STUDY PROTOCOL

COMPACT-2

(COMbining Plasma-filtration and Adsorption Clinical Trial-2)

Efficacy and safety of high dose CPFA (Coupled Plasma Filtration Adsorption) for Septic Shock in the ICU

GiViTI Experimental Study

Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva
(Italian Group for the Evaluation of Interventions in Intensive Care Medicine)

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SUMMARY

1. INTRODUCTION

1.1 General overview and study rationale

Septic shock is a complex, life-threatening clinical condition characterized by cardiovascular abnormalities as a consequence of infection.

Hospital mortality in these patients remains high: 57.4% in the GiViTI (Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva) cohort in 2010 [1], in line with other European statistics [2, 3].

Sepsis is currently thought as the result of an acute imbalance between pro- and anti-inflammatory mediators. Accordingly, one of the targets of the treatment is to re-establish the homeostasis of these mediators [4]. In this framework, the rationale for using extracorporeal depurative techniques consists in the removal of a large spectrum of molecules, in order to reset the possible imbalance among different types of mediators.

One of these techniques is CPFA (coupled plasmafiltration adsorption) that uses a sorbent once the separation between plasma and blood has been obtained with a plasmafilter. The sorbent consists of a synthetic resin in a cartridge housing. Pre-clinical and clinical studies have shown encouraging results [5-7], that led GiViTI to organize a randomized clinical trial (named COMPACT) in 2007 to evaluate the efficacy and safety of CPFA in the treatment of patients with septic shock in the intensive care unit (ICU). The study has been interrupted earlier than expected due to negative results at the planned interim analysis [8]. No difference in hospital mortality was observed between the control (44/93, 47.3%) and experimental group (41/91, 45.1%, p=0.76). A high number of protocol violations, in terms of low volume of plasma treated with CPFA, has however been observed. A pre-planned subgroup analysis showed that patients receiving a CPFA dose of >0.18 L/kg/day in the first 3-5 days had a lower mortality compared to controls (OR 0.36, 95%-CI 0.13-0.99). This result generated the hypothesis that CPFA might be effective, if a high volume of plasma were treated. Interestingly, regional anticoagulation with citrate is now available for CPFA making the technique easier, with the possibility to reach much higher volume of plasma treated, compared to the previous system [9-11].

In the light of these results, several centers continued to use CPFA in their clinical practice, although the clinical evidence cannot be considered satisfactory. For this reason, GiViTI launched the COMPACT-2 study, aimed at evaluating the efficacy and safety of high dose CPFA in the treatment of patients with septic shock in the ICU.

1.2 The GiViTI group

GiViTI is a network of Italian ICUs formed in 1991. The mission of the group is to promote and carry out independent research projects, oriented to the evaluation and improvement of intensive care medicine. At present, around 430 Italian ICUs join the GiViTI group.

Since 2002, the project "Margherita" (*Daisy* in English) for the continuous evaluation of ICU performance

is active. All the information are clearly defined and collected with a dedicated software, in order to guarantee the maximum conformity among the ICUs. A multitude of validity checks were done concurrently during the data entry. Thanks to the modular structure of the software, it is easy to expand the core data collection (the "Core" of the Margherita) to fulfill the requirements of specific research projects (the "Petals" of the Margherita). In this way, the software increases both the efficiency and quality of the research work in each department.

1.3 CPFA

CPFA is a specific method for the treatment of sepsis. It consists of:

1. a plasma-filter (polyethersulfone 0.45 m^2)
2. a hemofilter (polyethersulfone 1,4 m^2)
3. a cartridge (contains approximately 140 ml of hydrophobic styrenic resin)

The kit is lodged in the Bellco "Amplya" machine (Bellco Mirandola, Italy). The treatment consists of the separation of plasma from the whole blood with adsorption of the inflammatory mediators and cytokines from the plasma, and a subsequent purification step by way of a hemofilter.

2. STUDY OBJECTIVE

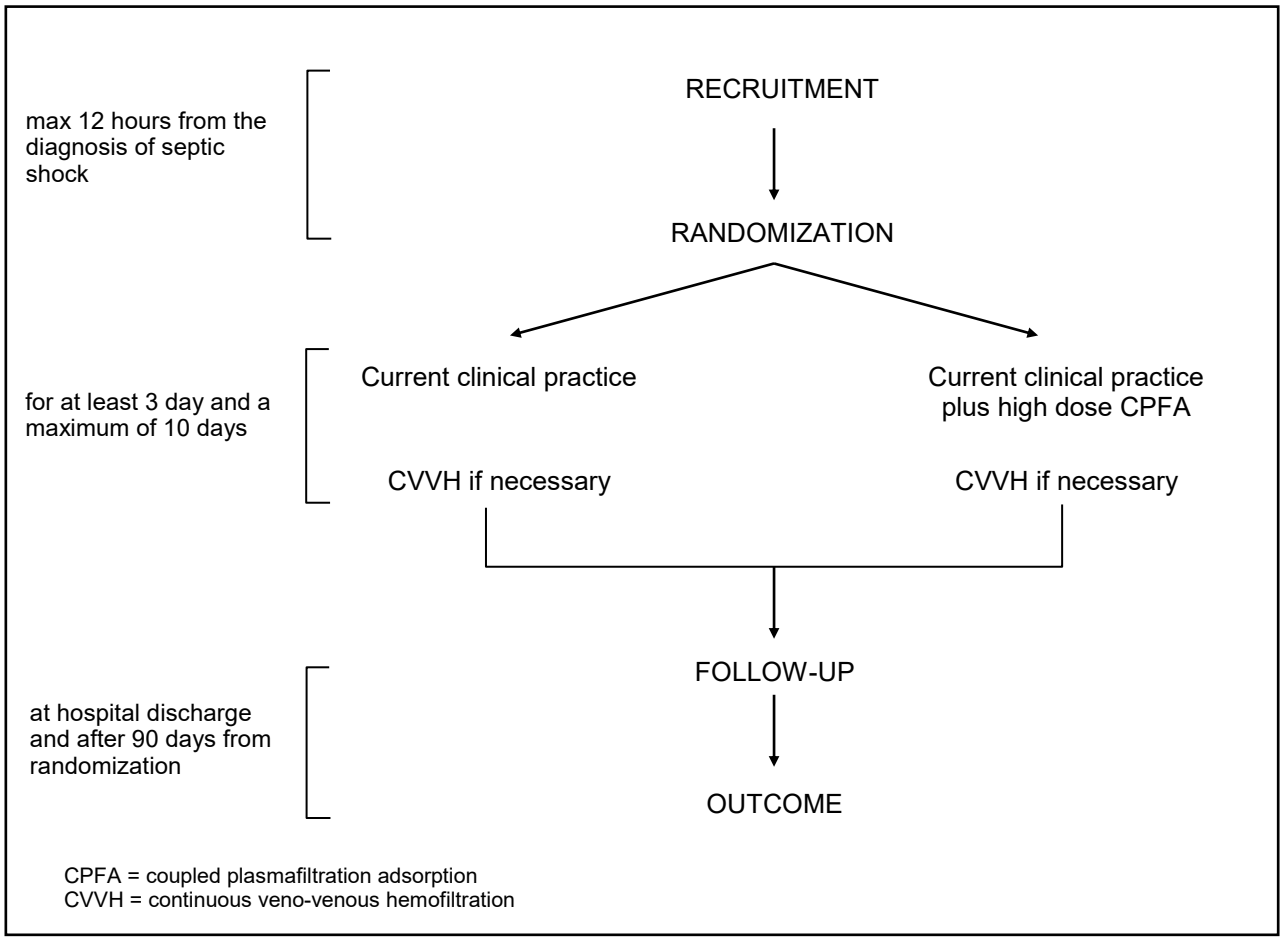
The study objective is to clarify whether the use of high dose CPFA, which guarantees an elevated volume of plasma treated, in addition to the current clinical practice is able to reduce hospital mortality of septic shock patients in ICU.

The secondary objective of the study is to determine whether high dose CPFA can increase the probability to recover from septic shock and reduce the length of ICU stay.

3. STUDY DESIGN

The clinical study will consist of a multicenter randomized controlled adaptive trial in which eligible patients will be randomized into two arms: current clinical practice for the treatment of septic shock (control arm) and current clinical practice plus high dose CPFA (experimental arm). The flow-chart of the study is presented in figure 1.

Figure 1.



a) Centers recruitment period: to guarantee the best possible treatment to the enrolled patients, a residential course on the treatment of septic shock, the use of extracorporeal depurative techniques, and the use of CPFA in critically ill patients will be organized.
b) Study period: eligible patients will be identified and enrolled in the study. They will have to follow their assigned treatment according to the protocol. In case of a second episode of septic shock, the originally assigned treatment should still be followed.
c) Follow-up: data of the recruited patients will be monitored and recorded. Health status upon hospital discharge and at 90 days from randomization will be collected. In this context, hospital discharge is intended as the discharge from the last hospital, for patients transferred to other hospital.
d) Adaptive design: two interim analyses will be performed, to decide whether to continue the study. The first will be based on protocol feasibility, the second on the treatment efficacy against an intermediate endpoint.

4. PARTICIPATING CENTERS

The study will include Italian adult ICUs adhering to the GiViTI group, who regularly use CPFA in the

treatment of septic shock. Since this is a spontaneous independent study, it will not be possible to reimburse ICUs for their participation, nor to provide them with required material. For this reason, the study is reserved to ICUs that, based on the promising but still incomplete evidence available, the results of the COMPACT study, and their specific experience, have decided to use CPFA in their routine practice. In other words, we ask these centers to use CPFA within a research program that will eventually inform on the real efficacy of the treatment.

5. STUDY POPULATION

5.1 Inclusion Criteria

All patients admitted to the ICU in septic shock or who develop septic shock while in the ICU will be eligible. Definition of septic shock is that provided by the international literature [12, 13] and reported in the annex 1. Patients will be considered eligible for the study only if it will be possible to initiate CPFA in less than 12 hours from the diagnosis of septic shock.

5.2 Exclusion Criteria

Patients with any of the following characteristics will not be eligible to the study:

- age less than 14 years
- pregnancy
- estimated life expectancy less than 90 days, according to clinical judgment
- presence of relative or absolute contraindications to extracorporeal depurative technique
- admission from another ICU where the patient remained for more than 24 hours
- absence of informed consent

6. STUDY PLAN AND METHODS

6.1 Recruitment of the Centers

The protocol will be presented and discussed with all eligible centers during a preliminary meeting. A residential course will be held for centers that give availability to participate in the study. The course will address the theoretical and practical aspects of the diagnosis and treatment of septic shock, as well as the CPFA technique.

6.2 Study Protocol

Eligible patients will be identified upon admission or during the stay in the ICU and randomized. Baseline data from each patient will be collected using the software MargheritaPROSAFE. A special module of the software will be developed to include the specific data required for the study (Petal COMPACT-2). The

randomization will be made by the software, according with the GiViTI standard operating procedures (SOP).

6.2.1 Control arm

Patients randomized to the control arm will be treated according to the ICU current clinical practice. The use of high-flow continuous venovenous hemofiltration is not allowed.

6.2.2 Experimental arm

Patients randomized to the experimental arm will be treated according to the ICU current clinical practice, with the addition of high dose CPFA. This means that the minimum volume of plasma treated per day should be greater than 0.2 L/kg/day.

The CPFA treatment should be initiated as early as possible but no later than 12 hours after the diagnosis of septic shock. It will be applied intermittently, lasting at least the time needed to reach the minimum target of volume to be treated, and could be followed by continuous renal replacement therapy in patients with renal failure. In any case, the CPFA duration should not be lower than 10 hours per day. CPFA will be repeated for a minimum of three and a maximum of ten consecutive days after randomization. After three days of treatment, CPFA will be discontinued if the patient will no longer be in septic shock, according to criteria reported below.

In case of admission during the afternoon or evening, the CPFA treatment on the second day will be anticipated to avoid further night-time treatments.

The blood flow must be maintained between 150 and 220 ml/min, while the plasma flow is controlled by filtration fraction of 10-22% of the blood flow. More specifically, the filtration fraction should be set to 10% in the first hour, then it should be gradually increased to 12%, 15% and finally to the target value of 22% (see operative manual). Regional anticoagulation with citrate is recommended, according to the protocol reported in the operative manual. The solution reinfused, sterile and pyrogen free, is described in the operative manual. All fluids must be administered at room temperature. Patient temperature must be maintained within physiologic limits. During the treatment it is possible to observe a reduction in temperature, which has to be maintained above 35°C.

6.3 Follow-up

The clinical follow up starts the day of randomization and finishes at the discharge from the ICU. During ICU stay, the daily SOFA score (Sequential Organ Failure Assessment) [14] will be recorded, together with further parameters to assess the various organs' function. The vital status will be recorded at ICU discharge, at hospital discharge, and at 90 days from the randomization. For patients discharged to other hospital, "vital status at hospital discharge" will be intended as the vital status at the discharge from the latest hospital in which the patients stayed.

6.4 Study Monitoring

Plenary meetings will be organized with all participating centers during the study period. The centers will be visited at least twice a year, with more frequent visits for centers with lower than expected recruitment rate or with a high number of protocol violations. A telephone line will be available 24 hours a day for any problems related to the protocol. In addition, both an expert intensivist and an expert nephrologist will be available for ad hoc visits to solve any further problem.

Data will be centrally monitored by GiViTI Coordinating Center, according to its SOP. Doubts about the data received will be discussed and solved with the centers.

7. SAFETY AND EFFICACY PARAMETERS

In agreement with the study rationale, lower mortality is expected in patients treated with high dose CPFA, compared to patients treated according to standard practice. Since in the first COMPACT study the target volume of plasma treated was reached only in one third of the patients, the feasibility of high dose CPFA should be guaranteed. Thus, although the data reported in the literature are reassuring in this regards when regional anticoagulation with citrate is used, an interim analysis on feasibility will be performed to decide the study continuation. Furthermore, since the COMPACT study was overall negative, a second interim analysis will be performed on clinical intermediate endpoints. Only if the interim analyses will be positive the study will continue till the achievement of the target size for the final outcome.

In light of these considerations, the following primary and secondary endpoints were chosen, for the different steps:

7.1 First interim analysis: feasibility

The aim of the first interim analysis is to assess the true feasibility of the study protocol.

Primary endpoint

- Percentage of patients with more than 0.2 L/kg/day of plasma treated with CPFA for at least three days.

Stopping rule → The study will continue only if this percentage will be greater than 90%.

7.2 Second interim analysis: activity

The aim of the second interim analysis is to assess the activity of high dose CPFA in increasing the probability to recover from septic shock.

Primary endpoint

- Days free of shock in the first 15 days from randomization.

The operative definition of shock is referred to a cardiovascular SOFA component > 2, or lactate > 4 mmol/L with $ScvO_2$ < 50% [15].

Stopping rule → The study will continue only if high dose CPFA will be able to increase the time free of shock of at least 2.5 days in the first 15 after randomization.

7.3 Final analysis: efficacy

The final analysis will address the hypothesis that high dose CPFA is able to reduce mortality of patients with septic shock. Only in this phase, secondary endpoints and subgroup analysis will be considered.

Primary endpoint

- Mortality at hospital discharge. For patients discharged to other hospital, it will be intended as mortality at the discharge from the latest hospital in which the patients stayed.

The correct primary endpoint of clinical trials in septic shock is still debated [16]. Most have adopted 28-day mortality due to FDA stipulations. However, the mortality rate attributable to sepsis continues long after the initiation of the acute event [17]; indeed, in the first COMPACT study 16.8% of patients of were still in the ICU beyond 28 days after randomization. On the other hand, over-extending the follow-up period has the disadvantage of diluting the phenomenon, with the inclusion of competing causes of death. We thus considered mortality at the time of discharge from the last hospital into which they were admitted following their septic shock episode. At that point, the patient no longer requires aggressive, specialized, interdisciplinary care, which means he or she had survived the septic shock episode. In other words, our objective is to assess whether high dose CPFA is able to help patients surviving the acute phase of septic shock.

Secondary endpoint

- Mortality within 90 days from randomization. With this endpoint it will be possible to evaluate whether a possible benefit obtained at short term (hospital discharge) is maintained afterwards.
- Days spent outside the ICU during the first 30 days from randomization. With this endpoint it will be possible to determine whether high dose CPFA can reduce the complexity of care of these patients.

Subgroup analyses

Hospital mortality will be compared between control group and two mutually exclusive subgroups: patients starting CPFA within 6 hours from septic shock onset and those who started it afterwards.

7.4 Safety parameters

Adverse events will be registered and classified according to what reported in section 9.

8. STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

8.1 Rationale for the sample size

8.1.1 First interim analysis: feasibility

As established in paragraph 7.1, the study will continue only if the target volume of plasma treated will be reached in more than 90% of the patients. To take into account for the estimate uncertainty, expressed as confidence interval (CI) of the percentage, the criteria for the study to be continued will be the following:

- After the first 20 patients in the experimental group, at least 13 (95% CI: 44-86%) will have to have reached the target volume of plasma treated.
- After the first 30 patients in the experimental group, at least 22 (95% CI: 58-89%) will have to have reached the target volume of plasma treated.
- After the first 50 patients in the experimental group, at least 39 (95% CI: 66-90%) will have to have reached the target volume of plasma treated.

8.1.2 Second interim analysis: activity

In the first COMPACT study, the number of days free of shock in the first 15 days from randomization has been 8.2 in the control group (SD, 5.7). A sample of 166 patients (83 in each arm) is needed to have 80% power to detect a difference of 2.5 days in the primary endpoint (corresponding to a relative increase of 30% in the treated group, from 8.2 to 10.7), with 5% type one error and using a two-tailed *t* test.

8.1.3 Final analysis: efficacy

In the COMPACT study, hospital mortality in the control group was 47%, while in the subgroup treated with high dose CPFA in the first three days it was 32%. To have 80% power of detecting such a difference with 5% type one error, 332 patients are needed. Increasing this estimate by about 5% to compensate possible subjects lost from the study, a total of 350 will have to be randomized.

A simulation with GiViTI data shows that time needed to enroll 350 patients with septic shock in 15 ICUs should be approximately three years.

8.2 Statistical analyses

Statistical analyses will be conducted at the GiViTI Coordinating Center.

Analyses will consider two different populations: the one defined by the "intention to treat" and the one defined by the "adhesion to the protocol". The first one will involve all randomized patients according to the arm they were originally assigned, the second one will involve patients that did not have relevant protocol violations. Interim analyses will be conducted only by intention to treat.

8.2.1 First interim analysis: feasibility

In this phase, the percentage of patients in the CPFA arm for whom the target of volume of plasma treated (at least 0.2 L/kg/day in the first 3 days) is achieved will be computed along with its 95% confidence interval, the latter calculated through the binomial distribution.

8.2.2 Second interim analysis: activity

The number of days free of shock in the first 15 days from randomization will be compared between the two study groups with the Mann-Withney U test or the Student *t* test.

8.2.3 Final analysis: efficacy

The principal analysis will compare hospital mortality in the two study groups with the Pearson chi-square test and will be carried out by intention to treat. The "per protocol" analysis will be done just to evaluate the impact on results of possible protocol violations.

In the case of important imbalances in potential prognostic factors between the two study groups, a multivariable logistic regression model will be used to adjust the estimates.

8.2.4 Secondary analyses

The secondary analysis will use the *t* test or the Mann-Whitney U test to compare the number of days spent outside the ICU during the first 30 days from randomization.

Survival curve, constructed with the Kaplan-Meier method, will be used to evaluate survival time within 90 days. Comparison of the curves will be done with the log-rank two-tailed test with α = 0.05. Any adjustments for confounding variables will be made using the Cox model.

8.2.5 Interim Analyses

A single interim analysis on primary endpoint (hospital mortality) will be performed using the Pearson chi-square test, once 166 patients have been enrolled. The study will be terminated for efficacy if the Haybittle-Peto criterion for multiple comparison will be satisfied. More specifically, any difference will be considered statistically significant if the *p*-value of the test will be lower than 0.01.

Conversely, the study will be interrupted for futility if the conditional power of obtaining a positive result at the end the study, under the main hypothesis used to compute the sample size, would be lower than 10%.

8.2.6 Subgroup analyses

Subgroup analyses will be conducted only on hospital mortality, using the Pearson chi-square or the Fisher exact test.

9. ADVERSE EVENTS

9.1 Definition

In the field of intensive care medicine, the incidence of critical events during the stay in the ICU is high by definition. For this reason, only unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease probably related to the experimental technique will be take into account.

9.2 Monitoring of adverse events

All patients showing a serious adverse event (as described above), will be monitored until the symptoms disappear, or the laboratory values return to normal, or until a reasonable explanation of the observed changes emerges, or until death. In the last case, the pathologist report should be provided, whenever possible.

All adverse events must be recorded on an ad hoc form, which includes: type of adverse event, severity (mild, moderate, severe), date and hour of occurrence, duration or date of resolution, any interventions performed, and the relationship of the event to the experimental technique.

The Coordinating Center will supply a copy of these reports to the External Data and Safety Monitoring Committee. No special procedure for recording non-serious adverse events will be required.

The Coordinating Center will routinely release reports on adverse events to the participating centers and their local Ethical Committees.

10. INTERRUPTION OF THE STUDY

10.1 Withdrawal from the study

The patients will have to interrupt the study for any of the following reasons:

- occurrence of serious adverse events related to the treatment;
- refusal to participate;
- the physician maintains that it is in the best interest of the patient to interrupt treatment.

The withdrawal reason and date must be documented. In any case, the centers will have to follow all randomized patients as outlined in the follow-up section.

10.2 Interruption of center participation

The participation of any center in the study can be prematurely interrupted for any of the following reasons:

- High rate of protocol violation
- Failure to randomize patients within 3 months from start-up

The decision of the premature interruption of a center will be taken by the Scientific Committee.

10.3 Data Input

Data will be collected with the MargheritaPROSAFE software, supplied free of charge to all participating centers. A specific module (Petal COMPACT-2) will be developed for the data collection.

11. EHTICAL CONSIDERATIONS

The study will be conducted according with Good Clinical Practice (Ministry decree 15 July 1997 "Recepimento delle linee-guida dell'Unione Europea di buona pratica clinica per la esecuzione delle sperimentazioni cliniche dei medicinali").

The protocol will be approved by the local Ethical Committees.

A continuous monitoring of the study, with particular attention to the safety profile of the experimental treatment, will be carried out by the Coordinating Center.

Coordinating Center will be responsible of:

1. maintaining contacts with participating centers;
2. monitoring the study participation;
3. assuring data quality;
4. data management;
5. statistical analyses

11.1 Informed consent

Before enrollment, all patients will be informed regarding the study's objectives, procedures and correlated risks. A specific information leaflet, to be reviewed by the Ethical Committees, has been developed. All patients will receive this before enrollment and will sign it once all doubts have been clarified.

In case the patient would not be able to give consent, the instructions provided by the National Ethics Committee in the document titled "La sperimentazione clinica in pazienti adulti o minori che non sono in grado di dare il consenso informato in situazioni di urgenza", 16 Ottobre 2012. More specifically, the recommendations at points d, e, f of the conclusions section are particularly important:

"The National Ethics Committee:

[omitted]

d) believes that in the face of incapacitated adults or children, consent to clinical trials can be given by the legal representative or by other persons identified by the legislator, in accordance with criteria already adopted in other circumstances where the health of the persons is involved;

e) considers necessary, as far as possible, to take into account the desire of the patient, as previously expressed in a formal and controlled way (e.g., through electronic health records) regarding a possible trial. "Deferred consent" of the patient, should (s)he regain capacity, or of the legal representative if the failure persists, should always be pursued;

f) in case it is still impossible to obtain consent in due time by the aforementioned individuals or ascertain

their previous will, the National Ethics Committee believes necessary to entrust the decision to include the patient in the trial to the attending physician or the medical team, who must adhere to the conditions, measures and methods described in the protocol approved by the Ethics Committee.

11.2 Privacy protection

In accordance with the Italian privacy protection law (decree 196/03), patients will be informed about the treatment of their personal data, including security policies and data ownership. Patients or legal representatives will be asked to give written consent to use their personal data, according to the current legislation.

12. STUDY ORGANIZATION

The study will be centrally coordinated at the GiViTI Coordinating Center, "Mario Negri" Institute for Pharmacological Research, Villa Camozzi, 24020 Ranica (Bergamo), Italy. The principal Investigators and the persons in charge of the Scientific Committee will have scientific and operative responsibilities. The External Data and Safety Monitoring Committee (EMC) will receive regular reports on patients recruitment, quality of data, treatment safety, and interim analyses results, not masked as to treatment assignment. EMC will have the authority to ask preliminary analyses or any other information related to the study conduction.

12.1 Committees

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* To be confirmed

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