ABBREVIATED CLINICAL STUDY REPORT:

A Phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, and anakinra, an interleukin-1 (IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection

Test Products: Emapalumab/Anakinra

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Study Initiation Date: *02 April 2020*
Data Cut-off Date: *18 January 2021*
Early Termination Date: *11 November 2020*
Study Completion Date: *18 January 2021*

Study Phase: 2/3

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Version 1.0 Final, Date 21 May 2021

2 Synopsis

Title of study

A Phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, and anakinra, an interleukin-1 (IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection

Protocol number

Sobi.IMMUNO-101

Sponsor

Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden

Study sites

Six sites in Italy and 7 sites in the United States were activated, of which 3 sites in Italy enrolled patients.

Study phase

Phase 2/3

Principal coordinating investigator

Dr. Emanuele Nicastri, MD

Publication

No publication based on the study was available at the date of the report.

Study period

02 April 2020 to 18 January 2021

Study design and methods

This was a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 infection).

Patients aged > 18 to < 85 years with documented presence of SARS-CoV-2 infection, respiratory distress, and hyperinflammation were eligible for inclusion.

The study consisted of screening, a 2-week treatment period and an 8-week follow-up period.

The 2-week treatment period was open, and the patients were randomized to treatment with standard of care and emapalumab or standard of care and anakinra or standard of care alone in a 1:1:1 ratio. Emapalumab was administered as intravenous infusions every 3rd day for a total of

5 infusions (Day 1: 6 mg/kg; Days 4, 7, 10, 13: 3 mg/kg). Anakinra was administered as 4-times daily intravenous infusions for 15 days (Days 1 to 15: 400 mg/day in total, divided into 4 doses given every 6 hours). The primary endpoint was evaluated at Day 15.

An early on-site follow-up visit was to be performed at Day 28. A follow-up by on-site visit or phone call was to be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).

The study duration for an individual patient did not exceed 10 weeks. The end of the study was defined as last patient last follow-up visit/phone call.

The study design had a total sample size of 54 patients and was planned to include 2 stages with a potential to stop for futility at the end of Stage 1, when the success rates were to be compared between each of the 2 treatment arms and standard of care.

A data review committee composed of independent experts in intensive care, inflammation, infection diseases was to be involved in study oversight, safety monitoring, and interpretation of the study results.

A safety review committee (SRC) consisting of internal Sobi members (voting/non-voting) and the Principal Coordinating Investigator (non-voting) was established to monitor study participant safety in the study. Clinical safety information was monitored and reviewed on a continuous basis by the SRC from study start to database lock. Details are described in separate written operating procedures for the SRC.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator was completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

Number of patients (planned and analyzed)

A total of 54 patients were planned to be randomized. A total of 16 patients were randomized and analyzed. During the timeframe of the study the standard of care treatment evolved, and this had a critical impact on recruitment. As a result, only a small number of patients would have been eligible to participate in the study, and it was not feasible to meet the planned enrollment target of 54 patients within a reasonable time period. Therefore, recruitment to the study was closed. Treatment and follow-up of the patients already enrolled in the study was completed according to the protocol.

Duration of study

The study duration for an individual patient did not exceed 10 weeks.

Summary of results and conclusions

Patient disposition:
A total of 16 patients completed screening and enrolled in the study at 3 sites in Italy under the protocol versions 4.0 and 5.0. Notably, protocol version 7.0 (including amendment 5), dated 24 June 2020, was approved in the US only; at the time recruitment to the study was stopped, approval of protocol version 7.0 in Italy was still pending. All patients that were enrolled were randomized and treated. Five patients received treatment with emapalumab, 5 patients received

treatment with anakinra, and 6 patients received standard of care. All 16 patients that were randomized and treated were included in the safety population and the modified intent-to-treat (mITT) population. All efficacy analyses were conducted on the mITT population which comprised all randomized patients except patients who did not receive study treatment or patients who tested negative to SARS-CoV-2 diagnosis confirmation by polymerase chain reaction (PCR) testing. The safety population comprised all patients who received at least one dose of study treatment or standard of care.

Efficacy results summary:
The primary objective of this study was to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection. The primary endpoint was treatment success, defined as not requiring invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) by Day 15.

- The number and percentage of patients with treatment success were similar in each group; 3 (60.0%) in the emapalumab group, 4 (80.0%) in the anakinra group, and 5 (83.3%) in the standard of care group.
- There was no statistically significant difference in the number of patients with treatment success between the emapalumab and standard of care groups, or between the anakinra and standard of care groups. In comparison to the standard of care group, the difference in success rate of the emapalumab group was -0.23 (97.5% CI: -0.74, 0.39; p-value 0.9394), and the difference in success rate of the anakinra group was -0.03 (97.5% CI: -0.57, 0.54; p-value 0.8182).
- The results of the sensitivity analysis of primary efficacy endpoint were consistent with those observed in the primary analysis.

In support of the primary objective, the secondary endpoints of time to mechanical ventilation; change from baseline in MEWS (modified early warning score), resting SpO_2, PaO_2/FiO_2, hemogasanalysis, oxygen supplementation, hyperinflammatory parameters, other relevant laboratory parameters were assessed.

- In comparison to standard of care, there was no statistically significant difference in the time to mechanical ventilation for the emapalumab group (hazard ratio 1.54 [90% CI: 0.15, 16.07]; p-value 0.7595) or the anakinra group (hazard ratio 0.98 [90% CI: 0.09, 10.15]; p-value: 0.9885).
- In comparison to standard of care, there was no statistically significant difference in the change from baseline in MEWS at Day 15 for the emapalumab group (difference in least-square means: -0.63 [90% CI: -1.83, 0.57]; p-value: 0.3532) or the anakinra group (difference in least-square means: 0.23 [90% CI: 1.01, 1.47]; p-value: 0.7352).
- In comparison to the standard of care, the difference in change from baseline in the hyperinflammatory parameters of ferritin, lactate dehydrogenase, and D-dimer at Day 15 was not statistically significant for the emapalumab group or the anakinra group.
- No statistically significant differences in the change from baseline in laboratory parameters, resting SpO_2 and oxygen supplementation, PaO_2/FiO_2, or blood gas parameters were observed between the emapalumab group and the standard of care group, or between the anakinra group and the standard of care group.

- No clinically relevant differences were observed in computed tomography or X-ray findings, overall survival, time to hospital discharge, or change from baseline in inflammatory biomarkers between either the emapalumab or anakinra group and standard of care, due to the small number of patients and/or large variability in mean value in each group.

Safety results summary:
The secondary objective of this study was to evaluate the safety and tolerability profile of emapalumab and anakinra in patients with SARS-CoV-2 infection.

- Seven out of 16 patients experienced treatment-emergent adverse events (TEAEs) in the safety population: 4 patients (80.0%) in the emapalumab group, 2 patients (40.0%) in the anakinra group, and 1 patient (16.7%) in the standard of care group.
- The most common TEAE preferred term (PT) was respiratory failure (emapalumab: 2 patients [40.0%]; anakinra: 1 patient [20.0%]). All other TEAE PTs were reported in single patients in each treatment group during this study.
- Treatment-related TEAEs were reported in 1 patient in each treatment group, and they were all mild to moderate in severity.
- Severe TEAEs were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. These patients each experienced severe respiratory failure, and none of them were related to study treatment.
- Treatment-emergent serious adverse events (SAEs) were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. No patients in the standard of care group experienced a treatment-emergent SAE. Three patients experienced the SAE of respiratory failure resulting in death, including 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. None of them were related to study treatment. No other SAEs were reported in this study.
- Two patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced TEAEs leading to withdrawal of study drug. One patient (20.0%) in the emapalumab group experienced atrial fibrillation, which led to withdrawal of study drug. One patient (20.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced respiratory failure, which led to withdrawal of study drug.
- No new infections in the emapalumab group or severe neutropenia in the anakinra group were reported during the study.
- No significant changes from baseline to Day 15 in mean values of laboratory parameters between the emapalumab or anakinra groups and the standard of care were observed during this study.
- No severe or serious adverse events related to laboratory parameters were reported.
- No clinically relevant trends over the course of the study or differences between the treatment groups in vital signs or electrocardiogram (ECG) changes from screening to Day 15 were observed.
- Samples were not collected for analyses of the presence of antidrug antibodies against emapalumab and anakinra, and the presence of neutralizing antibodies against anakinra.

Conclusions:

Due to the small number of patients in each group, no firm conclusions can be made from the study, but the main results are presented below.

- No statistically significant difference in the number and percentage of patients with treatment success were observed between the emapalumab and standard of care groups, or between the anakinra and standard of care groups. No significant differences were observed between the treatment groups for any of the secondary or exploratory endpoints either.
- No new safety findings were observed. The safety and tolerability profile of both emapalumab and anakinra remains unchanged.

Date of the report

Version 1.0 Final, Date 21 May 2021

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4 List of abbreviations and definition of terms

Abbreviation	Definition
ADA	Antidrug antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CYP450	Cytochrome P450
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
GCP	Good clinical practice
IRB	Institutional review board
i.v.	Intravenous
IMP	Investigational medicinal product
IMV	Invasive mechanical ventilation
IWRS	Interactive web response system
MEWS	Modified early warning score
ITT	Intent-to-treat
mITT	Modified intent-to-treat
N/A	Not applicable
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PRA	Pharmaceutical Research Associates
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
Sobi	Swedish Orphan Biovitrum AB
SOC	System organ class
SRC	Safety review committee
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

TID	Three times per day
US	United States of America

5 Ethics

Not applicable for abbreviated CSR. Refer to Section 2 of the protocol version 7.0. Appendix 16.1.1 includes a copy of the original protocol and all protocol amendments, and Appendix 16.1.2 contains a sample case report form.

6 Investigators and study administrative structure

Not applicable for abbreviated CSR. Refer to the title page and Appendix 2 of the protocol version 7.0, Appendix 16.1.1.

Six sites in Italy and 7 sites in the US were activated, of which 3 sites in Italy enrolled patients. Dr. Emanuele Nicastri in Italy was the Coordinating Investigator of this multicenter study. Sobi was the Sponsor of the study. The conduct of the study was outsourced to PRA Health Sciences, a CRO with headquarters in Raleigh, North Carolina, US.

A data review committee composed of independent experts in intensive care, inflammation, infectious diseases was to be involved in study oversight, safety monitoring, and interpretation of the study results.

An SRC consisting of internal Sobi members (voting/non-voting) and the Principal Coordinating Investigator (non-voting) was established to monitor study participant safety in the study. Clinical safety information was monitored and reviewed on a continuous basis by the SRC from study start to database lock. Details are described in separate written operating procedures for the SRC.

7 Introduction

Not applicable for abbreviated CSR. Refer to Section 3 of the protocol version 7.0, Appendix 16.1.1.

8 Study objectives and endpoints

Not applicable for abbreviated CSR. Refer to Section 4 of the protocol version 7.0, Appendix 16.1.1.

9 Investigational plan

9.1 Overall study design and plan

This was a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented SARS-CoV-2 infection.

The study consisted of screening, a 2-week treatment period, and an 8-week follow-up period.

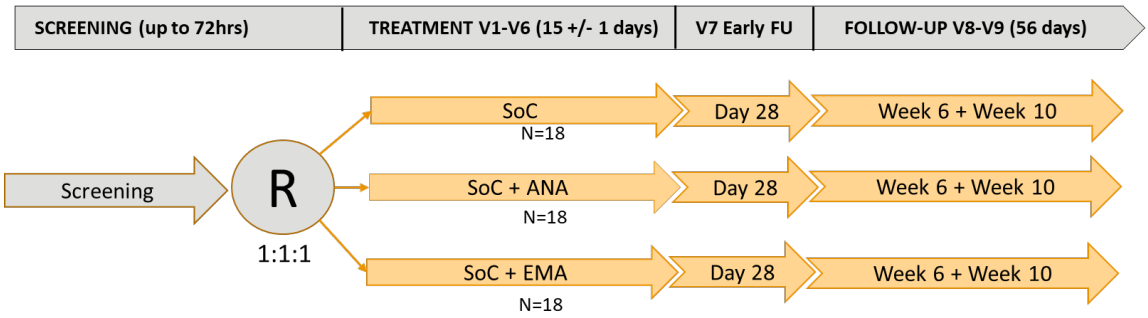
The 2-week treatment period was open, and the patients were randomized to treatment with standard of care and emapalumab or standard of care and anakinra or standard of care alone in a 1:1:1 ratio. Emapalumab was administered as i.v. infusions every 3rd day for a total of 5 infusions (Day 1: 6 mg/kg; Days 4, 7, 10, 13: 3 mg/kg). Anakinra was administered as 4-times daily i.v. infusions for 15 days (Days 1 to 15: 400 mg/day in total, divided into 4 doses given every 6 hours). The primary endpoint was evaluated at Day 15.

An early on-site follow-up visit was to be performed at Day 28. A follow-up by on-site visit or phone call was to be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).

The study duration for an individual patient did not exceed 10 weeks. The end of the study was defined as last patient last follow-up visit/phone call.

The schematic of study design is shown in Figure 1.

Figure 1 Schematic of study design



Abbreviations: ANA, anakinra; EMA, emapalumab; FU, follow-up; R, randomization; SoC, standard of care; V, Visit.

The study design had a total sample size of 54 patients and was planned to include 2 stages with a potential to stop for futility at the end of Stage 1, when the success rates were to be compared between each of the 2 treatment arms and standard of care.

A data review committee composed of independent experts in intensive care, inflammation, infectious diseases was to be involved in study oversight, safety monitoring, and interpretation of the study results.

An SRC consisting of internal Sobi members (voting/non-voting) and the Principal Coordinating Investigator (non-voting) was established to monitor study participant safety in the study. Clinical safety information was monitored and reviewed on a continuous basis by the SRC from study start to database lock. Details are described in separate written operating procedures for the SRC.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator was completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

9.2 Discussion of study design, including the choice of control groups

Refer to Section 5.2 of the protocol version 7.0, Appendix 16.1.1.

9.3 Selection of study population

Patients aged > 18 to < 85 years with documented presence of SARS-CoV-2 infection, respiratory distress, and hyperinflammation were eligible for inclusion.

Refer to Section 5.3 of the protocol version 7.0, Appendix 16.1.1 for additional information.

9.4 Treatment

The patients received IMPs according to the randomization schedule, see Table 1.

Table 1 Investigational medicinal products

Arm	IMP	Dosage form	Route	Daily dose	Dosage regimen
A	Emapalumab	Solution	i.v. infusion	Day 1: 6 mg/kg Days 4, 7, 10, 13: 3 mg/kg	Every 3rd day for in total 5 infusions
B	Anakinra	Solution	i.v. infusion	Days 1-15: 400 mg/day in total, divided into 4 doses given every 6 hours	4 times daily for 15 days
C	None	N/A	N/A	N/A	N/A

Abbreviations: i.v., intravenous; IMP, investigational medicinal product; N/A, not applicable.

Refer to Section 5.4 of the protocol version 7.0, Appendix 16.1.1 for additional information.

9.5 Efficacy and safety variables

Refer to Section 5.5 of the protocol version 7.0, Appendix 16.1.1.

9.6 Data quality assurance

Refer to Section 6 of the protocol version 7.0, Appendix 16.1.1.

9.7 Statistical analysis methods planned in the protocol and determination of sample size

Refer to Section 7 of the protocol version 7.0 and the SAP V3.0. Appendix 16.1.9 includes all versions of the SAP.

9.8 Changes in the conduct of the study or planned analyses

9.8.1 Changes in the conduct of the study

The protocol was amended 5 times during the study. The original protocol (dated 17 March 2020) and all protocol amendments are provided in Appendix 16.1.1. During the timeframe of the study, the standard of care treatment evolved, and this had a critical impact on recruitment. As a result, only a small number of patients would have been eligible to participate in the study, and it was not feasible to meet the planned enrollment target of 54 patients within a reasonable time period. Therefore, recruitment to the study was closed. Protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment. All patients in the study were enrolled at Italian sites under protocol versions 4.0 or 5.0.

The following change was made in Protocol Amendment 1 (dated 19 March 2020):

- The dosing preparation and administration of anakinra were corrected.

The following changes were made in Protocol Amendment 2 (dated 26 March 2020):

- Concomitant medication with hydroxychloroquine/chloroquine was allowed.
- A chest X-ray was added as an alternative to the performance of a high-resolution computed tomography scan.

The following changes were made in Protocol Amendment 3 (dated 13 May 2020):

- Number of sites that would participate in the study was increased.
- The age inclusion criterion was adjusted to allow adult patients >18 to <85 years at the time of screening.
- The inclusion criterion was adjusted with regards to the hyper-inflammation criterion, in particular for patients who had been pretreated with glucocorticoids prior to screening.
- The background therapy with glucocorticoids was adjusted to allow for daily dose divided into 2 to 3 doses per day.

The following changes were made in Protocol Amendment 4 (dated 18 May 2020):

- The study was changed from a local Italian study to an international multicenter study, with 12 to 20 sites in Italy and the US.
- The background therapy with methylprednisolone was no longer mandated and was removed.
- The limitation in the use of hydroxychloroquine, chloroquine, or glucocorticoid treatment as concomitant medications was removed.
- Patients were to be stratified based on glucocorticoid treatment at randomization to ensure equal distribution between treatment arms. A sensitivity analysis of the primary endpoint was to be conducted, using exact logistic regression adjusting for concurrent glucocorticoid treatment as the stratification factor.
- The IRBs were added as the study was to be conducted in the US.
- The secondary endpoint supporting the primary endpoint "change from Baseline in other relevant laboratory parameters during treatment until Day 15 with measurements performed every 3 days" was updated to also include electrolytes (sodium, potassium, and calcium) and glucose.
- Safety monitoring was updated to include all SAEs, AEs leading to premature discontinuation of study treatment, AEs of special interest, and abnormal lab findings. Specific safety monitoring/management was added for neutropenia, deteriorating renal function, and infusion-related reactions (including anaphylactic reactions).
- Local PCR testing was added to confirm diagnosis of SARS-CoV-2 infection at screening.
- Local TB screening to confirm patient's status was added.
- It was clarified that assuming no untoward safety signal was observed and no futility stopping occurred at Stage 1, the decision could be taken to increase the sample size beyond 54 patients in order to accrue further safety and efficacy data.
- All study efficacy analyses were to be conducted on the mITT population, which would comprise all randomized patients except those who did not receive study treatment or tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing.
- In case of exclusion due to tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing, additional patients could be recruited to ensure an adequate number of evaluable patients for the efficacy analyses.
- Exclusion Criterion 6 was updated to state "clinical suspicion of active or latent TB" and Exclusion Criterion 12 was added to state "clinical suspicion of active mycobacteria histoplasma capsulatum, herpes zoster, salmonella and shigella infections."
- For patients randomized to emapalumab, prophylaxis for herpes zoster virus infection had to be in place from the day before initiation of emapalumab treatment until end of study.
- PK and ADA samples were to be collected for patients randomized to emapalumab and anakinra.
- Clinical status based on a 7-point ordinal scale was added as the exploratory endpoint.
- Symptom onset information was to be captured at screening.
- eCRF as well as IWRS for randomization was introduced in the study.

The following changes were made in Protocol Amendment 5 (dated 24 June 2020):

- The exploratory biomarkers samples were to be sent for analysis to a central laboratory.
- The safety monitoring regarding SRC meeting, neutropenia, and serious infections caused by pathogens was updated.
- The administration of anakinra was updated to include the use of a particle-reducing inline filter.
- Closer monitoring of patients taking other treatments that were substrates for CYP450 with a narrow therapeutic index (e.g., warfarin and phenytoin) was recommended.
- Clarified the text around PK sampling.
- Viral shedding was added.
- A follow-up visit at Day 28 (Visit 7) was added.

9.8.2 Changes in the planned analyses

The SAP was amended twice, and all versions of the SAP are provided in Appendix 16.1.9.

The following changes were made from SAP V1.0 to V2.0, based on Protocol Amendment 3 (dated 13 May 2020) and Protocol Amendment 4 (dated 18 May 2020):

- An exploratory objective/endpoint was added.
- Stratification due to glucocorticoid use was added.
- ITT population was changed to mITT population.
- The age inclusion criterion was revised.

The following change was made from SAP V2.0 to V3.0, based on Protocol Amendment 5 (dated 24 June 2020):

- A follow-up visit at Day 28 (Visit 7) was added.

10 Study patients

10.1 Disposition of patients

The distribution of patients per study site is presented in Table 14.1.1 for the mITT population. The disposition of all enrolled patients is provided in Table 2 (Table 14.1.11) and summarized in Figure 2. Disposition data for all enrolled patients are presented by patient in Listing 16.2.1.1. The study population stratified by glucocorticoid use at inclusion in the study is presented in Table 14.1.2 for the mITT population.

A total of 16 patients completed screening and enrolled in the study at 3 sites in Italy under the protocol versions 4.0 and 5.0. Notably, protocol version 7.0 (including amendment 5), dated 24 June 2020, was approved in the US only; at the time recruitment to the study was stopped, approval of protocol version 7.0 in Italy was still pending. All patients that were enrolled were randomized and treated. Five patients received treatment with emapalumab, 5 patients received

treatment with anakinra, and 6 patients received standard of care. Twelve patients (75%) completed 2 weeks of study treatment and 4 patients (25%) discontinued study treatment early. The major reasons for discontinuation of study treatment early were adverse event (2 patients in the emapalumab group and 1 patient in the anakinra group) and lack of efficacy (1 patient in the standard of care arm). Twelve patients (75%) completed study and 4 patients (25%) discontinued study early. The major reasons for discontinuation of study early was death (1 patient each in the emapalumab and anakinra arm), adverse event (1 patient in the emapalumab arm), and lack of efficacy (1 patient in the standard of care arm).

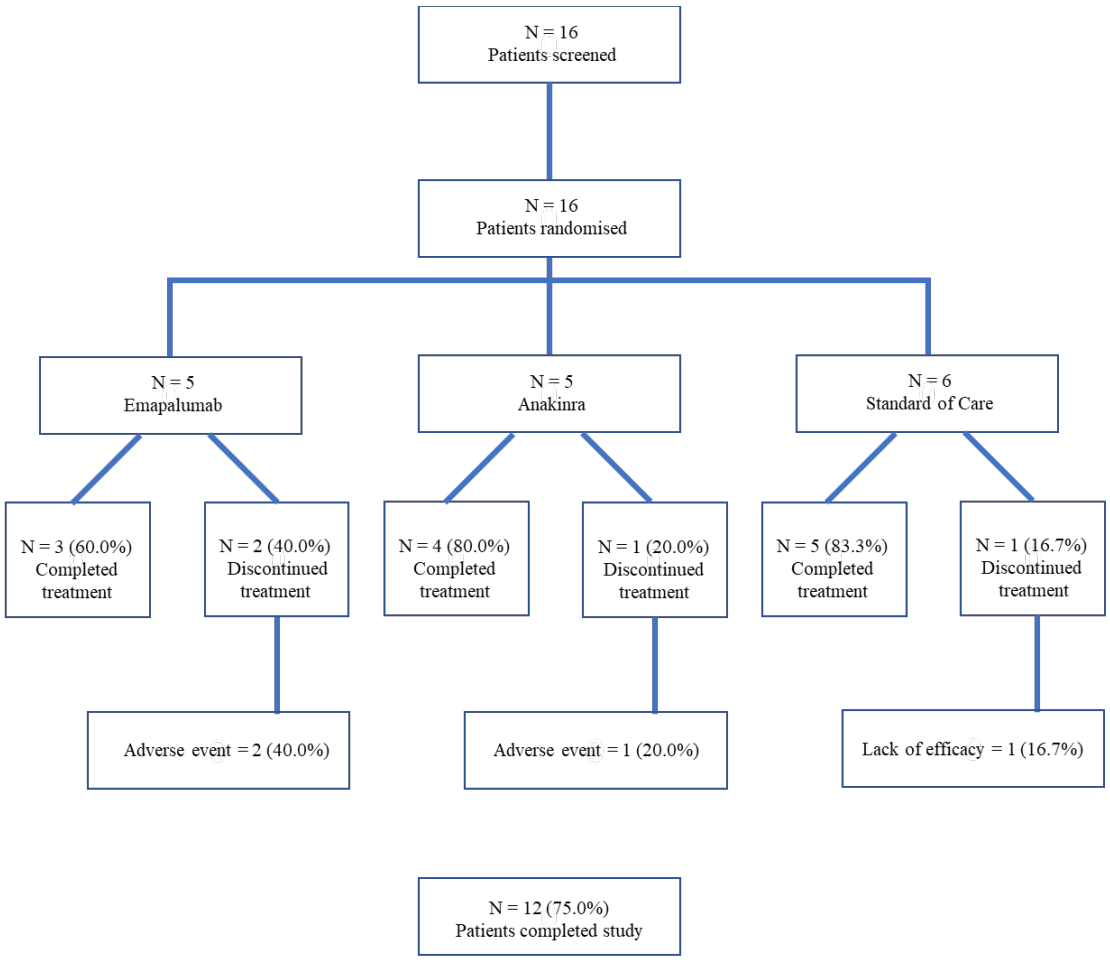
Glucocorticoid use was reported for 12 patients (75.0%) at inclusion in the study and was well balanced between the 3 treatment arms.

Table 2 Patient disposition (All enrolled patients)

	Number (%) of patients			
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**	**Total (N = 16)**
Completed screening				16 (100.0)
Did not complete screening				0
Death				0
No longer meets study criteria				0
Withdrawal by patient				0
Other				0
Randomized	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Not randomized				0
Death				0
No longer meets study criteria				0
Withdrawal by patient				0
Other				0
Received study treatment	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Completed 2 weeks of study treatment	3 (60.0)	4 (80.0)	5 (83.3)	12 (75.0)
Discontinued study treatment early	2 (40.0)	1 (20.0)	1 (16.7)	4 (25.0)
Adverse event	2 (40.0)	1 (20.0)	0	3 (18.8)
Lack of efficacy	0	0	1 (16.7)	1 (6.3)
Withdrawal by patient	0	0	0	0
Other	0	0	0	0
Completed study	3 (60.0)	4 (80.0)	5 (83.3)	12 (75.0)
Discontinued study early	2 (40.0)	1 (20.0)	1 (16.7)	4 (25.0)
Adverse event	1 (20.0)	0	0	1 (6.3)
Lack of efficacy	0	0	1 (16.7)	1 (6.3)
Lost to follow-up	0	0	0	0
Withdrawal by patient	0	0	0	0
Prohibited medication	0	0	0	0
Study terminated by Sponsor	0	0	0	0
Death	1 (20.0)	1 (20.0)	0	2 (12.5)
Other	0	0	0	0

Source: Table 14.1.11.
Abbreviations: N, Number (used as denominator for percent calculation with exception specified below).
Number of patients randomized was used as denominator for reason percent calculations in categories after not randomized.

Figure 2 Disposition of patients in protocol Sobi.IMMUNO-101



Source: Table 14.1.11
Abbreviations; N, Number

10.2 Protocol deviations

It was not planned to prepare a programmed listing of protocol deviations for this abbreviated CSR; however, all protocol deviations are presented in Appendix 16.2.2.

A total of 114 protocol deviations were reported, of which 37 were deemed important.

Seven important deviations related to eligibility were reported for 6 patients: 5 patients did not meet inclusion criterion #4 (presence of respiratory distress) and 1 patient did not meet inclusion criteria #4 and #5 (presence of hyperinflammation). Refer to Section 5.3 of the protocol version 7.0, Appendix 16.1.1 for information on inclusion and exclusion criteria.

Important deviations related to informed consent (4 patients), laboratory deviations (4 patients), study procedures (7 patients), and 'other' deviations (1 patient and 1 site level) were also reported.

10.3 Data sets analyzed

A summary of analysis sets for all randomized patients is presented in Table 14.1.3 and in-text Table 3. Patient inclusion in analysis sets is presented by patient in Listing 16.2.3.1.

Of the 16 patients that were randomized, none were excluded from the mITT population or the safety population. All efficacy analyses were conducted on the mITT population, which comprised all randomized patients except patients who did not receive study treatment or patients who tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing. The safety population comprised all patients who received at least one dose of study treatment or standard of care.

Table 3 Summary of analysis sets (All randomized patients)

	Number (%) of patients			
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**	**Total (N = 16)**
Efficacy evaluation[a]	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Patients in the mITT population	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Patients excluded from the mITT population	0	0	0	0
Did not receive study treatment	0	0	0	0
Tested negative to SARS-CoV-2 diagnosis confirmation by PCR testing	0	0	0	0
Safety evaluation[b]	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Patients in the Safety population	5 (100.0)	5 (100.0)	6 (100.0)	16 (100.0)
Patients excluded from the Safety population	0	0	0	0
Did not receive study treatment	0	0	0	0

Source: Table 14.1.3.

Abbreviations: mITT, Modified intention-to-treat; N, Number; PCR, Polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.
[a] Patients were included in the group to which they were randomized for all evaluations of efficacy.
[b] Patients were included in the group according to treatment received for all evaluations of safety.

10.4 Demographic and other baseline characteristics

Not applicable for abbreviated CSR.

Demographic and baseline characteristics for the mITT population are summarized in Table 14.1.4. Patient demographics for all randomized patients are presented by patient in Listing 16.2.4.1.

Physical examination findings are summarized for the mITT population in Table 14.1.5.

Medical history of particular interest is provided in Table 14.1.6 for the mITT population and by patient in Listing 16.2.4.2.

Other relevant medical history by SOC and PT for the mITT population is provided in Table 14.1.7 and by patient in Listing 16.2.4.3.

ECG data at screening are summarized for the safety population in Table 14.1.12.

Vital signs data at baseline are summarized for the safety population in Table 14.1.13.

Medications prior to randomization for the mITT population are presented in Table 14.1.14.

Concomitant medications at randomization for the mITT population are presented in Table 14.1.15.

Concomitant medications, initiated after randomization for the mITT population, are presented in Table 14.1.16.

Prior and concomitant medications for the mITT population are presented by patient in Listing 16.2.4.4.

10.5 Measurements of treatment compliance

Not applicable for abbreviated CSR.

10.6 Extent of exposure

Drug exposures of emapalumab, anakinra, and standard of care (methylprednisolone background therapy) are provided for the safety population in Table 14.1.8, Table 14.1.9, and Table 14.1.10, respectively. Patient exposure for the safety population is presented by patient in Listing 16.2.5.1.

11 Efficacy and other evaluations

11.1 Efficacy results

Recruitment to the study was closed prematurely. Due to the small number of patients in each group the results should be interpreted with caution.

Patient efficacy assessments are presented by patient for the mITT population in Listing 16.2.6.1.

11.1.1 Primary efficacy endpoint

The primary objective of this study was to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection.

The primary endpoint was treatment success, defined as not requiring IMV or ECMO by Day 15.

Treatment success by Day 15 in the mITT population is presented in Table 14.2.1 and in-text Table 4. The number and percentage of patients with treatment success were similar in each group; 3 (60.0%) in the emapalumab group, 4 (80.0%) in the anakinra group, and 5 (83.3%) in the standard of care group.

In comparison to the standard of care group, the difference in success rate of the emapalumab group was -0.23 (97.5% exact CI: -0.74, 0.39; p-value 0.9394), and the difference in success rate of the anakinra group was -0.03 (97.5% exact CI: -0.57, 0.54; p-value 0.8182). There was no statistically significant difference in success rate between emapalumab and standard of care, or between anakinra and standard of care.

A sensitivity analysis of treatment success by Day 15 in the mITT population was also performed and the results are presented in Table 14.2.2. In comparison to the standard of care group, the odds ratio of the emapalumab group was 0.36 (97.5% CI: <0.01, 8.67; p-value 0.4184), and the odds ratio of the anakinra group was 0.82 (97.5% CI: <0.01, 74.02; p-value 0.7188). The results of the sensitivity analysis were consistent with those observed in the primary analysis, i.e., there was no statistically significant difference in success rate between emapalumab and standard of care, or anakinra and standard of care.

Table 4 Treatment success by Day 15 (mITT population)

				Comparison between groups in response		
Group	**N**	**Number (%) of patients with treatment success[a]**	**95% exact CI for success rate[b]**	**Difference in success rate[c]**	**97.5% exact CI for difference**	**Fisher's exact test p-value**
Emapalumab	5	3 (60.0)	0.11, 0.96	-0.23	-0.74, 0.39	0.9394
Anakinra	5	4 (80.0)	0.24, 1.00	-0.03	-0.57, 0.54	0.8182
Standard of care	6	5 (83.3)	0.31, 1.00			

Source: Table 14.2.1.

Abbreviations: CI, Confidence interval; ECMO, Extracorporeal membrane oxygenation; IMV, Invasive mechanical ventilation; mITT, Modified intention-to-treat; N, Number.
[a] Not requiring IMV or ECMO.
[b] Clopper-Pearson method.
[c] A positive difference in response rates favored emapalumab/anakinra.

The number of patients in the mITT population requiring IMV or ECMO by Day 15 is presented in Table 14.2.3 and in-text Table 5. IMV by Day 15 was required for 2 patients: 1 patient (25.0%) in the emapalumab group and 1 patient (20.0%) in the standard of care group. No patients required ECMO by Day 15.

Table 5 IMV/ECMO by Day 15 (mITT population)

	Group	N[a]	Number (%) of patients requiring IMV or ECMO
IMV	Emapalumab	4	1 (25.0)
	Anakinra	4	
	Standard of care	5	1 (20.0)
ECMO	Emapalumab	4	
	Anakinra	4	
	Standard of care	5	
IMV or ECMO	Emapalumab	4	1 (25.0)
	Anakinra	4	
	Standard of care	5	1 (20.0)

Source: Table 14.2.3.
Abbreviations: ECMO, Extracorporeal membrane oxygenation; IMV, Invasive mechanical ventilation; mITT, Modified intention-to-treat; N, Number.
[a] Patients who ended study prior to Day 15 were censored from N.

Individual treatment success by visit and treatment duration for the mITT population is presented in Figure 14.2.3.

Of the 3 patients who achieved treatment success in the emapalumab group, 2 patients completed treatment and 1 patient discontinued treatment before Day 15 due to an adverse event. Of the 2 patients in this group that did not achieve treatment success, 1 patient completed treatment and 1 patient discontinued the study treatment and the study before Day 15 due to an adverse event.

In the anakinra group, 4 patients achieved treatment success and completed treatment. One patient did not achieve treatment success and discontinued treatment due to an adverse event.

In the standard of care group, 5 patients achieved treatment success; 4 of these patients completed treatment and 1 patient discontinued treatment due to lack of efficacy. One patient did not achieve treatment success and completed treatment.

11.1.2 Secondary efficacy endpoints

11.1.2.1 Time to mechanical ventilation

The time to mechanical ventilation is provided in Table 14.2.4 and in-text Table 6. A Kaplan-Meier plot of time to mechanical ventilation is displayed in Figure 14.2.1.

One patient in each group required mechanical ventilation. The median time to mechanical ventilation for each group was non-calculable. In comparison to standard of care, there was no statistically significant difference in the time to mechanical ventilation for the emapalumab group (hazard ratio 1.54 [90% CI: 0.15, 16.07]; p-value: 0.7595) or the anakinra group (hazard ratio 0.98 [90% CI: 0.09, 10.15]; p-value: 0.9885).

The time to IMV or ECMO is provided in Table 14.2.5 and as a Kaplan-Meier plot in Figure 14.2.2. Of the 3 patients who required mechanical ventilation, each received IMV. No patients received ECMO.

Table 6 Time to mechanical ventilation (mITT population)

	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Required mechanical ventilation, n (%)	1 (20.0)	1 (20.0)	1 (16.7)
Censored patients, n (%)	4 (80.0)	4 (80.0)	5 (83.3)
No mechanical ventilation at the time of analysis[a]	2 (40.0)	3 (60.0)	4 (66.7)
Terminated prior to mechanical ventilation	2 (40.0)	1 (20.0)	1 (16.7)
Adverse event	2 (40.0)	1 (20.0)	0
Lack of efficacy	0	0	1 (16.7)
Median time (90% CI) (days)[b]	NC (4.0, NC)	NC (13.0, NC)	NC (4.0, NC)
Hazard ratio (90% CI)[c]	1.54 (0.15, 16.07)	0.98 (0.09, 10.15)	Ref.
Two sided p-value[d]	0.7595	0.9885	

Source: Table 14.2.4.
Abbreviations: CI, Confidence interval; mITT, Modified intention-to-treat; N, Number of patients; NC, Non-calculable; Ref., Reference.
[a] Includes patients known to have not required mechanical ventilation by data cut-off.
[b] Calculated using the Kaplan-Meier technique.
[c] The analysis was performed using Cox proportional hazards model. A hazard ratio < 1 favors emapalumab/anakinra and indicates a reduction in risk of requiring mechanical ventilation as compared to standard of care.
[d] Pairwise comparison of emapalumab/anakinra vs standard of care using the log-rank test.

11.1.2.2 Change from baseline in MEWS at Day 15

The change from baseline in MEWS at Day 15 is presented in Table 14.2.6 and in-text Table 7.

The mean (SD) changes from baseline in MEWS at Day 15 were -1.00 (0.00), 0.00 (0.82), and -0.75 (0.96) in the emapalumab, anakinra, and standard of care groups, respectively.

The least-square means difference in the change from baseline in MEWS at Day 15 was not statistically significant between the emapalumab group and standard of care (-0.63 [90% CI: -1.83, 0.57]; p-value: 0.3532) or between the anakinra group and standard of care (0.23 [90% CI: -1.01, 1.47]; p-value: 0.7352).

Table 7 Change from baseline in MEWS at Day 15 (mITT population)

	Emapalumab (N = 5)	Anakinra (N = 5)	Standard of care (N = 6)
Baseline			
n	5	5	6
Mean (SD)	2.00 (1.00)	1.20 (0.84)	2.00 (0.89)
Median (Q1, Q3)	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)	2.00 (1.00, 3.00)
Min, max	1.0, 3.0	0.0, 2.0	1.0, 3.0
Day 15			
n	3	4	4
Mean (SD)	0.33 (0.58)	1.00 (0.82)	1.50 (1.00)
Median (Q1, Q3)	0.00 (0.00, 1.00)	1.00 (0.50, 1.50)	1.00 (1.00, 2.00)
Min, max	0.0, 1.0	0.0, 2.0	1.0, 3.0
Change from baseline at Day 15			
n	3	4	4
Mean (SD)	-1.00 (0.00)	0.00 (0.82)	-0.75 (0.96)
Median (Q1, Q3)	-1.00 (-1.00, -1.00)	0.00 (-0.50, 0.50)	-0.50 (-1.50, 0.00)
Min, max	-1.0, -1.0	-1.0, 1.0	-2.0, 0.0
Difference in change from baseline[a]			
Difference in LS means	-0.63	0.23	
90% two sided CI	(-1.83, 0.57)	(-1.01, 1.47)	
p-value	0.3532	0.7352	

Source: Table 14.2.6.
Abbreviations: ANCOVA, Analysis of covariance; CI, Confidence interval; LS, Least-square; MEWS, Modified early warning score; mITT, Modified intention-to-treat; N, Number; n, number; Q1, First quartile; Q3, Third quartile; SD, Standard deviation.
[a] Results based on ANCOVA including factors treatment arm and baseline MEWS.

11.1.2.3 Change from baseline in hyperinflammatory parameters over time

The change from baseline in hyperinflammatory parameters over time is provided in Table 14.2.7.

The mean (SD) changes from baseline in ferritin at Day 15 in the emapalumab, anakinra, and standard of care groups were -506.6 pmol/L (2518.2), -2045.2 pmol/L (3627.7), and -842.6 pmol/L (1020.0), respectively. The least-square means difference in the change from

baseline in ferritin at Day 15 was not statistically significant between the emapalumab group and standard of care (296.2 pmol/L [90% CI: -942.8, 1535.3]; p-value: 0.6775) or between the anakinra group and standard of care (-231.8 pmol/L [90% CI:-1494.2, 1030.6]; p-value 0.7491).

The mean (SD) changes from baseline in lactate dehydrogenase at Day 15 in the emapalumab, anakinra, and standard of care groups were -163.6 U/L (252.4), -20.6 U/L (274.8), and -158.4 U/L (108.3), respectively. The least-square means difference in the change from baseline in lactate dehydrogenase at Day 15 was not statistically significant between the emapalumab group and standard of care (20.6 U/L [90% CI: -197.4, 238.6]; p-value: 0.8688) or between the anakinra group and standard of care (124.7 U/L [90% CI: -92.2, 341.6]; p-value: 0.3259).

The mean (SD) changes from baseline in D-dimer at Day 15 in the emapalumab, anakinra, and standard of care groups were -6.84 nmol/L (12.67), 6.64 nmol/L (19.51), and -5.55 nmol/L (6.45), respectively. The least-square means difference in the change from baseline in D-dimer at Day 15 was not statistically significant between the emapalumab group and standard of care (0.40 nmol/L [90% CI: -13.77, 14.57]; p-value: 0.9606) or between the anakinra group and standard of care (9.74 nmol/L [90% CI: -4.51, 23.99], p-value: 0.2454).

Figure 14.2.4 displays box plots of treatment success and change from baseline in hyperinflammatory parameters at Day 15. The number of patients in each group is too small to allow for meaningful comparisons by treatment success and hyperinflammatory parameters.

Improvement in hyperinflammatory parameters by Day 15 is provided in Table 14.2.8 and in-text Table 8. An improvement of ≥50% from baseline in ferritin was observed in 1 patient (20.0%) in the emapalumab group and 2 patients (33.3%) in the standard of care group. Normalization of ferritin, from above the upper local laboratory reference range at baseline to within range at Day 15, was not reported for any patients.

An improvement of ≥50% compared to baseline and normalization of lactate dehydrogenase by Day 15 occurred in 1 patient in both the anakinra group (20.0%) and the standard of care group (16.7%). Lactate dehydrogenase was improved by ≥50% from baseline in 1 patient in each treatment group. Normalization of lactate dehydrogenase occurred in 2 patients in both the anakinra group (40.0%) and the standard of care group (33.3%).

An improvement of ≥50% compared to baseline and normalization of D-dimer by Day 15 occurred in 2 patients in both the anakinra group (40.0%) and the standard of care group (33.3%). D-dimer was improved by ≥50% from baseline in 2 patients (40.0%) in the emapalumab group, 2 patients (40.0%) in the anakinra group, and 3 patients (50.0%) in the standard of care group. Normalization of D-dimer occurred in 1 patient (20.0%) in the emapalumab group, 3 patients (60.0%) in the anakinra group, and 2 patients (33.3%) in the standard of care group.

Table 8 Improvement of hyper-inflammatory parameters by Day 15 (mITT population)

	Number (%) of patients		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Ferritin (pmol/L), both[a]	0 (0.0)	0 (0.0)	0 (0.0)
Improvement of ≥50% from baseline	1 (20.0)	0 (0.0)	2 (33.3)
Normalized[b]	0 (0.0)	0 (0.0)	0 (0.0)
Lactate Dehydrogenase (U/L), both[a]	0 (0.0)	1 (20.0)	1 (16.7)
Improvement of ≥50% from baseline	1 (20.0)	1 (20.0)	1 (16.7)
Normalized[b]	0 (0.0)	2 (40.0)	2 (33.3)
D-dimer (nmol/L), both[a]	0 (0.0)	2 (40.0)	2 (33.3)
Improvement of ≥50% from baseline	2 (40.0)	2 (40.0)	3 (50.0)
Normalized[b]	1 (20.0)	3 (60.0)	2 (33.3)

Source: Table 14.2.8.
Abbreviations: mITT, Modified intention-to-treat; N, Number.
[a] At least 50% improvement compared to baseline, and normalization, by Day 15.
[b] Shift from above upper local lab reference range at baseline to within range at Day 15.

11.1.2.4 Change from baseline in laboratory parameters

The change from baseline in laboratory parameters is provided in Table 14.2.9.

For the emapalumab group the difference in least-square means and/or the p-value at Day 15 could not be calculated for the parameters of direct bilirubin, indirect bilirubin, glucose, sodium, potassium, and calcium due to limited data. The least-square means difference in the change from baseline in all other laboratory parameters at Day 15 between the emapalumab group and the standard of care group was not statistically significant.

For the anakinra group the difference in least-square means and/or the p-value at Day 15 could not be calculated for the parameters of indirect bilirubin, troponin I, glucose, sodium, potassium, and calcium due to limited data. The least-square means difference in the change from baseline in all other laboratory parameters at Day 15 between the anakinra group and the standard of care group was not statistically significant.

11.1.2.5 Change from baseline in resting SpO_2 and oxygen supplementation

The change from baseline in resting SpO_2 and oxygen supplementation is provided in Table 14.2.10.

The least-square means difference in the change from baseline in capillary blood oxygen saturation at Day 15 between the emapalumab group and the standard of care (-4.137% [90% CI: -8.698, 0.423]) was not statistically significant (p-value: 0.1319). The least-square means difference in the change from baseline in capillary blood oxygen saturation at Day 15 between

the anakinra group and standard of care (-4.897% [90% CI: -9.458, -0.337]) was not statistically significant (p-value: 0.0798).

The least-square means difference in the change from baseline in oxygen flow rate at Day 15 between the emapalumab group and standard of care (9.6 L/min [90% CI: -0.8, 19.9]) was not statistically significant (p-value: 0.1272). The least-square means difference in the change from baseline in oxygen flow rate at Day 15 between the anakinra group and the standard of care (3.5 L/min [90% CI: -8.1, 15.0]) was not statistically significant (p-value: 0.6024).

11.1.2.6 Change from baseline in PaO_2/FiO_2

The change from baseline in PaO_2/FiO_2 is provided in Table 14.2.11.

The least-square means difference in the change from baseline in PaO_2/FiO_2 (-140.28 mmHg [90% CI:-389.73, 109.17]; p-value 0.2775), PaO_2 (1.05 mmHg [90% CI: -34.48, 36.58]; p-value 0.9489), and FiO_2 (7.0% [90% CI:-16.1, 30.1]; p-value 0.5698) at Day 15 between the emapalumab group and the standard of care was not statistically significant.

The least-square means difference in the change from baseline in PaO_2/FiO_2 (-59.73 mmHg [90% CI: -415.25, 295.79] p-value 0.7190), PaO_2 (-16.05 mmHg [90% CI: -61.82, 29.72]; p-value 0.4698), and FiO_2 (-9.3% [90%CI: -34.7, 16.2]; p-value 0.4968) at Day 15 between the anakinra group and the standard of care was not statistically significant.

11.1.2.7 Change from baseline in hemogasanalysis over time

The change from baseline in hemogasanalysis over time is presented in Table 14.2.12.

The least-square means differences in the change from baseline in any of the blood gas parameters at Day 15 between the emapalumab group and the standard of care, and between the anakinra group and the standard of care, were not statistically significant.

11.1.2.8 Change from screening in the findings of high-resolution CT scan or X-ray of the chest

The change from screening in the findings of high-resolution CT scan or X-ray of the chest is presented in Table 14.2.13 and in-text Table 9.

At screening, 4 patients in the emapalumab group had clinically significant abnormal findings; at Day 15, the findings for 1 patient (20.0%) had changed to abnormal and not clinically significant. There was no change in findings for the other 3 patients (60.0%) at Day 15.

In the anakinra group, 4 patients had clinically significant abnormal findings at screening; at Day 15, the findings for 3 patients (60.0%) had changed to abnormal and not clinically significant. There was no change in findings for 1 patient (20.0%) at Day 15.

In the standard of care group, 4 patients had clinically significant abnormal findings at screening; at Day 15, the findings for 1 patient (16.7%) had changed to normal and for 1 other patient (16.7%) to abnormal and not clinically significant. There was no change in findings for 2 patients (33.3%) at Day 15.

The number of patients in each group and overall was too small to observe relevant differences in CT or X-ray findings between the treatment groups.

Table 9 Change from screening in the findings of high-resolution CT scan or X-ray of the chest (mITT population)

	Emapalumab (N = 5) Screening			Anakinra (N = 5) Screening			Standard of care (N = 6) Screening		
	Normal	Abnormal (NC)	Abnormal (CS)	Normal	Abnormal (NC)	Abnormal (CS)	Normal	Abnormal (NC)	Abnormal (CS)
Day 15									
Normal	0	0	0	0	0	0	0	0	1 (16.7)
Abnormal (NC)	0	0	1 (20.0)	0	0	3 (60.0)	0	0	1 (16.7)
Abnormal (CS)	0	0	3 (60.0)	0	0	1 (20.0)	0	0	2 (33.3)

Source: Table 14.2.13.
Abbreviations: CS, Clinically significant; CT, Computed tomography; mITT, Modified intention-to-treat; N, Number; NC, not clinically significant.

11.1.2.9 Overall survival

Overall survival is provided in Table 14.2.14 and in-text Table 10.

A Kaplan-Meier plot of time to death is presented in Figure 14.2.5.

Two patients in the emapalumab group and 1 patient in the anakinra group died. Median survival was non-calculable for each group, and the number of patients in each group was too small to allow for meaningful comparisons to be made.

Table 10 Overall Survival (mITT population)

	Emapalumab (N = 5)	Anakinra (N = 5)	Standard of care (N = 6)
Death, n (%)	2 (40.0)	1 (20.0)	0
Censored patients, n (%)	3 (60.0)	4 (80.0)	6 (100.0)
Alive at data cut-off	3 (60.0)	4 (80.0)	5 (83.3)
Terminated prior to death	0	0	1 (16.7)
Lack of efficacy	0	0	1 (16.7)
Median survival (90% CI) (days)[a]	NC (7.0, NC)	NC (14.0, NC)	NC (NC, NC)
Hazard ratio (90% CI)[b]	911331 (0.00, NC)	804297 (0.00, NC)	Ref.
Two sided p-value[c]	0.1343	0.3173	

Source: Source 14.2.14.
Abbreviations: CI, Confidence interval; mITT, Modified intention-to-treat; N, Number of patients; NC, Non-calculable; Ref., Reference.
[a] Calculated using the Kaplan-Meier technique.

[b] The analysis was performed using Cox proportional hazards model. A hazard ratio < 1 favored emapalumab/anakinra and indicated a reduction in risk of death as compared to standard of care.
[c] Pairwise comparison of emapalumab/anakinra vs standard of care using the log-rank test.

11.1.2.10 Time to hospital discharge

The time to hospital discharge is provided in Table 14.2.15 and in-text Table 11.

A Kaplan-Meier plot of time to hospital discharge is presented in Figure 14.2.6.

Three patients in the emapalumab group, 4 patients in the anakinra group, and 5 patients in the standard of care group were discharged from hospital during the study. The median time to discharge in the emapalumab and anakinra groups was similar. The median time to discharge for the standard of care group was slightly longer than in the other treatment groups, however, due to the small number of patients, the results should be interpreted with caution. The number of patients in each group was too small to observe relevant differences in the time to hospital discharge between the treatment groups.

Table 11 Time to hospital discharge (mITT population)

	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Hospital discharge, n (%)	3 (60.0)	4 (80.0)	5 (83.3)
Censored patients, n (%)	2 (40.0)	1 (20.0)	1 (16.7)
Terminated prior to discharge	2 (40.0)	1 (20.0)	1 (16.7)
Death	1 (20.0)	1 (20.0)	0
Adverse event	1 (20.0)	0	0
Lack of efficacy	0	0	1 (16.7)
Median time to discharge (90% CI) (days)[a]	21.5 (20.0, NC)	20.0 (16.0, 25.0)	28.0 (15.0, 41.0)
Hazard ratio (90% CI)[b]	0.76 (0.22, 2.60)	2.61 (0.61, 11.22)	Ref.
Two sided p-value[c]	0.7427	0.2325	

Source: Table 14.2.15.
Abbreviations: CI, Confidence interval; mITT, Modified intention-to-treat; N, Number of patients; NC, Non-calculable; Ref., Reference.
[a] Calculated using the Kaplan-Meier technique.
[b] The analysis was performed using Cox proportional hazards model. A hazard ratio > 1 favored emapalumab/anakinra and indicated an increase in probability of hospital discharge as compared to standard of care.
[c] Pairwise comparison of emapalumab/anakinra vs standard of care using the log-rank test.

11.1.3 Other efficacy endpoints

11.1.3.1 Clinical Status

Data on clinical status based on a 7-point ordinal scale were not collected, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the

end of recruitment. All patients in the study were enrolled at sites in Italy under protocol versions 4.0 or 5.0.

11.2 Results of statistical issues encountered during the analysis

Not applicable for abbreviated CSR.

11.3 Pharmacokinetic, pharmacodynamic and other analyses results

11.3.1 Drug dose, drug concentration and relationships to response

11.3.1.1 Pharmacokinetic parameters

PK samples were not collected for analyses, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment. All patients in the study were enrolled at sites in Italy under protocol versions 4.0 or 5.0.

11.3.2 Other endpoints

11.3.2.1 Change from baseline in inflammatory biomarkers

The change from baseline in inflammatory biomarkers for the safety population is provided in Table 14.3.9. Appendix 16.1.13 includes the biomarker analysis report.

The mean (SD) changes from baseline at Day 15 in S-interleukin 1 alpha for the emapalumab, anakinra, and standard of care groups were 0.00 pg/mL (0.00), 0.03 pg/mL (0.06), and 0.00 pg/mL (0.00), respectively.

The mean (SD) changes from baseline at Day 15 in S-interleukin 1 beta for the emapalumab, anakinra, and standard of care groups were -0.283 pg/mL (0.633), 0.017 pg/mL (0.029), and 0.170 pg/mL (SD 0.706), respectively.

The mean (SD) changes from baseline at Day 15 in S-soluble interleukin 2 receptor for the emapalumab, anakinra, and standard of care groups were -63.743 pg/mL (879.064), -318.097 pg/mL (426.122), and -539.850 pg/mL (310.238), respectively.

The mean (SD) changes from baseline at Day 15 in S-interleukin 6 for the emapalumab, anakinra, and standard of care groups were 29.250 pg/mL (65.326), -4.657 pg/mL (1.301), and -4.370 pg/mL (25.365), respectively.

The mean (SD) changes from baseline at Day 15 in complement C3 for the emapalumab, anakinra, and standard of care groups were 0.054 g/L (0.094), -0.068 g/L (0.222), and -0.020 g/L (0.581), respectively.

The mean (SD) changes from baseline at Day 15 in complement C4 for the emapalumab, anakinra, and standard of care groups were 0.024 g/L (0.043), -0.108 g/L (0.080), and -0.007 g/L (0.192), respectively.

The mean (SD) changes from baseline at Day 15 in S-chemokine (C-X-C motif) ligand 9 for the emapalumab, anakinra, and standard of care groups were -238.080 pg/mL (178.418), -201.283 pg/mL (128.482), and -30.553 pg/mL (181.140), respectively.

The mean (SD) changes from baseline at Day 15 in S-interferon gamma for the emapalumab, anakinra, and standard of care groups were 383.225 pg/mL (692.310), -3.320 pg/mL (5.750), and -170.632 pg/mL (417.961), respectively.

No clinically relevant differences were observed in the change from baseline in inflammatory biomarkers between the emapalumab and the standard of care groups, or between the anakinra and the standard of care groups, due to the small number of patients and large variability in mean value in each group.

11.4 Efficacy results summary

Recruitment to the study was closed prematurely. Due to the small number of patients in each group the results should be interpreted with caution.

- The number and percentage of patients with treatment success were similar in each group; 3 (60.0%) in the emapalumab group, 4 (80.0%) in the anakinra group, and 5 (83.3%) in the standard of care group.
- There was no statistically significant difference in the number of patients with treatment success between the emapalumab and standard of care groups, or between the anakinra and standard of care groups. In comparison to the standard of care group, the difference in success rate of the emapalumab group was -0.23 (97.5% exact CI: -0.74, 0.39; p-value 0.9394), and the difference in success rate of the anakinra group was -0.03 (97.5% exact CI: -0.57, 0.54; p-value 0.8182).
- The results of the sensitivity analysis of primary efficacy endpoint were consistent with those observed in the primary analysis.
- In comparison to standard of care, there was no statistically significant difference in the time to mechanical ventilation for the emapalumab group (hazard ratio 1.54 [90% CI: 0.15, 16.07]; p-value 0.7595) or the anakinra group (hazard ratio 0.98 [90% CI: 0.09, 10.15]; p-value: 0.9885).
- In comparison to standard of care, there was no statistically significant difference in the change from baseline in MEWS at Day 15 for the emapalumab group (difference in least-square means: -0.63 [90% CI: -1.83, 0.57]; p-value: 0.3532) or the anakinra group (difference in least-square means: 0.23 [90% CI: 1.01, 1.47]; p-value: 0.7352).
- In comparison to the standard of care, the difference in change from baseline in the hyperinflammatory parameters of ferritin, lactate dehydrogenase, and D-dimer at Day 15 was not statistically significant for the emapalumab group or the anakinra group.
- No statistically significant differences in the change from baseline in laboratory parameters, resting SpO_2 and oxygen supplementation, PaO_2/FiO_2, or blood gas parameters were observed between the emapalumab group and the standard of care group, or between the anakinra group and the standard of care group.

- No clinically relevant differences were observed in CT or X-ray findings, overall survival, time to hospital discharge, or change from baseline in inflammatory biomarkers between either the emapalumab or anakinra group and standard of care, due to the small number of patients and/or large variability in mean value in each group.
- Data on clinical status and PK samples were not collected, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment. All patients in the study were enrolled at sites in Italy under protocol versions 4.0 or 5.0.

12 Safety evaluation

12.1 Adverse events

12.1.1 Brief summary of adverse events

An overall summary of TEAEs during the study for the safety population is provided in Table 14.3.1 and presented in in-text Table 12. All adverse events for all enrolled patients are presented by patient in Listing 16.2.7.1.

Seven out of 16 patients experienced TEAEs in the safety population: 4 patients (80.0%) in the emapalumab group, 2 patients (40.0%) in the anakinra group, and 1 patient (16.7%) in the standard of care group. Treatment-related TEAEs were reported in 1 patient in each treatment group.

Severe TEAEs were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. No patients in the standard of care group experienced a severe TEAE.

Treatment-emergent SAEs were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. No patients in the standard of care group experienced a treatment-emergent SAE. None of the treatment-emergent SAEs were considered related to study treatment (Listing 16.2.7.1).

Two patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced TEAEs leading to withdrawal of study drug.

Fatal TEAEs were reported for 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. No patients in the standard of care group experienced a fatal TEAE. None of the fatal TEAEs were considered related to study treatment (Listing 16.2.7.1).

Table 12 Overall summary of TEAEs during the study (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	4 (80.0)	2 (40.0)	1 (16.7)
Any severe TEAE	2 (40.0)	1 (20.0)	0
Any treatment-emergent non-SAE	2 (40.0)	1 (20.0)	1 (16.7)
Any treatment-emergent SAE	2 (40.0)	1 (20.0)	0
Any treatment-related TEAE[b]	1 (20.0)	1 (20.0)	1 (16.7)
Any fatal TEAE	2 (40.0)	1 (20.0)	0
Any TEAE leading to withdrawal of study drug	2 (40.0)	1 (20.0)	NA

Source: Table 14.3.1.
Abbreviations: N, Number; NA, Not applicable; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] Related to treatment (study drug or standard of care), as judged by the Investigator.

12.1.2 Most frequently reported adverse events

A summary of TEAEs by SOC and PT for the safety population is provided in Table 14.3.4 and presented in in-text Table 13.

The most common TEAE SOC was respiratory, thoracic and mediastinal disorders (emapalumab: 2 patients [40.0%]; anakinra: 1 patient [20.0%]). The most common TEAE by PT was respiratory failure (emapalumab: 2 patients [40.0%]; anakinra: 1 patient [20.0%]). All other TEAE PTs were reported in single patients in each treatment group during this study.

Table 13 TEAEs by SOC and PT (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	4 (80.0)	2 (40.0)	1 (16.7)
Blood and lymphatic system disorders	0	1 (20.0)	0
Thrombocytopenia	0	1 (20.0)	0
Cardiac disorders	1 (20.0)	0	0
Atrial fibrillation	1 (20.0)	0	0
Respiratory, thoracic and mediastinal disorders	2 (40.0)	1 (20.0)	0
Respiratory failure	2 (40.0)	1 (20.0)	0
Hepatobiliary disorders	0	0	1 (16.7)
Hypertransaminasaemia	0	0	1 (16.7)
Musculoskeletal and connective tissue disorders	1 (20.0)	0	0
Haematoma muscle	1 (20.0)	0	0

Source: Table 14.3.4.
Abbreviations: MedDRA, Medical dictionary of regulatory activities; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events at the same level of summarization were counted only once at that level. Patients with events at more than one level of summarization were counted once at each of those levels.
Note: MedDRA version 23.0.

12.1.3 Categorization of all adverse events

TEAEs by PT classified by relationship to treatment for the safety population is provided in Table 14.3.5 and in-text Table 14. One patient in each treatment group experienced TEAEs that were considered related to treatment: 1 patient (20.0%) in the emapalumab group experienced a treatment-related TEAE of atrial fibrillation; 1 patient (20.0%) in the anakinra group experienced a treatment-related TEAE of thrombocytopenia; and 1 patient (16.7%) in the standard of care group experienced a treatment-related TEAE of hypertransaminasaemia.

Table 14 TEAEs by PT classified by relationship to treatment, in descending order of frequency across groups (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	4 (80.0)	2 (40.0)	1 (16.7)
Related	1 (20.0)	1 (20.0)	1 (16.7)
Not related	3 (60.0)	1 (20.0)	0
Respiratory failure	2 (40.0)	1 (20.0)	0
Related	0	0	0
Not related	2 (40.0)	1 (20.0)	0
Atrial fibrillation	1 (20.0)	0	0
Related	1 (20.0)	0	0
Not related	0	0	0
Haematoma muscle	1 (20.0)	0	0
Related	0	0	0
Not related	1 (20.0)	0	0
Hypertransaminasaemia	0	0	1 (16.7)
Related	0	0	1 (16.7)
Not related	0	0	0
Thrombocytopenia	0	1 (20.0)	0
Related	0	1 (20.0)	0
Not related	0	0	0

Source: Table 14.3.5.
Abbreviations: MedDRA, Medical dictionary of regulatory activities; N, Number; PT, Preferred term; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events at the same level of summarization were counted only once at that level. Patients with events at more than one level of summarization were counted once at each of those levels.
Related to treatment (study drug or standard of care), as judged by the Investigator.
Note: MedDRA version 23.0.

A summary of TEAEs by PT classified by maximum severity for the safety population is provided in Table 14.3.6 and in-text Table 15. In total, 3 patients experienced severe TEAEs: 2 patients (40.0%) in the emapalumab group and 1 (20.0%) in the anakinra group. These patients each experienced severe respiratory failure, and they were not treatment related.

Three patients experienced moderate TEAEs; in the emapalumab group, 1 patient (20.0%) experienced atrial fibrillation and 1 patient (20.0%) experienced haematoma muscle; in the standard of care group, 1 patient (16.7%) experienced hypertransaminasaemia.

One patient (20.0%) in the anakinra group experienced a mild TEAE of thrombocytopenia.

Table 15 TEAEs by PT classified by maximum severity, in descending order of frequency across groups (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	4 (80.0)	2 (40.0)	1 (16.7)
Mild	0	1 (20.0)	0
Moderate	2 (40.0)	0	1 (16.7)
Severe	2 (40.0)	1 (20.0)	0
Respiratory failure	2 (40.0)	1 (20.0)	0
Mild	0	0	0
Moderate	0	0	0
Severe	2 (40.0)	1 (20.0)	0
Atrial fibrillation	1 (20.0)	0	0
Mild	0	0	0
Moderate	1 (20.0)	0	0
Severe	0	0	0
Haematoma muscle	1 (20.0)	0	0
Mild	0	0	0
Moderate	1 (20.0)	0	0
Severe	0	0	0
Hypertransaminasaemia	0	0	1 (16.7)
Mild	0	0	0
Moderate	0	0	1 (16.7)
Severe	0	0	0
Thrombocytopenia	0	1 (20.0)	0
Mild	0	1 (20.0)	0
Moderate	0	0	0
Severe	0	0	0

Source: Table 14.3.6.
Abbreviations: MedDRA, Medical dictionary of regulatory activities; N, Number; PT, preferred term; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events at the same level of summarization were counted only once at that level. Patients with events at more than one level of summarization were counted once at each of those levels. If the severity of the AE had changed, only the maximum severity of the event was recorded.
Note: MedDRA version 23.0.

12.2 Analysis of deaths, other serious adverse events, and other clinically meaningful adverse events

12.2.1 Deaths, other serious adverse events, discontinuations due to adverse events, and other adverse events of special interest

12.2.1.1 Deaths

SAEs and deaths for the safety population are presented by patient in Listing 14.3.1.

A total of 3 patients died: 2 patients in the emapalumab group and 1 patient in the anakinra group. These patients each experienced an SAE of respiratory failure with a fatal outcome. None of them were related to study treatment.

12.2.1.2 Other serious adverse events

Treatment-emergent SAEs by SOC and PT for the safety population are provided in Table 14.3.2 and in-text Table 16. Three patients each experienced the treatment-emergent SAE of respiratory failure: 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. None of them were related to study treatment. No other SAEs were reported in this study.

Narratives for patients with SAEs are provided in Section 14.3.3.

Table 16 Serious TEAEs by SOC and PT (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	2 (40.0)	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	2 (40.0)	1 (20.0)	0
Respiratory failure	2 (40.0)	1 (20.0)	0

Source: Table 14.3.2.
Abbreviations: MedDRA, Medical dictionary of regulatory activities; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events at the same level of summarization were counted only once at that level. Patients with events at more than one level of summarization were counted once at each of those levels.
Note: MedDRA version 23.0.

12.2.1.3 Discontinuations due to adverse events

A summary of TEAEs by SOC and PT leading to study drug withdrawal for the safety population are provided in Table 14.3.3 and in-text Table 17.

TEAEs leading to study drug withdrawal were reported in 3 patients within the SOCs of cardiac disorders (1 patient) and respiratory, thoracic, and mediastinal disorders (2 patients). One patient (20.0%) in the emapalumab group experienced atrial fibrillation, which led to withdrawal of

study drug. One patient (20.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced respiratory failure which led to withdrawal of study drug.

Table 17 TEAEs by SOC and PT leading to withdrawal of study drug (Safety population)

	Number (%) of patients[a]	
	Emapalumab (N = 5)	**Anakinra (N = 5)**
Any TEAE	2 (40.0)	1 (20.0)
Cardiac disorders	1 (20.0)	0
Atrial fibrillation	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (20.0)
Respiratory failure	1 (20.0)	1 (20.0)

Source: Table 14.3.3.
Abbreviations: MedDRA, Medical dictionary of regulatory activities; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment-emergent adverse event.
[a] Patients with multiple events at the same level of summarization were counted only once at that level. Patients with events at more than one level of summarization were counted once at each of those levels.
Note: MedDRA version 23.0.

12.2.1.4 Other adverse events of special interest

With respect to adverse events of special interest, TEAEs leading to study drug withdrawal are described in Section 12.2.1.3. No new infections in the emapalumab group or severe neutropenia in the anakinra group were reported during the study.

12.2.2 Narratives of deaths, other serious adverse events, and certain other clinically meaningful adverse events

Narratives of deaths and SAEs are provided in Section 14.3.3.

12.3 Clinical laboratory evaluation

12.3.1 Individual laboratory measurements by patient and abnormal laboratory values

Laboratory measurements and abnormal laboratory values for the safety population are presented by patient in Listing 16.2.8.1.

12.3.2 Evaluation of laboratory values

12.3.2.1 Laboratory values over time

The change from baseline in laboratory parameters was a secondary efficacy endpoint and is presented for the mITT population in Table 14.2.9; see Section 11.1.2.4.

The change from baseline in hyperinflammatory parameters over time was a secondary efficacy endpoint and is presented for the mITT population in Table 14.2.7; see Section 11.1.2.3.

The change from baseline in inflammatory biomarkers was an exploratory endpoint and is presented for the safety population in Table 14.3.9; see Section 11.3.2.

12.3.2.2 Individual patient changes in laboratory values

Individual patient changes in laboratory values are not provided for the safety population. Individual abnormal laboratory values by study visit are presented in Listing 16.2.8.1.

12.3.2.3 Individual clinically meaningful laboratory abnormalities

No severe or serious adverse events related to laboratory parameters were reported (Listing 16.2.7.1).

A nonserious adverse event of thrombocytopenia was reported for 1 patient in the anakinra group. The patient's platelet count was within the normal reference ranges (130 to 400 $\times 10^9$/L) on Days 1 through 10. The patient's platelet count was 94 $\times 10^9$/L on Day 13 and 66 $\times 10^9$/L on Day 15 (Listing 16.2.8.1). The event was mild and considered related to the study treatment. The dose of study treatment was not changed as a result of the event. At the time of reporting, the event was considered not recovered/not resolved (Listing 16.2.7.1).

A nonserious event of hypertransaminasaemia was reported for 1 patient in the standard of care group. For this patient, ALT and AST levels were within the normal reference ranges on Day 1. From Day 4 through Day 13, the ALT and AST levels were above the normal range. On Day 15, AST had returned to the normal reference range, although ALT remained elevated (Listing 16.2.8.1). The event was moderate and considered related to the standard of care. Action taken with the study treatment was reported as not applicable. The event recovered/resolved after 22 days. (Listing 16.2.7.1).

12.4 Vital signs, physical examinations, and other observations related to safety

12.4.1 Vital signs

Vital signs by study visit for the safety population are provided in Table 14.3.7 and are presented by patient in Listing 16.2.7.2.

Mean values of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature were similar across the treatment groups at baseline.

No relevant trends in vital signs over the course of the study were observed, however, the number of patients in each treatment group and overall was too small to allow for meaningful comparisons in vital signs between the treatment groups.

12.4.2 Physical examination findings

As per the schedule of assessments, a general physical examination was performed at screening only. Baseline physical examination findings are summarized for the mITT population in Table 14.1.5. Overall, the majority of patients had normal physical examination findings at baseline in general appearance, head, ears, eyes, nose, throat, cardiovascular system, skin, musculoskeletal, abdomen, neurology, mental status, and sensory system. One patient had an abnormal skin examination and 1 patient had an abnormal abdominal examination that were considered clinically relevant.

At baseline, clinically relevant abnormal examination of the thorax/lungs was reported in 7 patients (emapalumab: 3 [60.0%]; anakinra: 2 [40.0%]; standard of care: 2 [33.3%]). All 16 patients had clinically relevant abnormal chest imaging findings.

12.4.3 Other observations related to safety

12.4.3.1 ECG changes

The change from screening in ECG for the safety population is provided in Table 14.3.8.

In the emapalumab group, ECG changes from screening were reported for 2 patients; 1 patient had an abnormal ECG that was not clinically significant at screening and was normal at Day 15; and 1 patient had an abnormal ECG that was not clinically significant at screening that became clinically significant at Day 15.

No clinically significant abnormal ECGs or ECG changes from screening to Day 15 were reported for patients in the anakinra group.

One patient in the standard of care group had a normal ECG at screening and an abnormal ECG that was not clinically significant at Day 15.

The number of patients in each treatment group and overall was too small to allow for meaningful comparisons in ECG changes from screening to Day 15 between the treatment groups.

12.4.3.2 Anti-drug antibodies and neutralizing antibodies

Samples were not collected for analyses of the presence of antidrug antibodies against emapalumab and anakinra, and the presence of neutralizing antibodies against anakinra, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment. All patients in the study were enrolled at sites in Italy under protocol versions 4.0 or 5.0.

12.5 Safety results summary

- Seven out of 16 patients experienced TEAEs in the safety population: 4 patients (80.0%) in the emapalumab group, 2 patients (40.0%) in the anakinra group, and 1 patient (16.7%) in the standard of care group.
- The most common TEAE PT was respiratory failure (emapalumab: 2 patients [40.0%]; anakinra: 1 patient [20.0%]). All other TEAE PTs were reported in single patients in each treatment group during this study.
- Treatment-related TEAEs were reported in 1 patient in each treatment group, and they were all mild to moderate in severity.
- Severe TEAEs were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. These patients each experienced severe respiratory failure, and none of them were related to study treatment.
- Treatment-emergent SAEs were reported in 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. No patients in the standard of care group experienced a treatment-emergent SAE. Three patients experienced the SAE of respiratory failure resulting in death, including 2 patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group. None of them were related to study treatment. No other SAEs were reported in this study.
- Two patients (40.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced TEAEs leading to withdrawal of study drug. One patient (20.0%) in the emapalumab group experienced atrial fibrillation, which led to withdrawal of study drug. One patient (20.0%) in the emapalumab group and 1 patient (20.0%) in the anakinra group experienced respiratory failure, which led to withdrawal of study drug.
- No new infections in the emapalumab group or severe neutropenia in the anakinra group were reported during the study.
- No significant changes from baseline to Day 15 in mean values of laboratory parameters between the emapalumab or anakinra groups and the standard of care were observed during this study.
- No severe or serious adverse events related to laboratory parameters were reported.
- No clinically relevant trends over the course of the study or differences between the treatment groups in vital signs or ECG changes from screening to Day 15 were observed.
- Samples were not collected for analyses of the presence of antidrug antibodies against emapalumab and anakinra, and the presence of neutralizing antibodies against anakinra, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment. All patients in the study were enrolled at sites in Italy under protocol versions 4.0 or 5.0.

13 Discussion and overall conclusions

13.1 Discussion

The aim of this study was to investigate new possibilities to reduce the number of patients with SARS-CoV-2 infection requiring mechanical ventilation. This was intended to address the most urgent need to preserve the access to intense care unit support to the lower possible number of patients and may potentially reduce mortality.

This phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study was designed to investigate the efficacy and safety of emapalumab and anakinra, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.

During the timeframe of the study the standard of care treatment evolved, and this had a critical impact on recruitment. As a result, only a small number of patients would have been eligible to participate in the study, and it was not feasible to meet the planned enrollment target of 54 patients within a reasonable time period. Therefore, recruitment to the study was closed. Treatment and follow-up of the patients already enrolled in the study was completed according to the protocol.

As recruitment to the study was closed, this limited the available data in terms of the number of patients and so this should be taken into consideration in the interpretation of the trial results. A total of 16 patients were enrolled in the study at 3 sites in Italy under protocol versions 4.0 and 5.0 before recruitment closed. Notably, protocol version 7.0 (including amendment 5), dated 24 June 2020 was approved in the US only; at the time recruitment to the study was stopped, approval of protocol version 7.0 in Italy was still pending. Of the 16 patients that were enrolled, 5 were randomized to receive treatment with emapalumab, 5 patients to anakinra, and 6 to standard of care. All patients were included in the mITT population.

The primary objective of this study was to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection. The primary endpoint was treatment success, defined as not requiring IMV or ECMO by Day 15. The number and percentage of patients with treatment success were similar in each group, and there was no statistically significant difference in the number or percentage of patients with treatment success between emapalumab and standard of care, or between anakinra and standard of care.

In support of the primary objective, the secondary endpoints of time to mechanical ventilation; change from baseline in MEWS score, resting SpO_2, PaO_2/FiO_2, hemogasanalysis, oxygen supplementation, hyperinflammatory parameters, other relevant laboratory parameters were assessed. In comparison to standard of care, there was no statistically significant difference between either emapalumab or anakinra and the standard of care for these endpoints.

The secondary endpoints of changes in CT scan or X-ray findings; overall survival; and time to hospital discharge were also assessed. The number of patients in each group was too small to observe relevant differences between the treatment groups for these endpoints.

No clinically relevant trends were observed for the primary or secondary endpoint measures, however, the small number of patients in each treatment group and overall should be taken into account when reviewing these data.

The secondary objective of this study was to evaluate the safety and tolerability profile of emapalumab and anakinra in patients with SARS-CoV-2 infection. Seven out of 16 patients experienced TEAEs in the safety population: 4 (80.0%) in the emapalumab group, 2 (40.0%) in the anakinra group, and 1 (16.7%) in the standard of care group. The most common TEAE PT was respiratory failure (emapalumab: 2 patients [40.0%]; anakinra: 1 patient [20.0%]), and they were all assessed as SAEs resulting in death but not related to study treatment. All other TEAE PTs were reported in single patients, and no other SAEs were reported in this study. One patient in each treatment group experienced TEAEs that were considered related to study treatment and they were all mild to moderate in severity. Three patients experienced TEAEs that led to withdrawal of study treatment: 2 patients in the emapalumab group and 1 patient in the anakinra group. No new infections in the emapalumab group or severe neutropenia in the anakinra group were reported during the study.

No clinically relevant trends over time or differences between the treatment groups were observed in laboratory parameters, vital sign parameters, or other safety observations during the study, and results did not reveal any safety concerns. However, the small number of patients overall should be taken into account when reviewing these data. The presence of antidrug antbodies against emapalumab and anakinra, and the presence of neutralizing antibodies against anakinra were not collected for analyses, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment.

The exploratory objectives of this study included the assessment of the effect of anakinra and emapalumab on selected inflammatory biomarkers, evaluation of clinical status based on a 7-point ordinal scale, and evaluation of the PK of emapalumab and anakinra. The number of patients in each group was too small to observe relevant differences in the change from baseline in inflammatory biomarkers between emapalumab and standard of care or between anakinra and standard of care. Data on clinical status and PK samples was not collected, since protocol amendments 4 and 5 were not executed as they had not been approved at Italian sites before the end of recruitment.

13.2 Conclusions

Due to the small number of patients in each group, no firm conclusions can be made from the study, but the main results are presented below.

- No statistically significant difference in the number and percentage of patients with treatment success were observed between the emapalumab and standard of care groups, or between the anakinra and standard of care groups. No significant differences were observed between the treatment groups for any of the secondary or exploratory endpoints either.
- No new safety findings were observed. The safety and tolerability profile of both emapalumab and anakinra remains unchanged.

14 Tables and Figures

14.1 Demographic data

14.2 Efficacy data

14.3 Safety data

14.3.1 Displays of adverse events

14.3.2 Listing of deaths, other serious and clinically meaningful adverse events

14.3.3 Narratives of deaths, other serious adverse events and certain other clinically meaningful adverse events

Patient identifier	Reason for narrative
003-003	Serious adverse event; discontinuation due to adverse event; death
004-001	Serious adverse event; death
004-002	Serious adverse event; discontinuation due to adverse event, death

Patient identifier:	003-003
Treatment group:	Emapalumab
Criteria for the narrative:	Serious adverse event; discontinuation due to adverse event; death
Verbatim term:	End-stage respiratory failure
Preferred term/Coded term:	Respiratory failure
Patient demographics:	76 years old, female

Narrative:

Patient 003-003, a 76-year-old, white female was hospitalized prior to enrollment in the study for interstitial lung pneumonia, secondary to COVID-19. The patient was randomized to receive emapalumab, the first dose of which was administered on Day 1 at 6 mg/kg.

Medical history of particular interest included SARS-CoV-2 infection (diagnosed 8 days before randomization), interstitial pneumonia, hypertension, diabetes, chronic hematological disease, and malignant neoplasm (lymphoma). Other relevant medical history included hypothyroidism (start/end dates not reported) and hepatitis C (1994-1995). Prior and concomitant medications are presented in the table below.

The patient received her second and final dose of emapalumab at 3 mg/kg on Day 4.

The patient experienced severe respiratory failure (described as end-stage respiratory failure) on Day 7. The event was classified as a serious adverse event as it resulted in death.

Concomitant medication(s) on the start date of the event included azithromycin dihydrate; hydroxychloroquine; methylprednisolone; immunoglobulins; valganciclovir; insulin human; insulin; and primaquine. Concomitant medications may have also included acetylsalicylic acid; atovaquone; acyclovir; lamivudine; enoxaparin sodium; and levothyroxine (start/end dates not provided).

During hospitalization, the patient experienced progressive worsening of her condition with her respiratory function further deteriorating, with SaO_2 dropping to 75% on 15 L/min O_2, from a baseline of 92-94%. The treating physicians decided to permanently discontinue all medical treatments, including emapalumab.

As a result of the event of respiratory failure, the action taken with study drug was drug withdrawn and the patient was withdrawn from the study on Day 7. The outcome of the event of respiratory failure was fatal on Day 8. The event was considered not related to study drug. The

Investigator considered worsening of the disease under study, in addition to the patient's underlying lymphoma and hypothyroidism, as contributing factors to the event.

Prior and Concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/study day**
Acetylsalicylic acid	Unknown	100 (mg)	QD	Oral	
Azithromycin dihydrate	Fever due to disease under study	500 (mg)	QD	Oral	S: 2020-03-31/-24 E: 2020-04-30/7
Hydroxychloroquine	Disease under study	200 (mg)	BID	Oral	S: 2020-04-01/-23 E: 2020-04-30/7
Atovaquone	Disease under study	5 (mL)	BID	Oral	
Aciclovir	Disease under study	800 (mg)	QD	Oral	
Lamivudine	HBV prophylaxis	100 (mg)	QD	Oral	
Enoxaparin sodium	Medical history of particular interest	4000 (IU)	QD	Subcutaneous	
Levothyroxine sodium	Other relevant medical history: hypothyroidism	50 (mg)	QD	Oral	
Methylprednisolone	Disease under study	60 (mg)	QD	Other	S: 2020-04-03/-21 E: 2020-04-30/7
Remdesivir	Disease under study	100 (mg)	QD	Other	S: 2020-04-10/-14 E: 2020-04-19/-5
Immunoglobulins	Disease under study	30 (g)	ONCE	Other	S: 2020-04-13/-11 E: 2020-04-30/7
Valganciclovir	Disease under study	460 (mg)	BID	Oral	S: 2020-04-17/-7 E: 2020-04-30/7
Insulin human	Glucocortisoid-induced diabetes	4 (IU)	TID	Subcutaneous	S: 2020-04-19/-5 E: 2020-04-30/7
Insulin	Glucocortisoid-induced diabetes	14 (IU)	QD	Subcutaneous	S: 2020-04-20/-4 E: 2020-04-30/7
Primaquine	Disease under study	15 (mg)	QD	Oral	S: 2020-04-23/-1 E: 2020-04-30/7
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-24/1
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-25/2

Prior and Concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/study day**
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-26/3
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-27/4
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-28/5
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-29/6

Patient identifier:	004-001
Treatment group:	Emapalumab
Criteria for the narrative:	Serious adverse event; Death
Verbatim term:	Respiratory failure
Preferred term/Coded term:	Respiratory failure
Patient demographics:	70 years old, male

Narrative:

Patient 004-001, a 70-year-old, white male was randomized to receive emapalumab, the first dose of which was administered on Day 1 at 6 mg/kg.

Medical history of particular interest included SARS-CoV-2 infection and interstitial pneumonia. No other relevant medical history was reported. Prior and concomitant medications are presented in the table below.

The patient completed emapalumab treatment, as per protocol, receiving a further 4 infusions at 3 mg/kg, every 3 days, until Day 13, and then entered the follow-up period of the study.

The patient experienced severe respiratory failure (described as respiratory failure) on Day 41. The event was classified as a serious adverse event as it resulted in death.

Concomitant medication(s) on the start date of the event included enoxaparin; methylprednisolone; furosemide; and piperacillin sodium/tazobactam sodium.

The patient developed a progressive reduction of respiratory exchange most likely due to arterial-venous shunts associated with lung fibrosis and was treated with nitric oxide. The progressive disease due to COVID-19 infection led finally to terminal respiratory failure.

As a result of the event of respiratory failure, the action taken with study drug was not applicable as the patient had completed study treatment. The outcome of the event was fatal on Day 44. The event was considered not related to study drug. The Investigator considered disease under study and worsening of disease under study as contributing factors.

The patient discontinued the study on Day 44 due to death. An autopsy was not performed.

Prior and concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/Study day**
Nitric oxide	Respiratory failure	( )		Respiratory (inhalation)	
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-02/1
Enoxaparin sodium	Disease under study	6000 (IU)	QD	Subcutaneous	S: 2020-04-02/1 E: ONGOING
Enoxaparin	Disease under study	8000 (IU)	QD	Subcutaneous	
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-03/2
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-04/3
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-05/4
Methylprednisolone	Background therapy	20 (mg)		Intravenous	S: 2020-04-06/5
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-07/6
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-08/7
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-09/8
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-10/9
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-11/10
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-12/11
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-13/12

Prior and concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/Study day**
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-14/13
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-15/14
Furosemide	Disease under study	250 (mg)	TID	Other	S: 2020-04-19/18 E: ONGOING
Piperacillin sodium; tazobactam sodium	Disease under study	4.5 (g)	QID	Other	S: 2020-05-01/30 E: ONGOING
Methylprednisolone	Disease under study	20 (mg)	QD	Other	S: 2020-05-04/33 E: ONGOING

Patient identifier:	004-002
Treatment group:	Anakinra
Criteria for the narrative:	Serious adverse event; discontinuation due to adverse event, death
Verbatim term:	Respiratory failure
Preferred term/Coded term:	Respiratory failure
Patient demographics:	61 years old, male

Narrative:

Patient 004-002, a 61-year-old, white male was hospitalized prior to enrollment in the study for interstitial lung pneumonia, secondary to COVID-19. The patient was randomized to receive anakinra, the first doses of which were administered on Day 1 at 100 mg/kg QID.

Medical history of particular interest included SARS-CoV-2 infection (diagnosed 19 days before randomization), interstitial pneumonia, liver disease, and acute hepatitis C. Other relevant medical history included cirrhosis alcoholic (Child-Pugh score of A6, with portal hypertension [2011-ongoing]) and chronic hepatitis C (start/end dates not reported). Prior and concomitant medications are presented in the table below.

The patient experienced severe respiratory failure (described as respiratory failure) on Day 14. The event was classified as a serious adverse event as it was life-threatening and resulted in death.

The last dose of anakinra prior to the event was administered on Day 13.

Concomitant medication(s) on the start date of the event included fondaparinux; methylprednisolone; piperacillin/tazobactam; and teicoplanin.

During hospitalization, the patient's liver function deteriorated, reaching a Child-Pugh score of C10. His respiratory function progressively worsened, with O_2 saturations reportedly decreasing to below 80% in the 24 hours prior to his demise. Anakinra treatment was continued on Day 14 and the patient continued to receive noninvasive ventilatory support as the treating physicians did not consider mechanical ventilation to be an option due to his underlying severe liver disease. The patient continued to deteriorate and died on Day 15, due to respiratory failure.

As a result of the event of respiratory failure, the action taken with study drug was drug withdrawn, as the patient did not receive the final anakinra infusions on Day 15. The outcome of the event was fatal on Day 15 and the event was considered not related to study drug.

The final dose of anakinra was administered on Day 14. The patient discontinued the study on Day 15 due to death.

Prior and concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/Study day**
Hydroxychloroquine	Antiviral	200 (mg)	BID	Oral	S: 2020-03-28/-6 E: 2020-04-12/10
Ceftriaxone	To prevent or treat bacterial superinfection	2 (g)	QD	Other	S: 2020-03-29/-5 E: 2020-03-30/-4
Azithromycin	To prevent or treat bacterial superinfection	500 (mg)	QD	Oral	S: 2020-03-29/-5 E: 2020-04-09/7
Piperacillin; tazobactam	To prevent or treat bacterial superinfection	9 (g)	BID	Other	S: 2020-03-30/-4 E: 2020-04-07/5
Methylprednisolone	Background therapy	20 (mg)			S: 2020-04-03/1
Methylprednisolone	Background therapy	20 (mg)		Intravenous	
Fondaparinux	Antithrombotic (prophylaxis)	2.5 (mg)	QD	Subcutaneous	S: 2020-04-03/1 E: 2020-04-16/14
Methylprednisolone	Background therapy	20 (mg)			S: 2020-04-04/2
Methylprednisolone	Background therapy	20 (mg)		Intravenous	
Methylprednisolone	Background therapy	20 (mg)			S: 2020-04-05/3
Methylprednisolone	Background therapy	20 (mg)		Intravenous	
Methylprednisolone	Background therapy	20 (mg)			S: 2020-04-06/4
Methylprednisolone	Background therapy	20 (mg)		Intravenous	

Prior and concomitant medications					
Medication	**Indication**	**Dose**	**Frequency**	**Route**	**S: Start date/Study day** **E: End date/Study day**
Methylprednisolone	Background therapy	20 (mg)			S: 2020-04-07/5
Methylprednisolone	Background therapy	20 (mg)		Intravenous	
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-08/6
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-09/7
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-10/8
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-11/9
Methylprednisolone	Background therapy	10 (mg)		Intravenous	S: 2020-04-12/10
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-13/11
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-14/12
Teicoplanin	Not specified infection	400 (mg)	BID	Other	S: 2020-04-14/12 E: 2020-04-14/12
Piperacillin; tazobactam	Not specified infection	9 (g)	QD	Other	S: 2020-04-14/12 E: 2020-04-16/14
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-15/13
Teicoplanin	Not specified infection	400 (mg)	QD	Other	S: 2020-04-15/13 E: 2020-04-16/14
Methylprednisolone	Background therapy	5 (mg)		Intravenous	S: 2020-04-16/14

14.3.4 Data listings (each patient) for abnormal clinically meaningful laboratory values, vital signs, physical examinations and other observations related to safety

14.4 Other data

15 Reference list

Not applicable for abbreviated CSR

16 Appendices

Appendix 16.1 Study information

Appendix 16.1.1 Protocol and protocol amendments

Appendix 16.1.2 Sample case report form

Appendix 16.1.3 List of IECs or IRBs (not applicable for this abbreviated CSR)

Appendix 16.1.4 List and description of investigators and other important participants in the study (not applicable for this abbreviated CSR)

Appendix 16.1.5 Signatures of principal/coordinating Investigator and/or sponsor's responsible medical officer

Appendix 16.1.6 List of investigational product(s) batch numbers (not applicable)

Appendix 16.1.7 Randomization scheme and codes (not applicable for this abbreviated CSR)

Appendix 16.1.8 Audit certificate(s) (not applicable for this abbreviated CSR)

Appendix 16.1.9 Documentation of statistical methods

Appendix 16.1.10 Documentation of inter-laboratory standardisation methods and laboratory QA procedures if used (not applicable for this abbreviated CSR)

Appendix 16.1.11 Publications based on the study (not applicable for this abbreviated CSR)

Appendix 16.1.12 Important publications referenced in the report (not applicable for this abbreviated CSR)

Appendix 16.1.13 Optional appendix

Appendix 16.2 Patient data listings

Appendix 16.2.1 Discontinued subjects

Appendix 16.2.2 Protocol deviations

Appendix 16.2.3 Subjects excluded from the efficacy analysis

Appendix 16.2.4 Demographic data

Appendix 16.2.5 Compliance and/or drug concentration data

Appendix 16.2.6 Individual efficacy response data

Appendix 16.2.7 Adverse events listing

Appendix 16.2.8 Individual laboratory measurements and other safety observations

Appendix 16.3 Case report forms

Appendix 16.3.1 CRFs for death, other SAEs and withdrawal for AE

Appendix 16.3.2 Other CRFs submitted (not applicable for this abbreviated CSR)

Appendix 16.4 Individual subject data listing (see Appendix 16.2)