diagnoses at ICU admission were acute circulatory failure for 41 patients (22·0%), acute respiratory failure for 35 patients (18·8%) and trauma for 35 patients (18·8%). Baseline characteristics are reported in Table 1.

Intervention

Patients received in median 15·0 (IQR: 14·0-16·0) days of antibiotic therapy in the 15-day group versus 8·0 (IQR: 8·0-8·5) days in the 8-day group. The main reason for prolongation of the planned duration of antibiotic therapy (12 in the 15-day group and 16 in the 8-day group)

was the PA-VAP persistence (defined as presence of the original causative baseline pathogen(s) from a LRT culture obtained between end of treatment (EOT) and 72 after EOT) leading to a prolongation of antibiotic therapy, respectively for 5 patients in the 15-day group and 7 patients in the 8-day group (see Supplementary Table 1). Empirical treatment was based on combination of antibiotics in 130 (71 %) patients. Aminoglycosides were used in 118 (64·5 %) patients. Details of empirical and definitive antimicrobial therapy are presented in Supp. Table 2.

Primary and secondary outcomes

In the ITT population, 25 (25.5%) patients of the 15-day group and 31 (35.2%) patients of the 8-day group had a PA-VAP recurrence or were dead in ICU at 90-day (Table 2, Figure 2). The non-inferiority of 8-day group compared to the 15-day group was not demonstrated (difference 9·7%, 90% CI -2·4% to 21·9%), considering the upper bound of the 90% CI of the difference being greater than 10%, similar to the analysis performed on the PP population (n=152, difference 12·8%, 90% CI 0·0% to 25·6%). Considering a clinically relevant difference between groups at baseline on heart failure, hypertension, administration of catecholamines and PaO2/FiO2 ratio, a *post hoc* analysis adjusted on these variables was performed, taking into account the centre as random effect. Previous results were confirmed with an adjusted difference in the ITT population of 12·5% (90% CI 1·3% to 23·6%), similar to the analysis performed on the PP population 16·3% (90% CI 3·9% to 28·8%). The 90-day overall survival rate in the 15-day group and in the 8-day group were comparable (81·4%, 90% CI 73·8% to 87·0% and 75·6%, 90% CI 66·9% to 82·3% respectively, HR=1·37, 90% CI 0·81 to 2·33) (Supp. Figure 1). There was a trend toward a higher proportion (almost twice) of recurrence PA-VAP during the ICU stay in the 8-day compared to the 15-day group (17·0% versus 9·2%, difference 7.9%, 90% CI 0·0% to 16·8%). The Fine and Gray model showed a higher risk of

recurrence of PA-VAP in the 8-day group compared to the 15-day group (sHR 1·99, CI 90% 1·01 to 3·95) (Supp. Figure 2).

The 15-day and 8-day groups had similar median in duration of mechanical ventilation (25·0 (15·5-35·0) versus 22·0 (12·0-41·0)), duration of ICU stay (34·0 (23·0-56·0) versus 34·0 (20·0-54·0)), number of extra-pulmonary infections (1·0 (0·0-2·0) versus 1·0 (0·0-2·0)) and similar proportion of MDR pathogens acquisition during ICU stay (24·7% versus 20·2%) (Table 3). As expected, the median exposure to antibiotics was higher in the 15-day group compared to the 8-day group, respectively 23·0 days (15·0-34·0) versus 18.0 days (11·5-28·5), difference -5·0% (95% CI -9·0% to 0·0%).

Discussion

In this prospective randomized controlled trial, we showed no difference between a short duration strategy (8 days) compared to a long duration strategy (15 days) for the composite endpoint of mortality and PA-VAP recurrence occurring during hospitalization in the ICU within 90 days in adult patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia (PA-VAP). However, the patients in the 8-day group were twice as likely to have a PA-VAP recurrence as those in the 15-day group. Furthermore, the Fine and Gray model show a higher risk of PA-VAP recurrence considering the competing risk of death in 8-day group versus 15-day group. While patients in the 8-day group were indeed less exposed to antibiotics during the ICU stay, we did not find more multidrug-resistant pathogen acquisition in the 15-day group.

Although antibiotic duration for the treatment of VAP remains a challenge, only few randomized controlled trials have addressed this issue. Two studies compared 8 vs. 15 days of antibiotic durations[5,13], two others compared 7 vs. 10 days[14,15] and one study compared 8 vs.

12 days[16]. Two published systematic reviews found no difference between short and long durations of antibiotic therapy with regard to day-28 mortality[6], duration of mechanical ventilation or length of ICU stay[6,17]. However, in the subset of patients with non-fermenting Gram-negative bacteria, there was a trend toward lower recurrence for the long duration arms. In the study conducted by Capellier et al.[13], focusing on early-onset VAP, the rate of secondary infection was higher in the 8-day group than the 15-day group. In the PneumA study, patients with VAP caused by NF-GNB treated for 8 days had a higher recurrence-infection rate (40·6% versus 25·4%). Finally, among 274 patients with late-onset VAP, a randomized controlled trial shown that a 7-day course was found to have non-significant higher rates of clinical failure and 28-day mortality compared to a fixed 10-day course[15]. In our trial, the percentage of patients who died or had a recurrence of PA-VAP was 35.2 % in the 7-day group (ITT population), close that the mortality and/or recurrence of PA-VAP rate of 35.7 % observed by Planquette et al. in a retrospective study of 393 PA-VAP[11] in which the median antibiotic duration in survivors was 9 days (IQR, 6–12).

Despite a higher recurrence rate, the short duration strategy was not associated with an increased mortality, a longer duration of mechanical ventilation or length of ICU stay in our study. Thus, more research seems needed before any definitive conclusions about the best duration of antibiotic therapy for VAP due to non-fermenting GNB can be drawn. A duration of 8 days of treatment cannot be ruled out but our findings invite to a prudent approach based on a close clinical and biological monitoring, although this was not tested in our study. Biomarkers could be assessed to monitor specifically the duration of treatment in this setting.

To our knowledge, this study is the first randomized controlled trial specifically focused on PA-VAP. In our trial, the expected incidences of components of primary outcome were correctly estimated: the percentage of patients who died or had a recurrence of PA-VAP was

27·5% in the 15-day group and 40·3% in the 8-day group. These proportions are in agreement with results of available studies[17]. Protocol of planned antibiotic durations has been fully respected with median duration of 15 days and 8 days in 15-day and 8-day groups, respectively, and as expected. Compliance with the planned duration of antibiotic therapy was acceptable (around 80%) (See Supplemental Table 2).

The main limitation is that the study ultimately included only 33% of the patients initially planned despite the participation of 30 centres throughout France, including medical, surgical and general intensive care units in university and non-university hospitals. Indeed, because of the late-onset of PA-VAP during the ICU stay, many patients were already included in other interventional studies and as such could not be included in our trial. A *post hoc* sensitivity Bayesian analysis suggests that the probability of non-inferiority was close to 55% in the ITT population and 40% in the PP population (Supplementary File 2).

In conclusion, in this trial of patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia, we showed no difference for mortality and PA-VAP recurrence between 8 days and 15 days durations of antibiotic therapy. However, the lack of power limits the interpretation of our study.

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Declaration of interests

Declaration of interests
The authors declare no conflict of interests.

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TABLES

Table 1. Baseline Characteristics of the Intention-to-Treat Population.

	15-DAY GROUP (N=98)	8-DAY GROUP (N=88)
Demographic characteristics		
Age – yr, m±sd	59.2 ± 18.3	59.6 ± 16.4
Male sex – no (%)	71 (72.4)	70 (79.5)
Body mass index[1], m±sd	27.3 ± 6.3	26.5 ± 6.1
Medical history		
Hypertension – no (%)	31 (31.6)	16 (18.2)
Diabetes – no (%)	10 (10.2)	8 (9.1)
Heart failure – no (%)	17 (17.3)	8 (9.1)
Main diagnosis at admission – no (%)		
Sepsis	13 (13.3)	10 (11.4)
Neurologic impairment	10 (10.2)	2 (2.3)
Hemodynamic failure	20 (20.4)	21 (23.9)
Trauma	19 (19.4)	16 (18.2)
Acute Respiratory Failure	22 (22.4)	13 (14.8)
Acute Kidney Injury	0 (0)	1 (1.1)
Hemorrhagic shock	3 (3.1)	4 (4.5)
Metabolic impairment	0 (0)	2 (2.3)
Burn	3 (3.1)	0 (0)
Postoperative	7 (7.1)	16 (18.2)
Other	1 (1.0)	3 (3.4)
Reason for ICU admission – no (%)		
Medical	42 (42.9)	32 (36.4)
Urgent surgery	37 (37.8)	29 (33.0)
Elective surgery	19 (19.4)	27 (30.7)
Duration of ventilation before inclusion, days, median (IQR)	14.0 (9.0-18.0)	11.0 (7.5-18.5)
SOFA score at inclusion, m±sd	7.8 ± 3.7	7.1 ± 4.1
SAPS2, m±sd	45.9 ± 17.7	44.2 ± 16.6
Patients needing catecholamines at inclusion – no (%)	58 (59.2)	48 (54.5)
PaO_2:FiO_2 ratio at inclusion, median (IQR) [2]	227 (130-340)	250 (158-377)

[1] Data are available for 91 in "15-day" group and 86 patients in "8-day" group
[2] Data available: n=87 in "15-day" group, n=79 in "8-day" group

Table 2. Primary Outcome and its components, According to Study Group.

OUTCOME OR EVENT	15-DAY GROUP (N=98)	8-DAY GROUP (N=88)	DIFFERENCE (90% CI)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in ITT population – no. (%)	25/98 (25.5)	31/88 (35.2)	9.7% (0.0% to 21.2%)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in PP population – no. (%)	22/80 (27.5)	29/72 (40.3)	12.8% (0.0% to 25.6%)
PA-VAP recurrence rate during hospitalization in the ICU in ITT population — no. (%)	9/98 (9.2)	15/88 (17.0)	7.9% (0.0% to 16.8%)

PA-VAP denotes *Pseudomonas aeruginosa* ventilator-associated pneumonia, ICU denotes Intensive Care Unit, PP denotes per protocol, ITT denotes Intention-to-Treat.

Table 3. Secondary Outcomes, According to Study Group.

OUTCOME OR EVENT	15-DAY GROUP (N=98)	8-DAY GROUP (N=88)	DIFFERENCE (95% CI)
Duration of mechanical ventilation, days[1]	25.0 (15.5-35.0)	22.0 (12.0-41.0)	-3.0 (-9.0 to 5.0)
Duration of ICU stay, days	34.0 (23.0-56.0)	34.0 (20.0-54.0)	0.0 (-7.0 to 6.0)
Exposure to antibiotics during ICU stay, days	23.0 (15.0-34.0)	18.0 (11.5-28.5)	-5.0 (-9.0 to 0.0)
Number of extra pulmonary infections during ICU stay [1]	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.0 (-1.0 to 1.0)
Acquisition of MDR pathogens during ICU stay — no. (%)	24/97 (24.7)	17/84 (20.2)	-4.5% (-16.8% to 8.3%)

Data are no. (%) or median (IQR)

[1] Data available: n=96 in “15-day” group, n=84 in “8-day” group

FIGURES LEGENDS

Figure 1: Study flow chart.

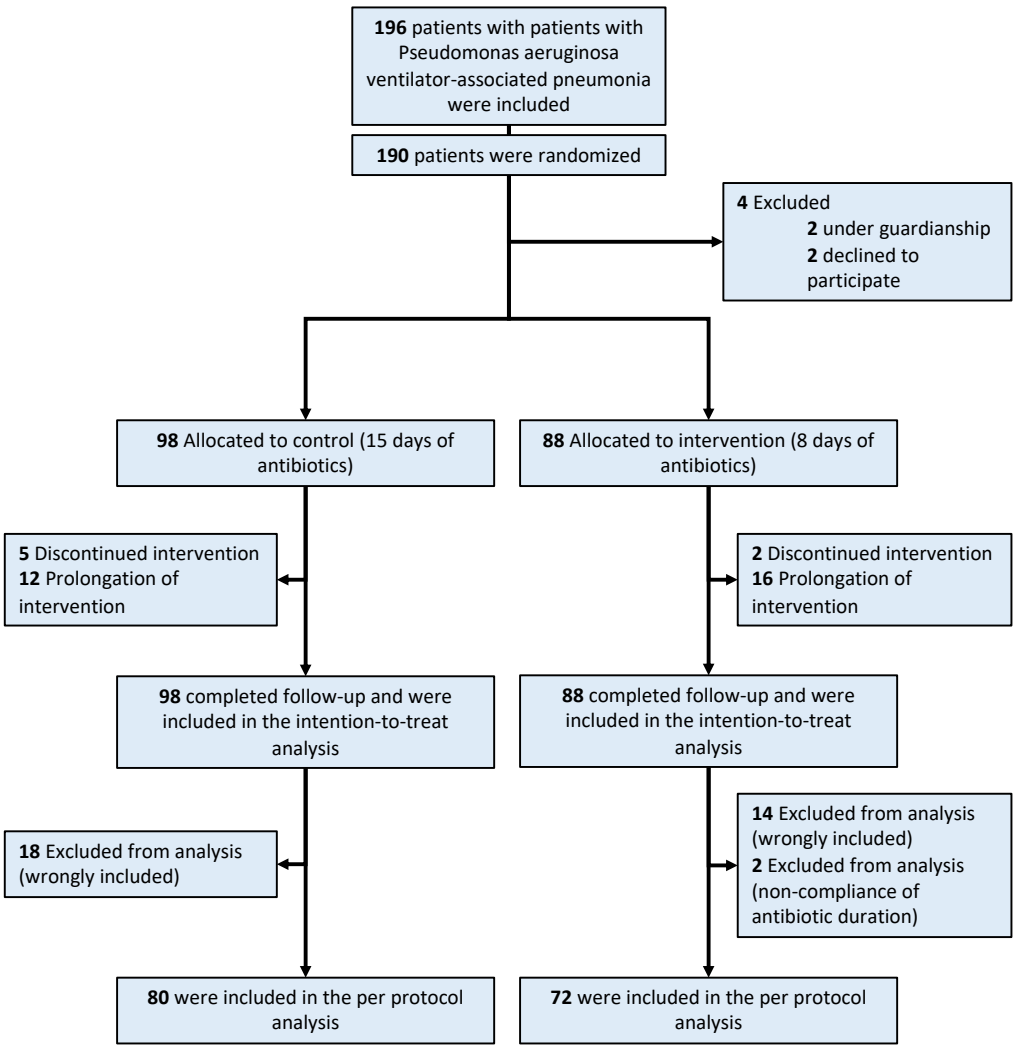
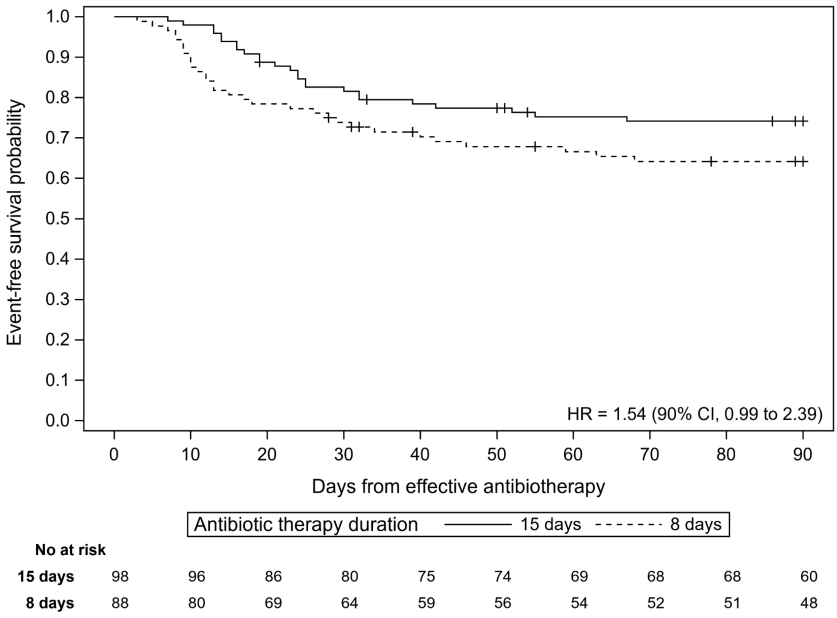
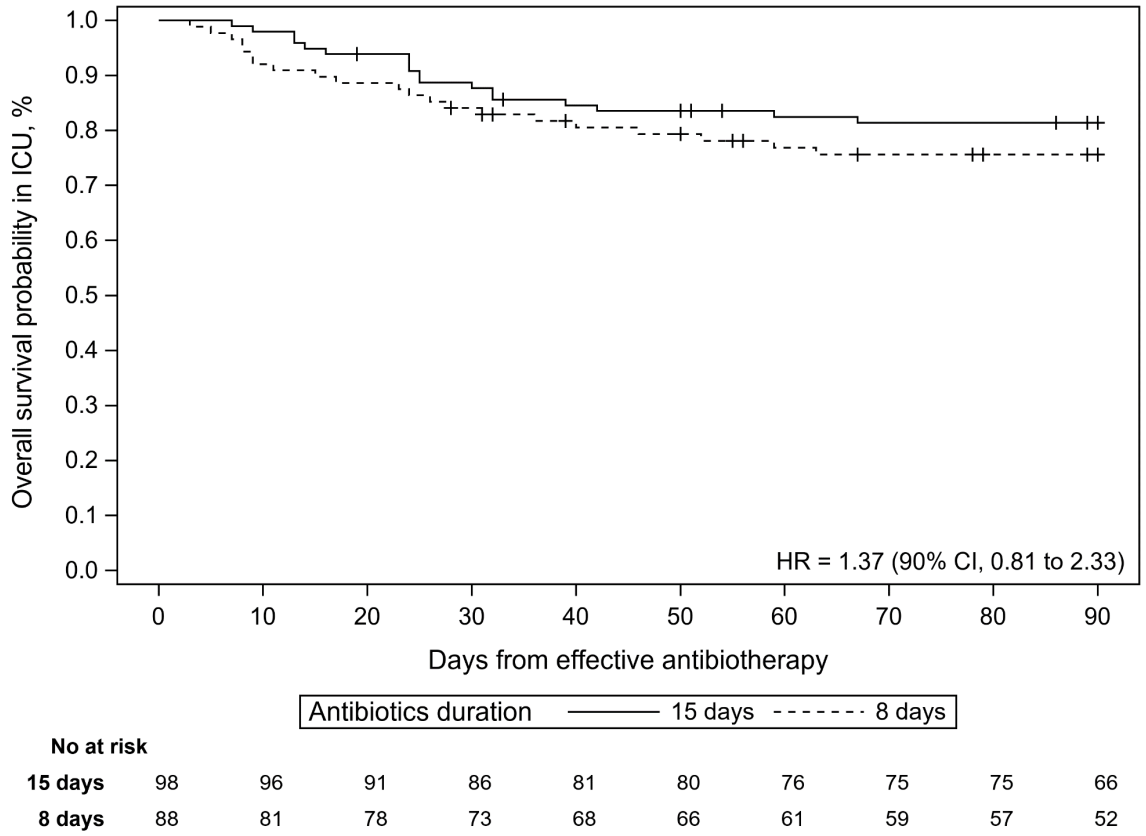


Figure 2: Event-free survival curves of the survival probability for VAP recurrence or death in ICU (Kaplan-Meier estimates) in the ITT population. Survival probability is for the 90 days since the start of effective antibiotic therapy as a function of the duration of antibiotic therapy.



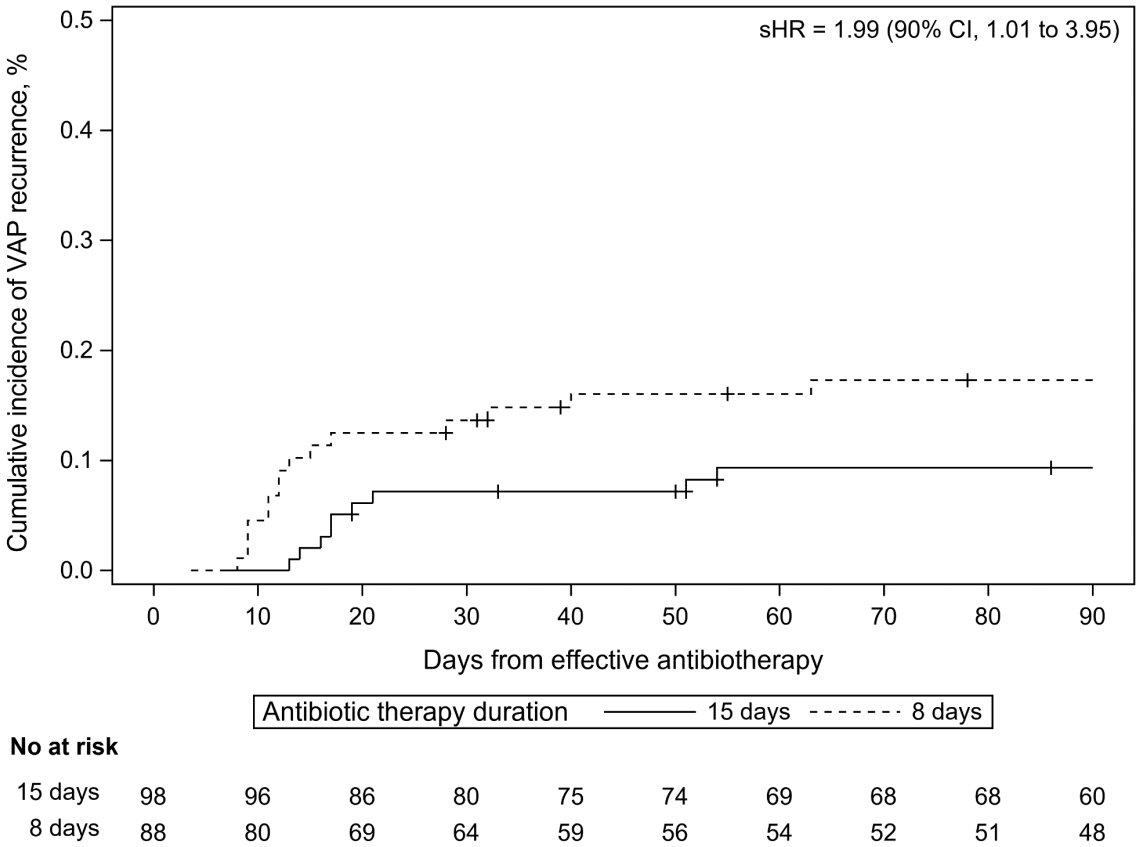
Supplementary Figure 1: Overall survival curves in ICU (Kaplan-Meier estimates) in the ITT population. Survival probability is for the 90 days since the start of effective antibiotic therapy as a function of the duration of antibiotic therapy.



No at risk										
15 days	98	96	91	86	81	80	76	75	75	66
8 days	88	81	78	73	68	66	61	59	57	52

Supplementary Figure 2: Cumulative incidence curves for recurrence of VAP in the ITT population.

Cumulative incidence of recurrence of VAP is for the 90 days since the start of effective antibiotic therapy by group (Fine and Gray method). Cumulative incidence of VAP recurrence is for the 90 days since the start of effective antibiotic therapy as a function of the duration of antibiotic therapy.



SUPPLEMENTARY FILE 1

CAUSES OF WRONGLY INCLUSION

32 patients did not meet the eligibility criteria and were wrongly included, 18 in the 15-days group and 14 in the 8-days group:

- 13 patients had been ventilated for less than 48 hours,
- 6 patients finally had no *Pseudomonas aeruginosa* VAP,
- 5 patients had been included in another interventional study,
- 2 patients had been ventilated for less than 48 hours and finally had no *Pseudomonas aeruginosa* VAP,
- 2 patients had been ventilated for less than 48 hours and had been included in another interventional study,
- 1 patient had been ventilated for less than 48 hours and was chronically colonized with *Pseudomonas aeruginosa,*
- 1 patient had been ventilated for less than 48 hours and was immunosuppressed,
- 1 patient had been ventilated for less than 48 hours, had been included in another interventional study and received an antibiotic therapy active on *Pseudomonas aeruginosa* for extra-pulmonary infection,
- 1 patient finally had no *Pseudomonas aeruginosa* VAP and had been included in another interventional study.

SUPPLEMENTARY FILE 2

Bayesian sensitivity post hoc analysis

The analysis is performed adopting a beta-binomial model (Berry D A. Statistics, 1996). The Bayesian approach is to consider the event rate as a random variable with prior density centered on the expected event rate.

Two identical beta densities are chosen, one for each arm, defined by two parameters a and b considering the sample size computation hypotheses (mean rate of 35.7%). The *a priori* expected mean of each density is $\mu = \frac{a}{a+b}$, with a variance given by $\text{Var} = \frac{ab}{(a+b)^2(a+b+1)}$. The Effective Sample Size (ESS – Morita et al. 2008), a tool that quantify the prior information in terms of equivalent number of patients, for a beta distribution is computed as $a + b$. For the sensitivity analysis, several ESS values will be tested; this analysis will allow giving more or less weight on observations relative to the initial *a priori* on the event rate (more the ESS is small, more the weight of observations increases and the variance of prior increases).

The Bayesian estimator of the event rate is the expected value of the *a posteriori* distribution, whose parameters are defined after n inclusions by $a_n = a + r$ and $b_n = b + n - r$, in each arm, where r is the number of events observed on n inclusions. So, we obtain the following expected value:

$$\tilde{\mu}_i = \frac{a_i + r_i}{a_i + b_i + n_i}, \qquad i = 0,1$$

where i represent the arm indicator, with 0 referring to the control arm.

The difference between the event rates in both arms of randomization is modeled by the random variable $\Delta = \tilde{\mu}_1 - \tilde{\mu}_0$. We study the random variable Δ, i.e. its distribution

(computed via MCMC technique), credibility intervals (90% CrI, equal tails), and the probability of non-inferiority, computed as $P(\Delta < 0.1)$.
The Bayesian statistical analysis was performed by Dr Moreno Ursino on R version 4.1.1 (2021-08-10) -- "Kick Things", Copyright (C) 2021 The R Foundation for Statistical Computing, Platform: x86_64-apple-darwin17.0 (64-bit).

Results

ITT population

ESS for each arm	**15-day group** $\tilde{\mu}_0$ (90% CrI)	**8-day group** $\tilde{\mu}_1$ (90% CrI)	**Difference** Δ (90% CrI)	$\boldsymbol{P(\Delta < 0.1)}$
10 a = 3.57, b = 6.43	0.265 (0.198,0.336)	0.353 (0.275,0.433)	0.088 (-0.017,0.193)	0.577
5 a = 1.785, b = 3.215	0.260 (0.192,0.333)	0.353 (0.273,0.435)	0.092 (-0.015,0.200)	0.548

PP population

ESS for each arm	**15-day group** $\tilde{\mu}_0$ (95% CrI)	**8-day group** $\tilde{\mu}_1$ (95% CrI)	**Difference** Δ (95% CrI)	$\boldsymbol{P(\Delta < 0.1)}$
10 a = 3.57, b = 6.43	0.284 (0.209,0.365)	0.397 (0.310,0.487)	0.113 (-0.005,0.229)	0.428
5 a = 1.785, b = 3.215	0.280 (0.203,0.362)	0.400 (0.310,0.493)	0.120 (-0.001,0.240)	0.394

References:
Berry D A. Statistics: a Bayesian perspective. Duxbury, Belmont Californie 1996.
Morita S, Thall PF, Müller P. Determining the effective sample size of a parametric prior. Biometrics. 2008 Jun;64(2):595-602. doi: 10.1111/j.1541-0420.2007.00888.x.

SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1. CHARACTERISTICS OF ANTIBIOTIC THERAPY, ACCORDING TO STUDY GROUP

CHARACTERISTIC	15 DAYS OF ANTIBIOTIC THERAPY (N=98)	8 DAYS OF ANTIBIOTIC THERAPY (N=88)
DURATION OF ANTIBIOTIC THERAPY- DAYS, MEDIAN (IQR)	**15.0 (14.0-16.0)**	**8.0 (8.0-8.5)**
COMPLIANCE WITH THE PLANNED DURATION OF ANTIBIOTIC THERAPY, N (%)		
YES	**81 (82.7)**	**70 (79.5)**
NO	**17 (17.3)**	**18 (20.5)**
TYPE OF NON-COMPLIANCE WITH THE PLANNED DURATION OF ANTIBIOTIC THERAPY, N (%)		
PREMATURE DISCONTINUATION OF THE ANTIBIOTIC THERAPY	**5/17 (29.4)**	**2/18 (11.1)**
PROLONGATION THE ANTIBIOTIC THERAPY	**12/17 (70.6)**	**16/18 (88.9)**
REASON FOR PREMATURE DISCONTINUATION OF THE ANTIBIOTIC THERAPY, N(%)		
CLINICAL CURE OF PA-VAP	**3/5**	**0/2**
DEATH	**2/5**	**2/2**
REASON FOR PROLONGATION OF THE ANTIBIOTIC THERAPY, N (%)		
PA-VAP PERSISTENCE	**5/17 (41.7)**	**7/18 (43.8)**
SUPERINFECTION	**3/17 (25.0)**	**0/18 (0)**
EXTRAPULMONARY INFECTION	**2/17 (16.7)**	**4/18 (25.0)**
PATIENT'S SEVERITY	**2/17 (16.7)**	**1/18 (6.3)**
OTHER REASON	**0/17 (0)**	**4/18 (25.0)**

SUPPLEMENTARY TABLE 2. ANTIMICROBIALS USED IN THE PRESCRIBED EMPIRICAL THERAPY, EFFECTIVE EMPIRICAL THERAPY, AND DEFINITIVE REGIMENS, ACCORDING TO STUDY GROUP

VARIABLE	INTENTION-TO-TREAT POPULATION N=186	15 DAYS OF ANTIBIOTIC THERAPY N=98	8 DAYS OF ANTIBIOTIC THERAPY N=88
	N (%)		
	N*	N*	N*
EMPIRICAL ANTIMICROBIAL THERAPY	183	96	87
AMOXICILLIN	1 (0.5)	0 (0)	1 (1.1)
AMOXICILLIN + CLAVULANATE	7 (3.8)	3 (3.1)	4 (4.6)
CEFOTAXIME	7 (3.8)	3 (3.1)	4 (4.6)
PIPERACILLIN	12 (6.6)	6 (6.3)	6 (6.9)
PIPERACILLIN + TAZOBACTAM	67 (36.6)	38 (39.6)	29 (33.3)
CEFEPIME	30 (16.4)	13 (13.5)	17 (19.5)
CEFTAZIDIME	31 (16.9)	18 (18.8)	13 (14.9)
IMIPENEM	14 (7.7)	7 (7.3)	7 (8.0)
MEROPENEM	11 (6.0)	5 (5.2)	6 (6.9)
CEFTOLOZANE + TAZOBACTAM	1 (0.5)	1 (1.0)	0 (0)
CIPROFLOXACINE	1 (0.5)	1 (1.0)	0 (0)
AZTREONAM	1 (0.5)	1 (1.0)	0 (0)
COMPANION MOLECULE	183	96	87
AMINOGLYCOSIDE	118 (64.5)	59 (61.5)	59 (67.8)
FLUOROQUINOLONE	11 (6.0)	8 (8.3)	3 (3.4)
AMINOSIDE + FLUOROQUINOLONE	1 (0.5)	1 (1.0)	0 (0)
NO	53 (29.0)	28 (29.2)	25 (28.7)
EFFECTIVE EMPIRICAL ANTIMICROBIAL THERAPY	161	86	75
PIPERACILLIN	12 (7.5)	6 (7.0)	6 (8.0)
PIPERACILLIN + TAZOBACTAM	64 (39.8)	36 (41.9)	28 (37.3)
CEFEPIME	29 (18.0)	13 (15.1)	16 (21.3)
CEFTAZIDIME	29 (18.0)	16 (18.6)	13 (17.3)
IMIPENEM	13 (8.1)	7 (8.1)	6 (8.0)
MEROPENEM	10 (6.2)	4 (4.7)	6 (8.0)
CEFTOLOZANE + TAZOBACTAM	1 (0.6)	1 (1.2)	0 (0)
CIPROFLOXACINE	2 (1.2)	2 (2.3)	0 (0)
AZTREONAM	1 (0.6)	1 (1.2)	0 (0)
DEFINITIVE ANTIMICROBIAL THERAPY	186	98	88
PIPERACILLIN	49 (26.3)	28 (28.6)	21 (23.9)
PIPERACILLIN + TAZOBACTAM	38 (20.4)	20 (20.4)	18 (20.5)
CEFEPIME	17 (9.1)	8 (8.2)	9 (10.2)
CEFTAZIDIME	50 (26.9)	24 (24.5)	26 (29.5)
IMIPENEM	11 (5.9)	4 (4.1)	7 (8.0)
MEROPENEM	7 (3.8)	5 (5.1)	2 (2.3)
CEFTOLOZANE TAZOBACTAM	3 (1.6)	2 (2.0)	1 (1.1)
CEFTAZIDIME AVIBACTAM	1 (0.5)	1 (1.0)	0 (0)
CIPROFLOXACINE	9 (4.8)	5 (5.1)	4 (4.5)
COLISTIN	1 (0.5)	1 (1.0)	0 (0)

SUPPLEMENTARY TABLE 3. IDIAPASON TRIAL INVESTIGATORS.

INVESTIGATORS	CENTERS
Dr. Adrien Bouglé	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Pr. Julien Amour	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Dr. Thomas Dessalle	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Dr. Florence Bellenfant Zegdi	Hôpital Européen Georges Pompidou, APHP, Paris
Pr. Bernard Cholley Dr. Julien Massot	Hôpital Européen Georges Pompidou, APHP, Paris
Pr. Jean-Michel Constantin	CHU Clermont-Ferrand, Clermont-Ferrand
Pr. Alexandre Demoule Dr. Julien Mayaux	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Dr. Vincent Dubée	Hôpital Saint-Antoine, APHP, Paris
Pr. Hervé Dupont	CHU Amiens, Amiens
Pr. Jacques Duranteau	Hôpital Bicêtre, APHP, Paris
Dr. Laura Federici	Centre Hospitalier Sud Francilien, Corbeil
Dr. Arnaud Foucrier	Hôpital Beaujon, APHP, Paris
Pr. Thomas Geeraerts	CHU Toulouse, Toulouse
Dr. Céline Guichon	Hôpital Croix Rousse, CHU Lyon, Lyon
Dr. Pierre Kalfon	Hôpital Louis Pasteur, CH de Chartres, Chartres
Dr. Éric Kipnis	CHRU Lille, Lille
Pr. Sigismond Lasocki	CHU Angers, Angers
Pr. Jean-Yves Lefrant	CHU Nîmes, Nîmes
Dr. Matthieu Legrand	Groupe Hospitalier Lariboisière – Saint Louis, APHP, Paris
Pr. Marc Leone	CHU Hôpital Nord, APHM, Marseille
Pr. Thomas Lescot	Hôpital Saint-Antoine, APHP, Paris
Pr. Bruno Lévy	CHU Nancy Brabois, Nancy
Dr. Joël Cousson	CHU Reims, Reims
Pr. Philippe Montravers Dr. Sébastien Tanaka	Hôpital Bichat, APHP, Paris
Dr. Emmanuel Novy	CHU Nancy Brabois, Nancy
Pr. Alexandre Ouattara	CHU Bordeaux, Bordeaux
Pr. Jean-François Payen	CHU Grenoble, Grenoble
Dr. Walter Picard	Centre Hospitalier de Pau, Pau
Dr. Pascale Poète	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Dr. Julien Pottecher	Nouvel Hôpital Civil, CHRU Strasbourg, Strasbourg
Dr. Christophe Quesnel Pr. Muriel Fartoukh	Hôpital Tenon, APHP, Paris
Pr. Anoine Tesniere Dr. Mélanie Fromentin	Hôpital Cochin, APHP, Paris
Pr. Jean-Jacques Rouby Dr. Qin Lu Pr. Olivier Langeron	Hôpitaux Universitaires Pitié-Salpêtrière, APHP, Paris
Dr. Pierre Squara	Clinique Ambroise Paré, Neuilly-sur-Seine
Dr. Eric Levesque	Hôpital Henri Mondor, APHP, Créteil
Dr. Nicolas Mongardon	Hôpital Henri Mondor, APHP, Créteil
Methodology and biostatistics team	
Pr. Tabassome Simon	Unité de Recherche Clinique du GH HUEP (URC-Est), Hôpital Saint-Antoine, APHP, Paris
Dr. Laurence Berard	
Marine Cachanado	
Nora Soussi	