Statistical Analysis Plan

HAP-DEX

Protocol RC23_0358

RC23_0358

Dexamethasone for treating severe hospital-acquired pneumonia in critically ill patients with a pro-inflammatory phenotype, an international phase III, double-blind, placebo-controlled, randomized trial - the HAP-DEX study

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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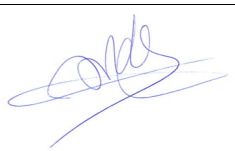
VERSION HISTORY AND SIGNATURE PAGE

Table [xx] – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	28/02/2024	Not Applicable	Initial release

SAP Version	DATE	NAME	FUNCTION	SIGNATURE
1	28/02/2024	Marie-Anne VIBET	Statistician	
1	1 March 2024	Pr Antoine Roquilly	Coordinating investigator	

1. INTRODUCTION

1.1. Objectives and [Endpoints and/or Estimands]

Objectives	Endpoints
Primary	
• To determine the efficacy of dexamethasone plus standard of care (SOC) as compared to placebo plus SOC for the treatment of severe hospital-acquired pneumonia in patients with a pro-inflammatory profile.	**Co-primary endpoints** • Clinical cure at the test-of-cure (TOC) visit • all-cause mortality at Day 28
Secondary	
• To demonstrate the **efficacy** of dexamethasone on pneumonia-associated morbidity and mortality reduction	• In case of a non-significant difference in the rate of clinical cure, the co-primary outcome (all-cause mortality at Day 28) will be presented as a secondary outcome. • All-cause mortality at Month 3 and Month 6 • Rate of pleural empyema at Day 28. • Rate of microbiological failure (defined as a positive respiratory culture at the ToC visit). • Rate of pneumonia relapse (defined as a second episode of HAP with one or more identical pathogens), rate of pneumonia recurrence (defined as a second episode of HAP with different pathogens) at Day 28. • Time course of body temperature, cardiac pulse rate, oxygen saturation, PaO2/FiO2, type of mechanical ventilation support (invasive, noninvasive, none) (daily evaluation at 8.00 am and 8.00 pm), and leukocyte counts (every 48 hours) for 10 days. • Rates of non-respiratory hospital-acquired infection at day 28: urinary tract infection, surgical site infection, invasive candidiasis, septicemia. • Antibiotic-free days at Day 28 (the number of antibiotic-free days is defined as the number of days between Day 1 and Day 28 for which living patients do not receive antibiotics. Dead patients will be ascribed 0 antibiotic-free days). • Duration of invasive mechanical ventilation and invasive mechanical ventilation-free days at Month 6 (defined as the number of days between Day 1 and Month 6 for which living patients breathe spontaneously. Dead patients will be ascribed 0 mechanical ventilation-free days).

Objectives	Endpoints
	• Duration of hospitalization and hospital-free days at Month 6 (the number of hospital-free days is defined as the number of days between Day 1 and Month 6 for which living patients are outside of a hospital. Dead patients will be ascribed 0 hospital-free days).
• To describe the safety of dexamethasone	• Rate of serious adverse reactions and suspected unexpected serious adverse reaction (SUSAR) at Day 28. • Rate of metabolic adverse events during the 5-7-day treatment period and at day 28. • Rate of gastric ulcer.
• To assess the economic efficiency of dexamethasone plus SOC compared to SOC.	• Economic endpoints at 6 months: Incremental cost-effectiveness ratio (ICER).
• To assess the suitability and acceptability of dexamethasone from the patients' perspectives.	• Changes in health-related quality of life (HRQoL) from three (M3) to six months (M6) after randomization measured with the Short Form (SF)-36 scale validated in French. • Changes in anxiety and depression from M3 to M6 were measured with the HADS scale validated in French. • Changes in subjective well-being from M3 to M6 measured with the Satisfaction With • Life Scale (SWLS) validated in French.
Exploratory	
• To develop biomarkers for the stratification of patients into responders and non-responders to dexamethasone.	• Value of biological prognostic factors (at screening), such as: ○
• To create a biobank of blood and respiratory samples collected from humans with hospital-acquired pneumonia.	

1.2. Study Design

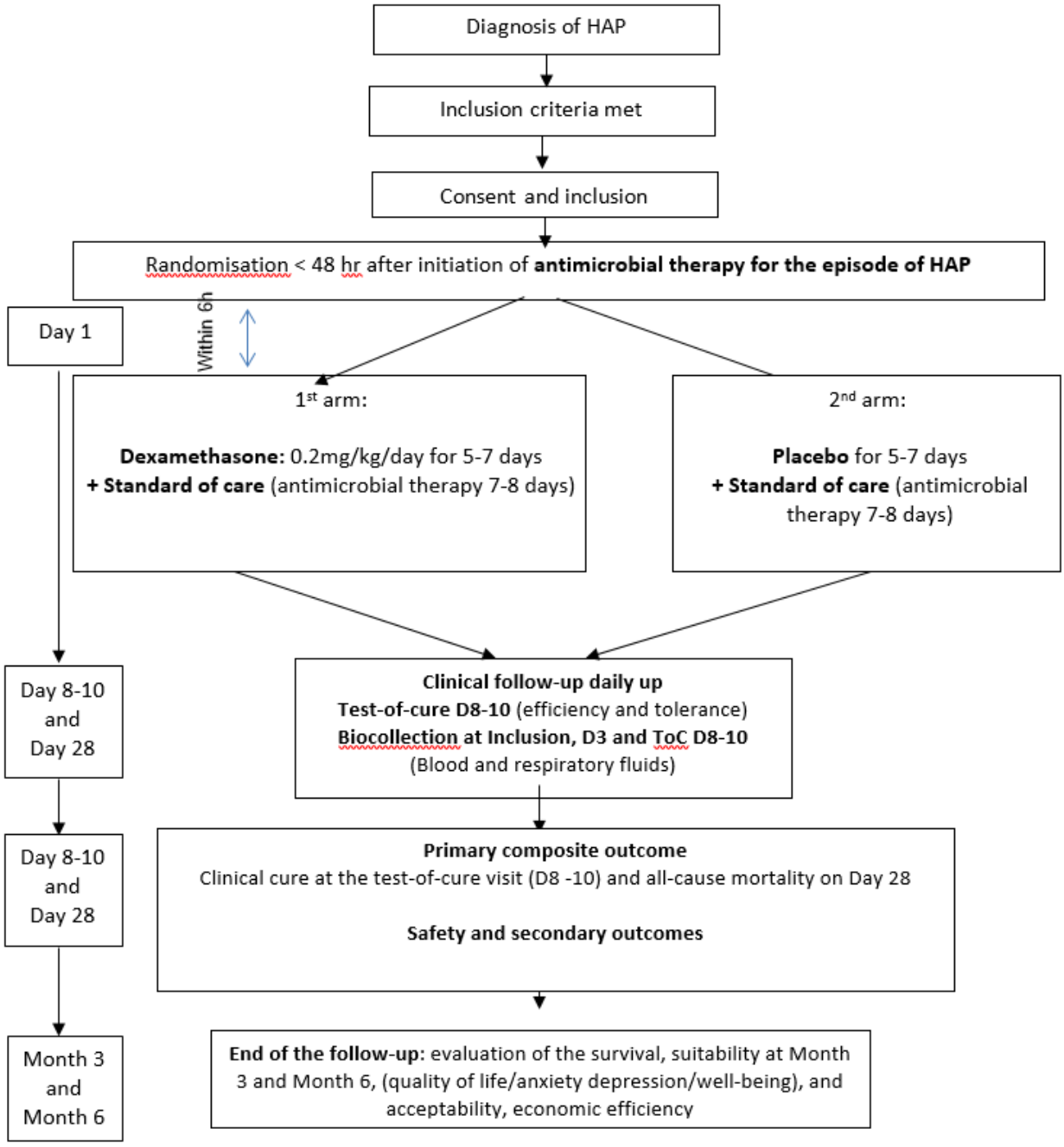


Figure 1: Study diagram

2. STATISTICAL HYPOTHESES

The objective of this trial is to determine the efficacy of dexamethasone (0.2 mg/kg/day) plus standard of care (SOC) as compared to placebo plus SOC for the treatment of severe hospital-acquired pneumonia in patients with a pro-inflammatory profile.

The co-primary hierarchic endpoints to demonstrate the efficacy of dexamethasone plus SOC compared to placebo plus SOC for the treatment of hospital-acquired pneumonia will be a clinical cure at the test-of-cure (TOC) visit and all-cause mortality at Day 28.

The null hypothesis is that there is no difference between investigated groups in terms of clinical cure at the TOC visit and in terms of all-cause mortality at day 28.

3. SAMPLE SIZE DETERMINATION

The maximum sample size is calculated in a frequentist framework as described below. However, the accrual will be re-evaluated using Bayesian interim monitorings for futility and efficacy.

The clinical cure rates ranged from 60% to 70%, and all-cause mortality rates reached 30% in recent studies including critically ill patients with HAP. The RR of death with steroids for ARDS and COVID-19 was around 0.80 in recent meta-analyses (20% reduction of all cause of death at day 28). The minimal clinically significant differences in clinical cure and all-cause mortality were set to 12.5% in non-inferiority trials evaluating new antimicrobial therapy [49], and by EMA (EMA/844951/2018 Rev. 3).

Assuming a 65% rate of clinical cure in the control group and 77% in the dexamethasone group, we have calculated that a total of 444 patients (222 patients per group) was needed to detect this difference with a 5%-type I error and a power of 80% in a two-sided test.

Assuming a 30% rate of all-cause mortality in the control group, and 18% in the dexamethasone group, we have calculated that a total of 392 patients (196 patients per group) was needed to detect this difference of mortality with a 5% type-I error and a power of 80% in a two-sided test.

To consider the loss of follow-up, we will include **a total of 450 patients**, thus enabling the hierarchical comparison of the two primary outcomes with an 80%-power and a 5% type-I error.

Given the adaptive design of the trial, the number of patients to include can be adapted to the study effects which are estimated during monitoring analysis (see paragraph 6.2.5, Potential decision 2 of Scientific Steering Committee). We aimed to define a range of study population size potential values that could enable us to conclude a significant effect of dexamethasone with an 80%-power. The values range was estimated using a simulation process, in a frequentist framework. We performed 200 simulations and evaluated each sample size from 200 to 400.

Binomial data were simulated for each treatment arm (p = 0.65 in the placebo group, and 0.77 in the dexamethasone group). Then a logistic regression was used to estimate the effect of dexamethasone versus placebo. The p-value was then stocked, and the power was given by the proportion of simulations that found a statistically significant effect of dexamethasone. We concluded that the expected study population size ranges from 225 to 250 patients/group.

Results of the simulation process – Potential values of the study population size.

Sample size / group	**150**	**175**	**200**	**225**	**250**	**275**	**300**
Statistical power	0.66	0.69	0.75	0.81	0.84	0.87	0.891

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The primary population analysis will be population ***as randomized*** defined as all randomized patients in the group in which they were randomized, regardless of the treatment received and breaches of the protocol.

A secondary population analysis will be conducted on full analysis set (FAS) (for the primary and secondary outcomes).

FAS: All randomized patients in the group in which they were randomized, regardless of the treatment received and breaches of the protocol. Subjects will be excluded from FAS if the following circumstances arises:

- the failure to satisfy major entry criteria, such as legal requirements (signed consent, legal age, …)
- the failure to take at least one dose of trial medication.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Visit Windows

Unless otherwise specified, data to be analyzed or listed over time will be presented by day and time point (as appropriate) that are recorded in the electronic case report form (eCRF).

5.1.2. Study Day and Relative Day

Study Day 1 refers to the start of the first dose of study treatment administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Study Day 1
- Visit date - date of Day 1, if visit date < date of Day 1

There is no 'Day 0'.

The randomization process might be done on Day 1 or the day before. However, the allocated treatment should be administered at most 6 hours after randomization.

Screening refers to the period between the start of HAP or admission in ICU for HAP and Day 1.

TOC visit: test-of-cure visit done at 8 to 10 days after randomization

5.1.3. Baseline

Baseline measurement is defined as the last non-missing measurement prior to the start of the first study intervention administration.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized

- Participants who received study intervention
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the study period.

The distribution of the time to discontinuation of study intervention will be displayed with Kaplan-Meier curves. Participants who discontinue study intervention at any time will be considered an 'Event' and their date of study intervention discontinuation will be used in the time to event calculation. Participants who complete study intervention will be censored and the date of last dose of study intervention will serve as the time of censoring.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The **co-primary hierarchic endpoints** to demonstrate the efficacy of dexamethasone plus SOC compared to placebo plus SOC for the treatment of hospital-acquired pneumonia will be a clinical cure at the test-of-cure (TOC) visit and all-cause mortality at Day 28.

We will use a **hierarchic procedure**. First, we will test the dexamethasone superiority on the clinical cure rate at the test-of-cure visit realized 8 days (acceptable time frame Day 8-10) after randomization or at the ICU discharge (if it occurs before). Second, if the superiority criterion is met at the test-of-cure visit, we will test the dexamethasone superiority on the rate of all-cause mortality on Day 28.

We have selected these two co-primary outcomes because the European Medicines Agency has recommended clinical cure at the test-of-cure as the primary outcome in studies testing the treatment of bacterial infection (EMA/844951/2018 Rev. 3), while the Federal Drug Agency has recommended all-cause mortality on Day 28.

At the ToC visit, the clinical outcome will be categorized as cure or failure according to the following definitions (EMA/844951/2018 Rev. 3):

Definition of clinical cure:

i) complete resolution of clinical signs and symptoms and/or

ii) sufficient improvement or return to baseline status ("pre-infection status") such that no further antibacterial therapy is required for the index infection (HAP).

Definition of Clinical treatment failure:

- i) Death before Day 10,
- or ii) no apparent response,
- or iii) incomplete response: persistence or progression of most or all the pre-therapy signs and symptoms such as antibacterial therapy is still required for the index infection (HAP).

Even if this a double-blind, placebo-controlled, randomized trial, **the primary outcome will be blindly adjudicated by a committee** composed of intensivists not involved in patient recruitment (list of the members in Appendix 7).

The **Adjudication Committee** will blindly review the eCRF and adjudicate clinical outcomes at the ToC visit. Guidelines will be provided to the members by the sponsor. The primary endpoint will be based on the review of the clinical cure by two independent members of the Adjudication Committee who will be kept blinded about the treatment allocation. *In case of disagreement between the two Adjudication Committee members, the arbitrage will be done by a third Adjudication Committee member.*

5.3.2. Estimand

Primary trial objective: to determine the efficacy of dexamethasone plus standard of care (SOC) as compared to placebo plus SOC for the treatment of severe hospital-acquired pneumonia in patients with a pro-inflammatory profile.

Primary Estimand 1

Scientific Question of Interest: What is the effect on clinical cure at the TOC visit of assigning participants to SOC + dexamethasone versus SOC + placebo, considering death before day 10 as a treatment failure?

- **Population**: all randomized patients with severe hospital-acquired pneumonia and with a pro-inflammatory profile.
- **Variable**: Clinical cure at the test-of-cure (TOC) visit
- **Study intervention**: dexamethasone plus standard of care (SOC) versus placebo plus SOC
- **Population-level summary**: proportion of patients in clinical cure at the TOC visit
- **Intercurrent-event and their corresponding strategies**:

Intercurrent Events before ToC visit	Strategy for Addressing Intercurrent Events
• **ICU discharge**	**Composite strategy:** Patients are considered as in clinical cure
• **Death**	**Composite strategy:**

	Patients are considered as not in clinical cure – *treatment failure*
• **Missing data** - Study data are not available for the evaluation of clinical cure - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing primary criterion will be imputed.
• **Study treatment dropouts** - No allocated treatment administration - Delay of the first administration not respected (> 6 hours from randomization) - Administration of allocated treatment stopped for toxicity adverse events	**Treatment Policy strategy:** The value for the clinical cure is used regardless of whether the intercurrent event occurs.
• **Concomitant or additional treatments** - A non-respiratory infection which required antimicrobial therapy before the TOC visit. - Any steroids administration as rescue therapy before day 10 - Unauthorized treatments (cf. 3.4.2)	**Treatment Policy strategy:** The value for the clinical cure is used regardless of whether the intercurrent event occurs.

Sensitivity estimand: hypothetical strategy

Estimand 2 Scientific Question of Interest: What is the effect on clinical cure at the TOC visit of assigning participants to SOC + dexamethasone versus SOC + placebo in patients who did not have additional or concomitant therapy, and considering death before day 10 as a treatment failure?

- **Population**: all randomized patients with severe hospital-acquired pneumonia and with a pro-inflammatory profile.
- **Variable**: Clinical cure at the test-of-cure (TOC) visit
- **Study intervention**: dexamethasone plus standard of care (SOC) versus placebo plus SOC
- **Population-level summary**: proportion of patients in clinical cure at the TOC visit
- **Intercurrent-event and their corresponding strategies**:

Intercurrent Events before ToC visit	**Strategy for Addressing Intercurrent Events**
• **ICU discharge**	**Composite strategy:** Patients are considered as in clinical cure
• **Death** •	**Composite strategy:** Patients are considered as not in clinical cure – *treatment failure*
• **Missing data** - Study data are not available for the evaluation of clinical cure - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing primary criterion will be imputed.
• **Study treatment dropouts** - No allocated treatment administration	**Treatment Policy strategy:** The value for the clinical cure is used regardless of whether the intercurrent event occurs.

- Delay of the first administration not respected (> 6 hours from randomization) - Administration of allocated treatment stopped for toxicity adverse events	
• **Concomitant or additional treatments** - A non-respiratory infection which required antimicrobial therapy before the TOC visit. - Any steroids administration as rescue therapy before day 10 - Unauthorized treatments (cf. 3.4.2)	**Hypothetical strategy:** All data collected after administration of additional treatment will be erased and imputed under the hypothetical strategy where no patient had had an additional treatment. After concomitant or additional treatment, assume similar efficacy for participants who had an additional or concomitant treatment as those participants from the same intervention group who did not.

Co-Primary trial objective: to assess the efficacy of dexamethasone plus standard of care (SOC) as compared to placebo plus SOC for the treatment of severe hospital-acquired pneumonia in patients with a pro-inflammatory profile.

Primary Estimand 1

Scientific Question of Interest: What is the effect all-cause mortality on day 28 of assigning participants to SOC + dexamethasone versus SOC + placebo, considering death before day 10 as a treatment failure?

- **Population**: all randomized patients with severe hospital-acquired pneumonia and with a pro-inflammatory profile.
- **Variable**: all-cause mortality on Day 28
- **Study intervention**: dexamethasone plus standard of care (SOC) versus placebo plus SOC
- **Population-level summary**: all-cause mortality rate at D28
- **Intercurrent-event and their corresponding strategies**:

Intercurrent Events	Strategy for Addressing Intercurrent Events
• **Missing data** - Administrative censure (such as consent withdrawal or lost-to-follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. The missing primary criterion will be imputed.
• **Study treatment dropouts** - No allocated treatment administration - Delay of the first administration not respected (> 6 hours from randomization) - Administration of allocated treatment stopped for toxicity adverse events - Dexamethasone or any steroid administration as rescue therapy. - Medical decision of care withdrawal before day 28	**Treatment Policy strategy:** Mortality will be used regardless of whether or not the intercurrent event occurs.

Sensitivity estimand: hypothetical strategy

Co-Estimand 2 Scientific Question of Interest: What is the effect on clinical cure at the TOC visit of assigning participants to SOC + dexamethasone versus SOC + placebo in patients who did not have additional or concomitant therapy, and considering death before day 10 as a treatment failure?

- **Population**: all randomized patients with severe hospital-acquired pneumonia and with a pro-inflammatory profile.
- **Variable**: all-cause mortality on Day 28
- **Study intervention**: dexamethasone plus standard of care (SOC) versus placebo plus SOC
- **Population-level summary**: proportion of patients in clinical cure at the TOC visit
- **Intercurrent-event and their corresponding strategies**:

Intercurrent Events	Strategy for Addressing Intercurrent Events
• **Missing data** - Administrative censure (such as consent withdrawal or lost-to-follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. The missing primary criterion will be imputed.
• **Study treatment dropouts** - No allocated treatment administration - Delay of the first administration not respected (> 6 hours from randomization) - Administration of allocated treatment stopped for toxicity adverse events - Dexamethasone or any steroid administration as rescue therapy. - Medical decision of care withdrawal before day 28	**Hypothetical strategy:** All data collected after administration of additional treatment will be erased and imputed under the hypothetical strategy where no patient had had a study treatment dropouts

5.3.3. Analysis Methods

The co-primary outcome will be analyzed in the intention-to-treat population following a hierarchical process:

- Differences in **clinical cure rates** at the test-of-cure visit will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).
- Differences **in all-cause mortality rates** on Day 28 will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

The hierarchic process will be carried out as follows:

1. First, we will test the superiority of dexamethasone on the clinical cure rate at the test-of-cure visit realized 8-10 days after randomization. The model will calculate posterior distributions for the absolute difference in percentages between the two study groups, including medians and 95%

credible intervals (CrIs), and the posterior probabilities of efficacy for the intervention compared with control. Superiority will be demonstrated if the 95% CrI of the arm parameter is higher than 0.

2. Second, if the superiority criteria is met at the test-of-cure visit, we will test the superiority of dexamethasone on the rate of all-cause mortality on Day 28. If the superiority criteria on test-of cure visit is not demonstrated, all-cause mortality on Day 28 will be considered as an exploratory secondary outcome. The model will calculate posterior distributions for the absolute difference in percentages between the two study groups, including medians and 95% credible intervals (CrIs), and the posterior probabilities of efficacy for the intervention compared with control. Superiority will be demonstrated if the 95% CrI of the arm parameter is higher than 0.

Details of the Bayesian logistic regression model for clinical cure

A Bayesian logistic regression model will be estimated using the "rstanarm" package and the "stan_glm" function. The model will estimate the effect of the allocated treatment group and be adjusted on HAP onset (early or late) and center will be used as a random effect.

A Student t prior will be first used to estimate with 1 degree of freedom, 0 for location and 2.5 for scale. In a sensitivity analysis, location and scale parameters will be modified in order to check for changes in results if any.

Details of the Bayesian logistic regression model for all-cause mortality

A Bayesian logistic regression model will be estimated using the "rstanarm" package and the "stan_glm" function. The model will estimate the effect of the allocated treatment group and be adjusted on HAP onset (early or late) and center will be used as a random effect.

A Student t prior will be first used to estimate with 1 degree of freedom, 0 for location and 2.5 for scale. In a sensitivity analysis, location and scale parameters will be modified in order to check for changes in results if any.

5.3.4. Subgroups analysis

To further explore the treatment effect on the two components of the primary outcome, interaction terms between treatment arm and the following covariates will be tested.

Subgroup	Variant	Definition
Onset of HAP	1	Late or early
Age Group	1	• < 65 years • >=65 years
Gram negative bacteria found in culture at HAP diagnostic	1	• Yes • No
Severity of HAP at the time of diagnosis	1	• Severe (100-200)

Subgroup	**Variant**	**Definition**
Definition: *PaO2/FiO2 < 100 under IMV,* *PaO2/FiO2 < 100-200 under IMV*		• Extremely severe (<100)
Time from initial antimicrobial therapy and randomisation	1	• < 12 hours • 12-24 hours • 24-48 hours
Failure of probabilistic antimicrobial therapy at HAP diagnosis *Definition*: *One or more pathogens identified in culture being resistant to the all treatments*		• Yes • No
Co-infection with a virus at HAP diagnosis		• Yes • No

5.4. Secondary Efficacy Endpoints Analysis

Secondary analysis will be evaluated in frequentist framework.

All statistical analyses will consider stratified randomization (early vs late HAP, and centers) as recommended in the CONSORT 2010 statement.

5.4.1. All-cause mortality

Differences in all-cause mortality rates at Month 3 and Month 6 will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

Missing data will be imputed as defined by the primary estimand in section 5.3.2.

All-cause mortality (at Month 3 and Month 6) will be also analyzed with a Cox Survival regression model adjusted for stratification factors and on center as a random effect. Median times before event will be compared.

5.4.2. Rate of pleural empyema at Day 28

Differences in rates at day 28 will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

If ICU discharge before day 28, the data will still be collected during hospitalization.

Intercurrent Events before day 28	**Strategy for Addressing Intercurrent Events**
• **ICU discharge / Hospital discharge**	**Treatment Policy strategy:** Data will be collected as much as can be (medical care, phone call…)
• **Death**	**Composite strategy:** Patients are considered *as not having pleural empyema*
• **Missing data** - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing criterion will be imputed.

5.4.3. Rate of microbiological failure

Microbiological failure is defined as a positive respiratory culture at the ToC visit.

Differences in rates of microbiological failure at ToC visit will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

The analysis will be done under the following strategies :

Intercurrent Events before ToC visit	Strategy for Addressing Intercurrent Events
• **Death**	**Composite strategy:** Patients are considered as *not having microbiological failure*
• **Missing data** - Study data are not available for the evaluation of microbiological failure - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing criterion will be imputed.

5.4.4. Rate of pneumonia relapse or recurrence at day 28

Second episode means that patients are cured from the initial HAP for at least 48 hours.

Pneumonia relapse is defined as a second episode of HAP with one or more identical pathogens.

Pneumonia recurrence is defined as a second episode of HAP with different pathogens.

Differences in rates of pneumonia relapse at day 28 will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

The analysis will be done under the following strategies:

Intercurrent Events before day 28	Strategy for Addressing Intercurrent Events
• **ICU discharge / Hospital discharge**	**Treatment Policy strategy:** Data will be collected as much as can be (medical care, phone call…)
• **Death**	**Composite strategy:** Patients are considered *as not having a relapse*
• **Missing data** - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing criterion will be imputed.

Differences in rates of pneumonia recurrence at day 28 will be analyzed with a Bayesian logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

The analysis will be done under the following strategies:

Intercurrent Events before day 28	Strategy for Addressing Intercurrent Events
• **ICU discharge / Hospital discharge**	**Treatment Policy strategy:** Data will be collected as much as can be (medical care, phone call…)
• **Death**	**Composite strategy:** Patients are considered *as not having a recurrence*
• **Missing data** - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing criterion will be imputed.

5.4.5. Clinical examination

Clinical exam includes time course of body temperature, cardiac pulse rate, oxygen saturation, PaO2/FiO2, type of mechanical ventilation support (invasive, noninvasive, none) (daily evaluation at 8.00 am and 8.00 pm), and leukocyte counts (every 48 hours) for 10 days.

The time course of body temperature, cardiac pulse rate, oxygen saturation, PaO2/FiO2, and leukocyte counts will be analyzed with linear mixed effects models in order to estimate a treatment effect, a time effect and an interaction treatment group and time.

The type of mechanical ventilation support will be evaluated using an ordinal regression model with three categories: none, non-invasive, invasive.

5.4.6. Rate of non-respiratory hospital-acquired infection at day 28

Non-respiratory tract hospital-acquired infection is defined by any of the following infection: urinary tract infection, surgical site infection, invasive candidiasis, septicemia.

Differences in rates of non-respiratory tract hospital-acquired infection at day 28 will be analyzed with a logistic regression model, adjusted for stratification factors (HAP onset as a fixed effect and center as a random effect).

The analysis will be done under the following strategies:

Intercurrent Events before day 28	Strategy for Addressing Intercurrent Events
• **ICU discharge / Hospital discharge**	**Treatment Policy strategy:** Data will be collected as much as can be (medical care, phone call…)
• **Death**	**Composite strategy:** Patients are considered as not having non-respiratory hospital-acquired infection
• **Missing data** - Administrative censuring (such as consent withdrawal or lost to follow-up)	**Treatment Policy strategy:** Data will be censure at the date of last news. Missing criterion will be imputed.

5.4.7. Antibiotic-free days at Day 28

The number of antibiotic-free days is defined as the number of days between Day 1 and Day 28 for which living patients do not receive antibiotics. Patients who died between day 1 and day 28 will be ascribed 0 antibiotic-free days. Administrative censure will be imputed by multiple imputation technique.

Comparison between both groups in terms of antibiotic-free days will be carried out using a zero-inflated negative binomial regression adjusted on stratification factors.

References:

Klompas M, McKenna C, Ochoa A, Ji W, Chen T, Young J, Rhee C; Prevention Epicenters Program, Centers for Disease Control and Prevention. Ultra-Short-Course Antibiotics for Suspected Pneumonia With Preserved Oxygenation. Clin Infect Dis. 2023 Feb 8;76(3):e1217-e1223. doi: 10.1093/cid/ciac616. PMID: 35883250; PMCID: PMC10498383.

Renard Triché, L., Futier, E., De Carvalho, M. et al. Sample size estimation in clinical trials using ventilator-free days as the primary outcome: a systematic review. Crit Care 27, 303 (2023). https://doi.org/10.1186/s13054-023-04562-y

Verghis RM, McDowell C, Blackwood B, Lee B, McAuley DF, Clarke M. Re-analysis of ventilator-free days (VFD) in acute respiratory distress syndrome (ARDS) studies. Trials. 2023 Mar 13;24(1):183. doi: 10.1186/s13063-023-07190-7. PMID: 36907882; PMCID: PMC10008713.

5.4.8. Invasive mechanical ventilation-free days

The number of Invasive mechanical ventilation-free (IMV-free) ***days*** is defined as the number of days between Day 1 and Month 6 for which living patients breathe spontaneously. Patients who died between day 1 and 6 months will be ascribed 0 mechanical-free days. Administrative censure will be imputed by multiple imputation technique.

Comparison between both groups in terms of antibiotic-free days will be carried out using a zero-inflated negative binomial regression adjusted on stratification factors.

References:

Klompas M, McKenna C, Ochoa A, Ji W, Chen T, Young J, Rhee C; Prevention Epicenters Program, Centers for Disease Control and Prevention. Ultra-Short-Course Antibiotics for Suspected Pneumonia With Preserved Oxygenation. Clin Infect Dis. 2023 Feb 8;76(3):e1217-e1223. doi: 10.1093/cid/ciac616. PMID: 35883250; PMCID: PMC10498383.

Renard Triché, L., Futier, E., De Carvalho, M. et al. Sample size estimation in clinical trials using ventilator-free days as the primary outcome: a systematic review. Crit Care 27, 303 (2023). https://doi.org/10.1186/s13054-023-04562-y

Verghis RM, McDowell C, Blackwood B, Lee B, McAuley DF, Clarke M. Re-analysis of ventilator-free days (VFD) in acute respiratory distress syndrome (ARDS) studies. Trials. 2023 Mar 13;24(1):183. doi: 10.1186/s13063-023-07190-7. PMID: 36907882; PMCID: PMC10008713.

5.4.9. Duration of invasive mechanical ventilation (IMV) at 6 months

Time from randomization to weaning of IMV will be estimated and compared by a cause-specific hazard regression models to consider the informative censoring and the competing risk of death.

5.4.10. Duration of hospitalization

Time from randomization to initial hospital discharge will be estimated and compared by a cause-specific hazard regression models to consider the informative censoring and the competing risk of death.

5.4.11. Hospital-free days at 6 months

The ***number of hospital-free days*** is defined as the number of days between Day 1 and Month 6 for which living patients are outside of a hospital. Patients who died between day 1 and month 6 will be ascribed 0 hospital-free days. Administrative censure will be imputed by multiple imputation technique.

Comparison between both groups in terms of hospital-free days will be carried out using a zero-inflated negative binomial regression adjusted on stratification factors.

References:

Klompas M, McKenna C, Ochoa A, Ji W, Chen T, Young J, Rhee C; Prevention Epicenters Program, Centers for Disease Control and Prevention. Ultra-Short-Course Antibiotics for Suspected Pneumonia With Preserved Oxygenation. Clin Infect Dis. 2023 Feb 8;76(3):e1217-e1223. doi: 10.1093/cid/ciac616. PMID: 35883250; PMCID: PMC10498383.

Renard Triché, L., Futier, E., De Carvalho, M. et al. Sample size estimation in clinical trials using ventilator-free days as the primary outcome: a systematic review. Crit Care 27, 303 (2023). https://doi.org/10.1186/s13054-023-04562-y

Verghis RM, McDowell C, Blackwood B, Lee B, McAuley DF, Clarke M. Re-analysis of ventilator-free days (VFD) in acute respiratory distress syndrome (ARDS) studies. Trials. 2023 Mar 13;24(1):183. doi: 10.1186/s13063-023-07190-7. PMID: 36907882; PMCID: PMC10008713.

5.5. Secondary Safety Endpoints Analysis

To describe the safety of dexamethasone

- Rate of serious adverse reactions and suspected unexpected serious adverse reaction (SUSAR) at Day 28.
- Rate of metabolic adverse events during the 5-7-day treatment period (number of days with a blood level of potassium < 3.5 mmol/l, number of days with of sodium < 135 mmol/l, daily dose of insulin).
- Rate of gastric ulcer.

5.6. Health Economics Analysis

Objective: To assess the economic efficiency of dexamethasone plus SOC compared to SOC.

Endpoint: Economic endpoints at 6 months: Incremental cost-effectiveness ratio (ICER).

The cost-effectiveness analysis will be performed for France only given that information about the use of health care resources will be obtained using the French National Health System database (SNDS, Système National des Données de Santé) and that crossing health care databases from various countries would be very difficult [a]. As recommended by French national guidelines about economic evaluation[b], it will adopt a collective perspective, which implies including all the stakeholders directly involved in the production of the intervention under consideration and a 6 month time horizon. Given this time horizon, costs and QALYs will not be discounted.

Costs estimation

Information about resource consumption at the hospital and outside will be collected using two sources of information:

i) A database query into the SNDS to obtain information about healthcare consumption during the initial hospitalization and after the hospital discharge;
ii) A few questions packed with the quality-of-life questionnaires to ask the patients retrospectively about their use of domestic help resources (time from caregivers, relatives, or professionals) after the hospital discharge.

A monetary value per unit of resource will be determined using the French database about hospitals' services unit costs (https://www.atih.sante.fr/actualites/referentiel-de-couts-des-unites-d-oeuvre) and NHI official tariffs. Caregivers' time (professional or informal) will be valued using prices charged by professionals. Productivity losses, which will be included in a sensitivity analysis (as recommended by the French guidelines) will be estimated using the human capital method and mean French-charged wages. Total costs will be determined by multiplying the number of resources consumed by their monetary unit value.

Quality-Adjusted Life-Years (QALYs)

The measure of health outcomes for the economic evaluation will be the number of QALYs. QALYs represent a measure of survival (life-years) weighted by health-related quality of life factors such that a weight of 0 represents death and a weight of 1 represents the best imaginable health state or perfect health (negative weights are also possible for impoverished health states). QALYs thus combine information about the length and the quality of life in a single index

[a] *Moulis et al. Clin Epidemiol 2018.*
[b] *Haute Autorité de Santé. Choices in Methods for Economic Evaluation 2020.*

measure. QALYs will be estimated from answers to the EuroQol EQ-5D-5L quality of life questionnaire at Month 3 and Month 6. Given that at baseline all patients will be unconscious, they will be ascribed a common health utility score obtained from published valuation studies for the EQ-5D-5L that included the state 'being unconscious'. Since published utility scores for this state may vary between studies and no score was provided for France, various values will be tested in sensitivity analyses. If the patient cannot complete the questionnaire on Month 3 and Month 6, we will allow a relative or a health care professional to act as a proxy respondent to assess the patient's situation (using the proxy version of the EQ-5D-5L questionnaire). The answers to the EQ-5D-5L questionnaires will be converted into health utility scores using the French-published tariffs[a].

Missing data

The cost-effectiveness analysis will be conducted on an intention-to-treat basis with imputed missing data on costs and QALYs to avoid biases due to the analysis of complete cases (those patients with no missing data). If missing data on costs and QALYs are lower than 5%, they will be imputed to the mean. Otherwise, missing data will be imputed using a multiple imputation method. This will consist of using regression techniques to predict plausible values for missing data, to fill in missing data with these values several times -to create several sets of imputed data- and combine these imputed sets to obtain mean estimates of costs and QALYs, their variances, and confidence intervals[b].

Results of the cost-effectiveness analysis (only in the French sample)

Differences in costs and QALYs with their corresponding 95% confidence intervals (CI), and the mean ICER will be presented. To account for the uncertainty surrounding the estimation of the ICER we will construct an acceptability curve plotting the probability for an intervention to be cost-effective for various values of the society's willingness to pay an additional unit of effectiveness (i.e., an additional QALY). We will also perform sensitivity analyses to assess the robustness of the results to the main assumptions of the analysis, such as the method to manage missing data and the inclusion of production losses, for instance.

5.7. Secondary Quality of life Endpoints Analysis

To assess the suitability and acceptability of dexamethasone from the patients' perspectives.

- Changes in health-related quality of life (HRQoL) from three (M3) to six months (M6) after randomization measured with the Short Form (SF)-36 scale validated in French.
- Changes in anxiety and depression from M3 to M6 were measured with the HADS scale validated in French.
- Changes in subjective well-being from M3 to M6 measured with the Satisfaction With Life Scale (SWLS) validated in French.

[a] *Andrade et al. PharmacoEconomics 2020.*
[b] *Faria et al. Pharmacoeconomics 2014.*

Change in patient-reported outcomes data (quality of life, anxiety, depression) from Month 3 to Month 6 will be analyzed using longitudinal Rasch Measurement Theory (RMT)[a] models from the family of generalized random effects models, according to the fit of the RMT models. Mixed models on observed scores will be used otherwise. The RespOnse Shift ALgorithm at Item-level (ROSALI)[44] based on these models and validated in a simulation study [45] will be used to assess whether patients change (between M3 and M6) their interpretation of the items and response scale of the questionnaire (i.e. response shift) which may be linked with (mal)adaptation. ROSALI will be developed and validated to enable the use of RMT models as latent regression models to include covariates such as treatment, gender, and country. The development of ROSALI will allow investigating covariates' effects on PRO (e.g. quality of life) changes over time as well as on patients' adaptation through response shift analyses.

Individual semi-structured interviews will be conducted at Month 3 and Month 6 with patients and caregivers to gain more insight into the understanding and interpretation of quantitative data[b]. An interview guide will be developed based on the literature dealing with the psychological consequences of immune intervention for patients. Interviews will be audiotaped and transcribed verbatim by the interviewer with the patients' consent. Qualitative data will be analyzed using a lexical analysis to describe what patients have told, together with a reflexive thematic analysis to create themes and describe the dataset[c].

5.8. Biomarkers analysis

To develop biomarkers for the stratification of patients into responders and non-responders to dexamethasone. Value of biological prognostic factors (at screening)

To create a biobank of blood and respiratory samples collected from humans with hospital-acquired pneumonia.

[a] *Fischer et al. Rasch Models: Foundations, Recent Developments, and Applications. New York: Springer-Verlag; 1995.*
[b] *Paillé & Muchielli. L'analyse qualitative en sciences humaines et sociales. Paris: Armand Colin. 2005.*
[c] *Braun & Clarke. Qualitative research in psychology 2006.*

5.9. Interim monitoring

After the inclusion of 250 patients (depending on the inclusion rate) a safety analysis and a descriptive efficacy analysis (without statistical tests for efficacy) will be performed before the decision to stop the study, to modify the study protocol. Since no statistical test is performed for the primary outcome at these interim analyses, no adaptation of the type-I error is needed. Based on these analyses provided by the sponsor, the DSMB and Scientific Steering committee will recommend one of the following:

5.9.1. Potential decision 1 - Potential harm

The study discontinuation for the potential harm if the relative risk (RR) of frequent SAR reaches the predefined thresholds. The RR thresholds are defined based on their severity and frequency in critically ill patients treated with the standard of care alone and their frequency in patients treated with dexamethasone:

- Observed RR of SAR > 1.5. The expected rate of SAR in the control group is 40% (i.e. 90 patients at the safety analysis, based on the PNEUMOCARE study 4).
- Observed RR of secondary pneumonia > 2. The expected rate of secondary pneumonia in the control group is 20% (i.e. 45 patients at the second interim analysis, based on the PNEUMOCARE study 4).

The RR thresholds to recommend study discontinuation were fixed based on the expected incidence of SAR in the control group to reach a reasonable statistical power but limiting the risk of false positive results in interim analysis with a low number of patients.

5.9.2. Potential decision 2 - Futility, impossibility to conclude or efficacy

Following Connor et al.48, the following model will be assessed. Each of the two treatment arms is modeled independently. For each treatment T, we assume the probability of response (clinical cure at TOC), θT, has a uniform Beta prior distribution with parameter 1 and 1, as advocated by Berry et al (Berry SM, Carlin BP, Lee JJ, Muller P. Bayesian Adaptive Methods for Clinical Trials. Chapter 5. Boca Raton: CRC Press; 2011). Then the posterior distribution of clinical cure at TOC is a Beta distribution with parameters 1+XT and 1+NT-XT. NT the total number of patients currently enrolled in arm T, XT the number of patients in arm T with clinical cure at TOC. The treatment with the highest true (but unknown) response rate is labelled tmax, while the treatment with the lowest response rate is labelled tmin. During the trial, we will not know which treatment is tmax and which is tmin, though we can calculate probabilities that each of the two treatments is tmax and tmin.

Interim monitoring for futility

This monitoring will begin after 250 patients have been enrolled and will be repeated after every additional 100 patients are enrolled (note, this number will be adapted to the estimation of the total

number of patients to include to reach conclusion). Each arm will be monitored independently and terminated if there is a clinically unacceptable response rate. If the probability a treatment offers at least a 25% response rate is less than 5%, the study will be terminated for futility.

The second futility-stopping criterion applies if the trial is unlikely to achieve its primary objective, i.e., to identify the most effective and/or the least effective treatment. This trial will stop early for futility if the predictive probability of identifying either the most effective (tmax) or the least effective treatment (tmin) at the maximum sample size is less than 5%.

Interim monitoring for efficacy

Interim monitoring for success will begin after 250 patients have been enrolled and will be repeated after every additional 100 patients are enrolled (or a number defined based on the estimation of the total number of patients to include do conclude). Early success stopping is based on identifying a superior treatment. This trial will stop early for success if we have identified the maximum effective treatment with at least 97.5% probability, that is if $P(T=tmax) > 0.975$

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses