Efficacy of ketamine in refractory convulsive status epilepticus in children: a sequential-design, multicentre, randomized, controlled, open-label, non-profit trial (KETASER01)

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Efficacy of ketamine in refractory convulsive status epilepticus in children: a sequential-design, multicentre, randomized, controlled, open-label, non-profit trial (KETASER01)

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**Keywords:** refractory status epilepticus, ketamine, children, anaesthetics, endotracheal intubation

**Word count:** 2450
ABSTRACT

Introduction:

Status epilepticus (SE) is a life-threatening neurological emergency. SE lasting longer than 120 minutes and not responding to first- and second-line antiepileptic drugs is defined as “refractory” (RCSE) and requires intensive care unit treatment. There is currently no evidence or consensus to guide both the optimal choice of therapy and treatment goals for RCSE, which is generally treated with coma induction using conventional anaesthetics (high dose midazolam, thiopental and/or propofol). Increasing evidence indicates that ketamine (KE), a strong N-methyl-D-aspartate glutamate receptor antagonist, may be effective in treating RCSE. We hypothesized that intravenous KE is more efficacious and safe than conventional anaesthetics in treating RCSE.

Methods and analysis: A multicentre, randomized, controlled, open-label, non-profit, with sequential-design study will be conducted to assess the efficacy of KE compared with conventional anaesthetics in the treatment of RCSE in children. Ten Italian centres/hospitals are involved in enrolling 57 patients aged 1 month to 18 years with RCSE. Primary outcome is the resolution of SE up to 24 hours after withdrawal of therapy and is updated for each patient treated according to the sequential method.

Ethics and dissemination: The study received ethical approval from the Tuscany Paediatric Ethics Committee (12/2015). The results of this study will be published in peer-reviewed journals and presented at international conferences.

Trial registration number: Protocol version 02 of October 21, 2014; EudraCT number 2013-004396-12; ClinicalTrial.gov identification number: NCT02431663.
INTRODUCTION

Background and Rationale

Status epilepticus (SE) is a life-threatening neurological emergency traditionally defined as ‘an acute epileptic condition characterized by continuous seizures for at least 30 minutes, or by 30 minutes of intermittent seizures without full recovery of consciousness between seizures’.\[1\] Convulsive SE is the most common and harmful form. There is now consensus, based on an improved understanding of pathophysiology, that any seizure lasting longer than five minutes should be treated as SE.\[2\]

SE lasting longer than 120 minutes and not responding to first- (benzodiazepines) and second-line (midazolam at high dose, phenytoin and phenobarbital) antiepileptic drugs (AEDs) is defined as “refractory” and requires intensive care unit (ICU) treatment \[2\]. The term “super-refractory” defines SE that continues, or recurs, for 24 hours or longer or recurs after withdrawal of the anaesthetic therapy.\[3\]

Even with current best practices, neurological sequelae occur in >50% of children with refractory convulsive status epilepticus (RCSE).\[4,5\] The mortality rate of RCSE ranges between 2.7 and 5.2%, and increases up to 5-8% when only ICUs admission are taken into account.\[4,5\]

There is general consensus regarding the first- and second-line treatments of SE. Although the types of drugs available are similar in different countries, algorithms/protocols may differ among countries and even among different institutions in the same country; there is currently no evidence or consensus to guide both the optimal choice of therapy and treatment goals for RCSE.\[3,6-8\] RCSE is generally treated with coma induction using high dose midazolam (MDZ) or conventional anaesthetics such as thiopental (TPS) or propofol (PR),\[6-8\] which all require endotracheal intubation, a negative prognostic factor of morbidity and mortality.\[9-11\] All conventional anaesthetics commonly used in RCSE act on inhibitory-$\gamma$-aminobutyric acid (GABA$\_A$) receptors.\[6-8\] Experimental models suggest that, with continuing seizures, GABA$\_A$ receptors are internalized in clathrin-coated vesicles, and excitatory N-methyl-D-aspartate (NMDA) receptors are
mobilized to the membrane.[12,13] This receptor trafficking results in decreased inhibitory control and increased excitation that may foster SE.[12,13] Conventional anaesthetics will therefore be less active, making higher doses necessary, which will in turn enhance their adverse events, especially hypotension, requiring vasopressor administration.[11] In this scenario, NMDA modulating molecules, such as ketamine (KE), represent an attractive treatment alternative for SE.[14]

Increasing evidence indicates that KE, a strong NMDA glutamate receptor antagonist, may be effective in treating RCSE.[14] Due to its sympathomimetic action KE has no cardiac depressant properties and does not cause hypotension.[15] KE use does not necessarily require amine administration or mechanical ventilation. Its administration, therefore, does not imply emergent endotracheal intubation, a prognostic factor of increased morbidity and mortality risk in critically ill adults and children.[9-11] Between 15 and 39% of emergent endotracheal intubations in adults are associated with one or more complications including severe hypoxemia, hemodynamic collapse, and death.[9,11] The complication rate is even higher in the paediatric population, in which acute deterioration can occur rapidly as a result of age-related differences in physiology, oxyhemoglobin dissociation, oxygen consumption, and pulmonary mechanics.[10] Large doses of KE and rapid intravenous boluses may cause hallucinations, which are less frequent in children than in adults and can be reduced with benzodiazepine premedication.[15] Moreover, KE exerts a neuroprotective action by preventing the transduction of signals to destructive intracellular mechanisms through the blockade of NMDA receptors.[15,16]

The literature contains good evidence about efficacy and safety of KE in both the adult and paediatric RCSE populations.[3,14] However, the heterogeneity of prior treatments, timing of KE administration, and KE dosage and duration make available information on seizure responsiveness difficult to interpret.

In November 2009 the Paediatric Neurology Unit at the Meyer Children’s Hospital (Florence, Italy) adopted a treatment protocol for RCSE including intravenous KE infusion.[17] As of January 2013, in order to avoid mechanical ventilation, we have used KE (Ketamina®, Molteni
S.p.A., Italy) before considering conventional anaesthetics.[18]

Our paediatric series [17,18] shows that treatment with KE in RCSE is effective and safe and its use could be considered before TPS and PR, unless specific contraindications exist. Based on these encouraging results, we designed a nationwide multicentre randomized sequential trial that has been approved by the Italian Medicines Agency and includes ten paediatric hospitals (EudraCT number 2013-004396-12; ClinicalTrial.gov identification number: NCT02431663).

**Objectives**

We hypothesized that intravenous KE is more effective and safer than conventional anaesthetics (high dose MDZ, TPS and/or PR) in treating RCSE.

*Primary objective:*

To assess the efficacy of KE compared with conventional anaesthetics in the treatment of RCSE in children.

*Secondary objective:*

To assess the short-time safety profile of KE compared with conventional anaesthetics and, in particular, to evaluate the possibility of administering KE, thus avoiding mechanical ventilation.

**METHODS AND ANALYSIS**

**Study design**

KETASER01 is an Italian, multicentre, randomized, controlled, open-label, non-profit, study with sequential design (ClinicalTrials.gov identifier: NCT02431663) involving ten centres/hospitals.

**Study setting**

Patients will be enrolled and treated in the ICUs at ten Italian hospitals: 1) Meyer Children's Hospital, Florence; 2) Bambino Gesù Children's Hospital, IRCCS, Rome; 3) Gemelli Hospital, Catholic University, Rome; 4) University Hospital, Padua; 5) Ospedali Riuniti, Ancona; 6)
University Hospital, Verona; 7) Burlo Garofolo Institute for Maternal and Child Health, IRCCS, Trieste; 8) Regina Margherita Children’s Hospital, Turin; 9) Buzzi Children's Hospital, ICP, Milan; 10) Sant'Orsola-Malpighi University Hospital, Bologna.

Patients will be randomized to the intervention arm or control arm with a computer-assisted system.

Block randomization with fixed size blocks and age stratification (<4, 5-10, and 11-18 years) will be used.

**Eligibility criteria**

**Inclusion criteria**

Patients are eligible if (1) they are aged 1 month to 18 years of age, (2) they present with SE refractory to first- (benzodiazepines per os or pr) and second-line (phenytoin 20 mg/kg and/or phenobarbital 20 mg/kg and midazolam up to 6 mcg/kg/min) antiepileptic drugs, (3) their parents provide written consent.

**Exclusion criteria**

Patients will be excluded if (1) they have a contraindication to the use of one of the drugs in the study protocol, (2) they have a presumed or ascertained pregnancy status, (3) they had already been enrolled in the KETASER01 study for an antecedent RCSE episode.

Patients with RCSE that is not responsive to first- and second-line drugs will be transferred from the neurological department to the ICU. They will be enrolled in the study by the neurologist and anaesthesiologist in the ICU after assessing the eligibility criteria and obtaining informed consent from the parents.

**Interventions**

**The experimental arm: KE**

KE is administered starting with an initial bolus of 2-3 mg/kg followed by continuous infusion of 10 mcg/kg/min, increasing the infusion rate by 5-10 mcg/kg/min every 10 minutes up to...
a maximum of 100 mcg/kg/min, with every increment being preceded by a bolus of 1-2 mg/kg. KE is always administered in association with 2-4 mcg/kg/min MDZ. For patients treated with continuous infusion of MDZ (second-line therapy) for less than 5 days, the dosage of the benzodiazepine is reduced from 6 mcg/kg/min to 2 mcg/kg/min to prevent the emergence reactions. For patients treated with MDZ for 5 or more days, the dose of the benzodiazepine is reduced from 6 mcg/kg/min to 3-4 mcg/kg/min to avoid seizure occurrence secondary to abrupt benzodiazepine withdrawal and prevent emergence reactions. Dosages above 4 mcg/kg/min, although previously not efficacious, could interfere with the evaluation of the effectiveness of KE.

In case of RCSE resolution, the effective dosage of KE is continued for a minimum of 48 hours up to a maximum of 7 days. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment failure is declared. KE is discontinued gradually by reducing the starting dose by 25% every 12 hours for infusion dosages between 50 and 100 mcg/kg/min; withdrawal may be more rapid (25% of the starting dose every 6 hours) for dosages <50 mcg/kg/min or a lesser duration of infusion (48 hours) (see Figure 1).

**The control arm: MDZ and (TPS and/or PR)**

The administration of conventional anaesthetics for the treatment of RCSE follows the current guidelines that consider MDZ at anaesthetic dosage as the first therapeutic option, followed by PR and/or TPS. The decision to administer PR or TPS first is at the clinician’s discretion.

MDZ is administered as follows: using increasing doses of MDZ up to a maximum of 12 mcg/kg/min, the dosage is increased by 2 mcg/kg/min every 5 min, with every increment being preceded by a bolus of 0.15 mg/kg. In the case of RCSE resolution, the effective dosage of MDZ is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, MDZ is discontinued and treatment is continued with PR or TPS.

During the weaning process MDZ is decreased by 1 mcg/kg/min every 15 minutes if the infusion duration was less than 72 hours; otherwise, weaning is to be performed more slowly. In fact, studies
conducted on weaning from BDZ showed a higher incidence of tolerance and, therefore, of abstinence, in patients who received higher doses and for a longer period (≥ 3 days).[21] We recommend a reduction of 10-15% of the initial infusion dose every 6-8 h in patients receiving infusions for short periods (<3-5 days), and a reduction of 10-20% per day in patients receiving infusions for longer periods (>5-7 days).

TPS is administered as follows: an initial bolus of 1-2 mg/kg, increasing the speed of continuous infusion by 1 mg/kg/h every 30 minutes, always preceding with a bolus of 2 mg/kg, up to a maximum dosage of 6 mg/kg/h. In the case of RCSE resolution, the effective dosage of TPS is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment is continued with PR, if provided in the hospital, or treatment failure is declared.

During the weaning process TPS is discontinued gradually by reducing the starting dose by 25% every 3 hours. Phenobarbital therapy (5 mg/kg given twice) is initiated during TPS reduction.

PR is administered as follows: an initial bolus of 1-2 mg/kg, increasing the speed of continuous infusion by 1 mg/kg/h every 5 minutes, always preceding with a bolus of 1-2 mg/kg, up to a maximum dosage of 5 mg/kg/h. In the case of RCSE resolution, the effective dosage of PR is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment failure is declared.

During the weaning process PR is gradually discontinued by reducing the initial dose by 10% every 12 hours if the maximal dose of 5 mg/kg/h has been reached and administered for 48 hours; withdrawal may be more rapid for smaller doses or infusion durations (see Figure 1).

**Relevant concomitant care and interventions**

The antiepileptic therapy is administered simultaneously with the study drugs and the choice of the antiepileptic drug is at the discretion of the clinician. Supportive therapy (e.g. amine), when necessary, is allowed (see Table 1).
Sample size

A sample size of 57 patients was estimated assuming 80% power, an alpha error of 5%, a percentage of success in the experimental arm of 85% and a percentage of success in the control arm of 60%. The study adopts a sequential design with a non-truncated triangular test.[22]

Outcomes

Primary outcome

The control of SE up to 24 hours after the withdrawal of therapy is defined by the following EEG features: (1) appearance of suppression-burst pattern and/or, (2) appearance of widespread beta activity and/or, (3) appearance of slow activity in the absence of widespread or lateralized, continuous or subcontinuous, and periodic abnormalities (periodic lateralized epileptiform discharges (PLEDs), for example).

Definition of treatment success

No recurrence of SE from the highest dose of the study drugs until the 24th hour after withdrawal of the therapy.

Definition of treatment failure

The study treatments (control arm and treatment arm) end when a therapeutic failure is declared, namely:
- therapy completely failed to control SE
- recurrence of SE while therapy is being tapered or within 24 hours of its withdrawal
- withdrawal of the study drug due to adverse events
- death during treatment with the study drugs or within 24 hours after their withdrawal.
Secondary outcomes

1) Number of patients requiring mechanical ventilation during treatment with KE;

2) Frequency of seizures during treatment, from the time at which the maximum dose of study drugs is reached until outcome assessment;

3) Frequency of seizures from outcome assessment to hospital discharge;

4) Number of patients requiring drugs for cardiovascular support (amines);

5) Number of patients who respond to alternative therapy administered after a treatment failure in their study arm;

6) Number of patients requiring treatment withdrawal due to adverse events;

7) Mortality rate;

8) Duration of mechanical ventilation;

9) Duration of stay in the ICU;

10) Total length of hospital stay.

Data collection methods

An electronic case report form (eCRF) with security input rules has been developed in order to ensure accurate data collection. Demographic, clinical and anamnestic data (made anonymous) are recorded at the time of enrolment and throughout follow-up. Laboratory tests and continuous EEG recordings are included in the patient file. The final efficacy outcome is recorded in each eCRF for the sequential analysis. All adverse events are collected in the ‘adverse event’ section of the eCRF. Serious adverse events are also immediately reported to the European Medicines Agency (EudraVigilance).

Statistical Methods

As the trial follows a randomized controlled sequential model, the assessment of efficacy is updated after each patient concludes treatment.[22] Sequential methods are a commonly used frequentist
approach to control the inflation of the false positive error rate generated by multiple tests. This method of analysis regards only the primary outcome and has the advantage of allowing the early discontinuation of the study in case of the clear superiority of the intervention arm or the clear futility of the treatment. The sequential analysis model allows an early termination of the trial in case of large differences between the two groups in terms of efficacy. Secondary outcomes are reported in a descriptive analysis as proportions, averages and medians.

**Data Monitoring**

The coordinating centre (Meyer Children’s Hospital, Florence) oversees the activity of the participating sites through regular visits. The coordinating centre itself is supported by the local internal Clinical Trial Office for internal audits.

**ETHICS AND DISSEMINATION**

The study was approved by the local Ethics Committee on October 21, 2014 and was registered on the site ClinicalTrial.gov (number: NCT02431663). Any amendment will be submitted to the local Ethics Committee. Signed informed consent is required from both parents (supplementary file). We will disseminate the results of our study via presentations at international conferences and publications in peer-reviewed journals.
REFERENCES


12 Wasterlain CG, Chen JW. Mechanistic and pharmacologic aspects of status epilepticus and its


Contributors.

AR, LI, ML, SDM, AB, RG conceptualized the research design, wrote the research protocol, secured funding and are coordinating the project team. AB, GF were responsible for the sample size calculation and statistical methods and for the acquisition of data. KM contributed to the preparation of the manuscript. LDS and AP coordinated the management of study drugs. FV, RB, SS, AP, PB contributed to the design of the study protocol. RB, FS, LF, SP, DB, AP, SS, PB, EF, EC, DM, PC, RM, RV, AC, AW, MM, CM, EF, LM, FV contributed to the implementation of the study at the 10 Italian sites. All authors have read and approved the final version of the protocol.

Funding. Molteni® Pharmaceuticals, which contributed 15,000 euros to the study, did not limit the independent sponsor (Meyer Children's Hospital, Viale Pieraccini 24, Florence, Italy) in any way. Only the independent sponsor will have access to the final trial dataset.

Competing interests. None.

Ethics approval. The study received ethical approval from the Tuscany Paediatric Ethics Committee, Florence, Italy (12/2015).

Strengths and limitations of this study

- This is the first randomized controlled study assessing the efficacy of third-line therapy in RCSE in children.
- It employs a sequential model approach, which allows efficacy to be demonstrated with a small number of patients.
- It assesses the possibility of avoiding endotracheal intubation in the treatment of RCSE.
- RCSE is a rare condition, which may result in a longer than originally planned duration of the study.
- Enrolment of patients already on high dosages of midazolam, which could require intubation in some.
Flow-chart
335x221mm (96 x 96 DPI)
TABLE 1. Timeline Table

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INFORMED Consent  
KETASER01 Study

The undersigned …………………………………………………………… born on ................................................ in ................................................. residing in ….............................. address ................................................ telephone number ………………………………………………………………………

As the mother/father/legal representative of the minor ……………………………………. born on ................................................ in …………………......................................... and residing in …....................……………….. address ..........................................................……………… telephone number ………………………………………………………………………

DECLARES the following:

The nature, purposes, expected benefits, and possible risks and drawbacks of this study entitled “Efficacy of ketamine in refractory convulsive status epilepticus in children: a multicentre, randomized, controlled, open-label, non-profit, with sequential design study” have been clearly explained to me by Dr. ……………………………..

1. I have received a copy of the information sheet with comprehensive details on the planned study.

2. I have been given sufficient time to reflect on the information received and to discuss it with others and ask any questions.

3. I have been informed that the study protocol has received a favourable opinion from the Ethics Committee as well as approval from the responsible health/regulatory authority (Italian Medicines Agency).

4. It has been clearly explained to me that I can decide that my child or minor not take part in the study and that I can withdraw consent to participate at any time.

5. I have been assured that should I desire not to adhere to the research or to abandon it while it is underway, this will not modify the relationships with the doctors and the facility at which my child or minor is being treated in any way.
6. □ I grant / □ I do not grant

authorization to make contact with my child or minor’s paediatrician/family doctor.

7. I am aware that the study can be interrupted at any time if the person responsible for the
research decides to do so, without prejudice to the health of my child or minor.

8. I have been informed that I will be made aware of any new information that may
compromise the study’s safety and that I can speak to the doctors who are treating my child
or minor for any problems or questions.

9. I have been informed regarding the contraindication to participation in the study in the case
in which my daughter or minor is pregnant or is presumed to be.

10. I have been informed that the results of the study will be made known to the scientific
community, that my identity and that of my child or minor will not be mentioned in any
report of the study, and that all of the information obtained during the trial will be treated as

I therefore freely consent that my child or minor participate in the study.

FIRST AND LAST NAME OF THE PARENT ______________________ SIGNATURE ____________________________________________

FIRST AND LAST NAME OF THE PARENT ______________________ SIGNATURE ____________________________________________

FIRST AND LAST NAME OF THE LEGAL GUARDIAN ______________________

SIGNATURE ____________________________________________

DATE:........................................

The undersigned Dr. ................................................................. confirms to have duly informed,
offering the opportunity to ask clarifying questions, Mr./Ms. ..................................................... with
regard to the nature, purposes, expected benefits, and possible risks and drawbacks of the study in
question, as well as with regard to his/her rights and those of the child or minor that he/she
represents.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

<table>
<thead>
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<th>Item No</th>
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<th>Addressed on page number</th>
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<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
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<td>Date and version identifier</td>
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<td>Sources and types of financial, material, and other support</td>
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<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
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<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
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<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)  

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<tr>
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<td>N/A</td>
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**Introduction**

**Background and rationale**

- 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

- 6b Explanation for choice of comparators

**Objectives**

- 7 Specific objectives or hypotheses

**Trial design**

- 8 Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)

**Methods: Participants, interventions, and outcomes**

**Study setting**

- 9 Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

**Eligibility criteria**

- 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)

**Interventions**

- 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

- 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

- 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

- 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Outcomes

Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

Participant timeline

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

Sample size

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

Recruitment

Strategies for achieving adequate participant enrolment to reach target sample size.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation

Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Allocation concealment mechanism

Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Implementation

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Blinding (masking)

Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how.

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.

Methods: Data collection, management, and analysis
### Data collection methods

18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

### Data management

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

### Statistical methods

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

### Methods: Monitoring

#### Data monitoring

21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

#### Harms

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

#### Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

### Ethics and dissemination
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<td>Protocol amendments</td>
<td>Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
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<td>26a</td>
<td>Consent or assent</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
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<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
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<td>Confidentiality</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
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<td>28</td>
<td>Declaration of interests</td>
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<td>Access to data</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
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<td>30</td>
<td>Ancillary and post-trial care</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
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<td>31a</td>
<td>Dissemination policy</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
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<td>Authorship eligibility guidelines and any intended use of professional writers</td>
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<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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<td>32</td>
<td>Appendices</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
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**Appendices**
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<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*
Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential-design, multicentre, randomized, controlled, open-label, non-profit trial (KETASER01).
<table>
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<tr>
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<th>Institutions</th>
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<tr>
<td>Mondardini, Cristina; Sant'Orsola-Malpighi Hospital, University of Bologna, Department of Paediatric Anaesthesia and Intensive Care</td>
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<tr>
<td>Franzoni, Emilio; Sant'Orsola-Malpighi Hospital, University of Bologna, Child Neuropsychiatry Unit</td>
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<td>McGreevy, Kathleen; Meyer Children's Hospital, Research, Innovation and International Relations</td>
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<td>Di Simone, Lorena; Meyer Children's Hospital, Pharmacy Unit</td>
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<td>Pugi, Alessandra; Meyer Children's Hospital, Clinical Trial Office</td>
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<td>Mirabile, Lorenzo; Meyer Children's Hospital, Intensive Care Unit</td>
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<td>Vigevano, Federico; Bambino Gesù Children's Hospital, IRCCS, Department of Neuroscience, Neurology Unit</td>
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<tr>
<td>Guerrini, Renzo; Meyer Children's Hospital, Paediatric Neurology Unit</td>
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**Primary Subject Heading:** Neurology  
**Secondary Subject Heading:** Anaesthesia  
**Keywords:** Epilepsy < NEUROLOGY, Anaesthesia in neurology < ANAESTHETICS, Paediatric intensive & critical care < ANAESTHETICS, Paediatric neurology < NEUROLOGY
Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential-design, multicentre, randomized, controlled, open-label, non-profit trial (KETASER01).

Anna Rosati1, Lucrezia Ilvento1, Manuela L’Erario2, Salvatore De Masi3, Annibale Biggeri4, Giancarlo Fabbro4, Roberto Bianchi5, Francesca Stoppa6, Lucia Fusco7, Silvia Pulitano8, Domenica Battaglia9, Andrea Pettenazzo10, Stefano Sartori11, Paolo Biban12, Elena Fontana13, Elisabetta Cesaroni14, Donatella Mora15, Paola Costa16, Rosanna Meleleo17, Roberta Vittorini18, Alessandra Conio19, Andrea Wolfler20, Massimo Mastrangelo21, Maria Cristina Mondardini22, Emilio Franzoni23, Kathleen S. McGreevy24, Lorena Di Simone25, Alessandra Pugi3, Lorenzo Mirabile2, Federico Vigevano7, Renzo Guerrini1

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8 Intensive Care Unit, Catholic University, Rome, Italy
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11 Paediatric Neurology Unit, Department of Woman's and Child's Health, University Hospital of Padua, Padua, Italy
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Keywords: refractory status epilepticus, ketamine, children, anaesthetics, endotracheal intubation

Word count: 2458
ABSTRACT

Introduction:

Status epilepticus (SE) is a life-threatening neurological emergency. SE lasting longer than 120 minutes and not responding to first- and second-line antiepileptic drugs is defined as “refractory” (RCSE) and requires intensive care unit treatment. There is currently no evidence or consensus to guide both the optimal choice of therapy and treatment goals for RCSE, which is generally treated with coma induction using conventional anaesthetics (high dose midazolam, thiopental and/or propofol). Increasing evidence indicates that ketamine (KE), a strong N-methyl-D-aspartate glutamate receptor antagonist, may be effective in treating RCSE. We hypothesized that intravenous KE is more efficacious and safe than conventional anaesthetics in treating RCSE.

Methods and analysis: A multicentre, randomized, controlled, open-label, non-profit, with sequential-design study will be conducted to assess the efficacy of KE compared with conventional anaesthetics in the treatment of RCSE in children. Ten Italian centres/hospitals are involved in enrolling 57 patients aged 1 month to 18 years with RCSE. Primary outcome is the resolution of SE up to 24 hours after withdrawal of therapy and is updated for each patient treated according to the sequential method.

Ethics and dissemination: The study received ethical approval from the Tuscan Paediatric Ethics Committee (12/2015). The results of this study will be published in peer-reviewed journals and presented at international conferences.

Trial registration number: Protocol version 02 of October 21, 2014; EudraCT number 2013-004396-12; ClinicalTrial.gov identification number: NCT02431663.
Strengths and limitations of this study

- This is the first randomized controlled study assessing the efficacy of third-line therapy in RCSE in children.
- It employs a sequential model approach, which allows efficacy to be demonstrated with a small number of patients.
- It assesses the possibility of avoiding endotracheal intubation in the treatment of RCSE.
- RCSE is a rare condition, which may result in a longer than originally planned duration of the study.
- Enrolment of patients already on high dosages of midazolam, which could require intubation in some.
INTRODUCTION

Background and Rationale

Status epilepticus (SE) is a life-threatening neurological emergency traditionally defined as ‘an acute epileptic condition characterized by continuous seizures for at least 30 minutes, or by 30 minutes of intermittent seizures without full recovery of consciousness between seizures’. [1] Convulsive SE is the most common and harmful form. There is now consensus, based on an improved understanding of pathophysiology, that any seizure lasting longer than five minutes should be treated as SE. [2]

SE lasting longer than 120 minutes and not responding to first-line (benzodiazepines) and second-line (midazolam at high dose, phenytoin and phenobarbital) antiepileptic drugs (AEDs) is defined as “refractory” and requires intensive care unit (ICU) treatment. [2] The term “super-refractory” defines SE that continues, or recurs, for 24 hours or longer or recurs after withdrawal of the anaesthetic therapy. [3]

Even with current best practices, neurological sequelae occur in >50% of children with refractory convulsive status epilepticus (RCSE). [4,5] The mortality rate of RCSE ranges between 2.7 and 5.2%, and increases up to 5-8% when only ICUs admission are taken into account. [4,5]

There is general consensus regarding the first- and second-line treatments of SE. Although the types of drugs available are similar in different countries, algorithms/protocols may differ among countries and even among different institutions in the same country; there is currently no evidence or consensus to guide both the optimal choice of therapy and treatment goals for RCSE. [3,6-8] RCSE is generally treated with coma induction using high dose midazolam (MDZ) or conventional anaesthetics such as thiopental (TPS) or propofol (PR), [6-8] which all require endotracheal intubation, a negative prognostic factor of morbidity and mortality. [9-11] All conventional anaesthetics commonly used in RCSE act on inhibitory-γ-aminobutyric acid (GABA_A) receptors. [6-8] Experimental models suggest that, with continuing seizures, GABA_A receptors are internalized in clathrin-coated vesicles, and excitatory N-methyl-D-aspartate (NMDA) receptors are
mobilized to the membrane.[12,13] This receptor trafficking results in decreased inhibitory control and increased excitation that may foster SE.[12,13] Conventional anaesthetics will therefore be less active, making higher doses necessary, which will in turn enhance their adverse events, especially hypotension, requiring vasopressor administration.[11] In this scenario, NMDA modulating molecules, such as ketamine (KE), represent an attractive treatment alternative for SE.[14]

Increasing evidence indicates that KE, a strong NMDA glutamate receptor antagonist, may be effective in treating RCSE.[14] Due to its sympathomimetic action KE has no cardiac depressant properties and does not cause hypotension.[15] KE use does not necessarily require amine administration or mechanical ventilation. Its administration, therefore, does not imply emergent endotracheal intubation, a prognostic factor of increased morbidity and mortality risk in critically ill adults and children.[9-11] Between 15 and 39% of emergent endotracheal intubations in adults are associated with one or more complications including severe hypoxemia, hemodynamic collapse, and death.[9,11] The complication rate is even higher in the paediatric population, in which acute deterioration can occur rapidly as a result of age-related differences in physiology, oxyhemoglobin dissociation, oxygen consumption, and pulmonary mechanics.[10] Large doses of KE and rapid intravenous boluses may cause hallucinations, which are less frequent in children than in adults and can be reduced with benzodiazepine premedication.[15] Moreover, KE exerts a neuroprotective action by preventing the transduction of signals to destructive intracellular mechanisms through the blockade of NMDA receptors.[15,16]

The literature contains good evidence about efficacy and safety of KE in both the adult and paediatric RCSE populations.[3,14] However, the heterogeneity of prior treatments, timing of KE administration, and KE dosage and duration make available information on seizure responsiveness difficult to interpret.

In November 2009 the Paediatric Neurology Unit at the Meyer Children’s Hospital (Florence, Italy) adopted a treatment protocol for RCSE including intravenous KE infusion.[17] As of January 2013, in order to avoid mechanical ventilation, we have used KE (Ketamina®, Molteni
Our paediatric series [17,18] shows that treatment with KE in RCSE is effective and safe and its use could be considered before TPS and PR, unless specific contraindications exist. Based on these encouraging results, we designed a nationwide multicentre randomized sequential trial that has been approved by the Italian Medicines Agency and includes ten paediatric hospitals (EudraCT number 2013-004396-12; ClinicalTrial.gov identification number: NCT02431663).

**Objectives**

We hypothesized that intravenous KE is more effective and safer than conventional anaesthetics (high dose MDZ, TPS and/or PR) in treating RCSE.

**Primary objective:**

To assess the efficacy of KE compared with conventional anaesthetics in the treatment of RCSE in children.

**Secondary objective:**

To assess the short-time safety profile of KE compared with conventional anaesthetics and, in particular, to evaluate the possibility of administering KE, thus avoiding mechanical ventilation.

**METHODS AND ANALYSIS**

**Study design**

KETASER01 is an Italian, multicentre, randomized, controlled, open-label, non-profit, study with sequential design (ClinicalTrials.gov identifier: NCT02431663) involving ten centres/hospitals.

**Study setting**

Patients will be enrolled and treated in the ICUs at ten Italian hospitals: 1) Meyer Children's Hospital, Florence; 2) Bambino Gesù Children's Hospital, IRCCS, Rome; 3) Gemelli Hospital, Catholic University, Rome; 4) University Hospital, Padua; 5) Ospedali Riuniti, Ancona; 6)
University Hospital, Verona; 7) Burlo Garofolo Institute for Maternal and Child Health, IRCCS, Trieste; 8) Regina Margherita Children’s Hospital, Turin; 9) Buzzi Children's Hospital, ICP, Milan; 10) Sant'Orsola-Malpighi University Hospital, Bologna.

Patients will be randomized to the intervention arm or control arm with a computer-assisted system. Block randomization with fixed size blocks and age stratification (<4, 5-10, and 11-18 years) will be used.

Eligibility criteria

Inclusion criteria

Patients are eligible if (1) they are aged 1 month to 18 years of age, (2) they present with SE refractory to first- (benzodiazepines per os or pr) and second-line (phenytoin 20 mg/kg and/or phenobarbital 20 mg/kg and midazolam up to 6 mcg/kg/min) antiepileptic drugs, (3) their parents provide written consent.

Exclusion criteria

Patients will be excluded if (1) they have a contraindication to the use of one of the drugs in the study protocol, (2) they have a presumed or ascertained pregnancy status, (3) they had already been enrolled in the KETASER01 study for an antecedent RCSE episode.

Patients with RCSE that is not responsive to first- and second-line drugs will be transferred from the neurological department to the ICU. They will be enrolled in the study by the neurologist and anaesthesiologist in the ICU after assessing the eligibility criteria and obtaining informed consent from the parents.

Interventions

The experimental arm: KE

KE is administered starting with an initial bolus of 2-3 mg/kg followed by continuous infusion of 10 mcg/kg/min, increasing the infusion rate by 5-10 mcg/kg/min every 10 minutes up to
a maximum of 100 mcg/kg/min, with every increment being preceded by a bolus of 1-2 mg/kg. KE is always administered in association with 2-4 mcg/kg/min MDZ. For patients treated with continuous infusion of MDZ (second-line therapy) for less than 5 days, the dosage of the benzodiazepine is reduced from 6 mcg/kg/min to 2 mcg/kg/min to prevent the emergence reactions. For patients treated with MDZ for 5 or more days, the dose of the benzodiazepine is reduced from 6 mcg/kg/min to 3-4 mcg/kg/min to avoid seizure occurrence secondary to abrupt benzodiazepine withdrawal and prevent emergence reactions.[19] Dosages above 4 mcg/kg/min, although previously not efficacious, could interfere with the evaluation of the effectiveness of KE.

In case of RCSE resolution, the effective dosage of KE is continued for a minimum of 48 hours up to a maximum of 7 days based on the EEG features of a continuous recording analysed by a neurologist. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment failure is declared. KE is discontinued gradually by reducing the starting dose by 25% every 12 hours for infusion dosages between 50 and 100 mcg/kg/min; withdrawal may be more rapid (25% of the starting dose every 6 hours) for dosages <50 mcg/kg/min or a lesser duration of infusion (48 hours) (see Figure 1).

The control arm: MDZ and (TPS and/or PR)

The administration of conventional anaesthetics for the treatment of RCSE follows the current guidelines that consider MDZ at anaesthetic dosage as the first therapeutic option, followed by PR and/or TPS. The decision to administer PR or TPS first is at the clinician’s discretion.

MDZ is administered as follows: using increasing doses of MDZ up to a maximum of 12 mcg/kg/min, the dosage is increased by 2 mcg/kg/min every 5 min, with every increment being preceded by a bolus of 0.15 mg/kg. In the case of RCSE resolution, the effective dosage of MDZ is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, MDZ is discontinued and treatment is continued with PR or TPS. During the weaning process MDZ is decreased by 1 mcg/kg/min every 15 minutes if the infusion
duration was less than 72 hours; otherwise, weaning is to be performed more slowly. In fact, studies conducted on weaning from BDZ showed a higher incidence of tolerance and, therefore, of abstinence, in patients who received higher doses and for a longer period (≥ 3 days).[19] We recommend a reduction of 10-15% of the initial infusion dose every 6-8 h in patients receiving infusions for short periods (<3-5 days), and a reduction of 10-20% per day in patients receiving infusions for longer periods (>5-7 days).

TPS is administered as follows: an initial bolus of 1-2 mg/kg, increasing the speed of continuous infusion by 1 mg/kg/h every 30 minutes, always preceding with a bolus of 2 mg/kg, up to a maximum dosage of 6 mg/kg/h. In the case of RCSE resolution, the effective dosage of TPS is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment is continued with PR, if provided in the hospital, or treatment failure is declared.

During the weaning process TPS is discontinued gradually by reducing the starting dose by 25% every 3 hours. Phenobarbital therapy (5 mg/kg given twice) is initiated during TPS reduction.

PR is administered as follows: an initial bolus of 1-2 mg/kg, increasing the speed of continuous infusion by 1 mg/kg/h every 5 minutes, always preceding with a bolus of 1-2 mg/kg, up to a maximum dosage of 5 mg/kg/h. In the case of RCSE resolution, the effective dosage of PR is continued for 48 hours. In the case of no response (persistence of SE at the maximum treatment dose) or adverse events, the drug is discontinued and treatment failure is declared.

During the weaning process PR is gradually discontinued by reducing the initial dose by 10% every 12 hours if the maximal dose of 5 mg/kg/h has been reached and administered for 48 hours; withdrawal may be more rapid for smaller doses or infusion durations (see Figure 1).

**Relevant concomitant care and interventions**

The antiepileptic therapy is administered simultaneously with the study drugs and the choice of the antiepileptic drug is at the discretion of the clinician. Supportive therapy (e.g. amine), when necessary, is allowed (see Table 1).[20,21]
Table 1. Table timeline

<table>
<thead>
<tr>
<th></th>
<th>Pre-enrolment</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>T1</th>
<th>T2</th>
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<tr>
<td></td>
<td></td>
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<td>0-48 hours</td>
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<td>Eligibility assessment</td>
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<td>Administration PIM III (Paediatric Index of Mortality) and STESS</td>
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<tr>
<td>Informed consent</td>
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<tr>
<td>Allocation</td>
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<td><strong>INTERVENTIONS</strong></td>
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<tr>
<td>Administration of MDZ/TPS/PR or KE up to a maximum or up to SE resolution</td>
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<td>Administration of maximum dosage of MDZ/TPS/PR up to reduction-withdrawal</td>
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<td></td>
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<tr>
<td>Administration of maximum dosage of KE up to reduction-withdrawal</td>
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<td>Etiologic classification</td>
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<td>Need of mechanical ventilation</td>
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<tr>
<td>Frequency of seizures from outcome assessment to hospital discharge</td>
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<td></td>
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<tr>
<td>Adverse events</td>
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<td>Tolerability</td>
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<tr>
<td>Other variables (laboratory investigations, monitoring video-EEG, monitoring cardiorespiratory parameters, etc.)</td>
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</table>
Sample size

A sample size of 57 patients was estimated assuming 80% power, an alpha error of 5%, a percentage of success in the experimental arm of 85% and a percentage of success in the control arm of 60%. The study adopts a sequential design with a non-truncated triangular test.[22]

Outcomes

Primary outcome

The control of SE up to 24 hours after the withdrawal of therapy is defined by the following EEG features: (1) appearance of suppression-burst pattern and/or, (2) appearance of widespread beta activity and/or, (3) appearance of slow activity in the absence of widespread or lateralized, continuous or subcontinuous, and periodic abnormalities (periodic lateralized epileptiform discharges (PLEDs), for example).

Definition of treatment success

No recurrence of SE from the highest dose of the study drugs until the 24th hour after withdrawal of the therapy.

Definition of treatment failure

The study treatments (control arm and treatment arm) end when a therapeutic failure is declared, namely:
- therapy completely failed to control SE
- recurrence of SE while therapy is being tapered or within 24 hours of its withdrawal
- withdrawal of the study drug due to adverse events defined according to the Common Toxicity Criteria for Adverse Events (CTCAE) [23]
- death during treatment with the study drugs or within 24 hours after their withdrawal.
Secondary outcomes

1) Number of patients requiring mechanical ventilation during treatment with KE;
2) Frequency of seizures during treatment, from the time at which the maximum dose of study drugs is reached until outcome assessment;
3) Frequency of seizures from outcome assessment to hospital discharge;
4) Number of patients requiring drugs for cardiovascular support (amines);
5) Number of patients who respond to alternative therapy administered after a treatment failure in their study arm;
6) Number of patients requiring treatment withdrawal due to adverse events;
7) Mortality rate;
8) Duration of mechanical ventilation;
9) Duration of stay in the ICU;
10) Total length of hospital stay.

Data collection methods

An electronic case report form (eCRF) with security input rules has been developed in order to ensure accurate data collection. Personal data are made anonymous and codified by the system. Demographic, clinical and anamnestic data are recorded at the time of enrolment and throughout follow-up. Laboratory tests and continuous EEG recordings are included in the patient file. The final efficacy outcome is recorded in each eCRF for the sequential analysis. All adverse events are collected in the ‘adverse event’ section of the eCRF. Serious adverse events are also immediately reported to the European Medicines Agency (EudraVigilance).

Statistical Methods

As the trial follows a randomized controlled sequential model, the assessment of efficacy is updated
after each patient concludes treatment. Sequential methods are a commonly used frequentist approach to control the inflation of the false positive error rate generated by multiple tests. This method of analysis regards only the primary outcome and has the advantage of allowing the early discontinuation of the study in case of the clear superiority of the intervention arm or the clear futility of the treatment. The sequential analysis model allows an early termination of the trial in case of large differences between the two groups in terms of efficacy. Secondary outcomes are reported in a descriptive analysis as proportions, averages and medians.

**Data Monitoring**

The coordinating centre (Meyer Children’s Hospital, Florence) oversees the activity of the participating sites through regular visits. The coordinating centre itself is supported by the local internal Clinical Trial Office for internal audits.

**ETHICS AND DISSEMINATION**

The study was approved by the Tuscan Paediatric Ethics Committee on October 21, 2014 and was registered on the site ClinicalTrial.gov (number: NCT02431663). Any amendment will be submitted to the local Ethics Committee. Signed informed consent is required from both parents (supplementary file). We will disseminate the results of our study via presentations at international conferences and publications in peer-reviewed journals.
REFERENCES


23. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events,

Contributors.

AR, LI, ML, SDM, AB, RG conceptualized the research design, wrote the research protocol, secured funding and are coordinating the project team. AB, GF were responsible for the sample size calculation and statistical methods and for the acquisition of data. KM contributed to the preparation of the manuscript. LDS and AP coordinated the management of study drugs. FV, RB, SS, AP, PB contributed to the design of the study protocol. RB, FS, LF, SP, DB, AP, SS, PB, EF, EC, DM, PC, RM, RV, AC, AW, MM, MCM, EF, LM, FV contributed to the implementation of the study at the 10 Italian sites. All authors have read and approved the final version of the protocol.

Funding. Molteni Pharmaceuticals was not involved in: study design; collection, management, analysis, and interpretation of data; writing of the report; the decision to submit the report for publication. Molteni Pharmaceuticals, which contributed 15,000 euros to the study, did not limit the independent sponsor (Meyer Children's Hospital, Viale Pieraccini 24, Florence, Italy) in any way. Only the independent sponsor will have access to the final trial dataset.

Competing interests. None.

Ethics approval. The study received ethical approval from the Tuscany Paediatric Ethics Committee, Florence, Italy (12/2015).
Figure 1
254x190mm (300 x 300 DPI)
INFORMED CONSENT
KETASER01 STUDY, version 03 of 04.03.2015

The UNDERSIGNED …………………………………………………………… born on ……………………… in ……………………… residing in ………………………
address ……………………………………………………………………… telephone number ………………………

As the mother/father/legal representative of the minor …………………………………… born on ……………………… in ……………………… and residing in ………………………
address ……………………………………………………………………… telephone number ………………………

DECLARES the following:

The nature, purposes, expected benefits, and possible risks and drawbacks of this study entitled “Efficacy of ketamine in refractory convulsive status epilepticus in children: a multicentre, randomized, controlled, open-label, non-profit, with sequential design study” have been clearly explained to me by Dr. ……………………………

1. I have received a copy of the information sheet with comprehensive details on the planned study.

2. I have been given sufficient time to reflect on the information received and to discuss it with others and ask any questions.

3. I have been informed that the study protocol has received a favourable opinion from the Ethics Committee as well as approval from the responsible health/regulatory authority (Italian Medicines Agency).

4. It has been clearly explained to me that I can decide that my child or minor not take part in the study and that I can withdraw consent to participate at any time.

5. I have been assured that should I desire not to adhere to the research or to abandon it while it is underway, this will not modify the relationships with the doctors and the facility at which my child or minor is being treated in any way.
6. □ I grant / □ I do not grant

authorization to make contact with my child or minor’s paediatrician/family doctor.

7. I am aware that the study can be interrupted at any time if the person responsible for the research decides to do so, without prejudice to the health of my child or minor.

8. I have been informed that I will be made aware of any new information that may compromise the study’s safety and that I can speak to the doctors who are treating my child or minor for any problems or questions.

9. I have been informed regarding the contraindication to participation in the study in the case in which my daughter or minor is pregnant or is presumed to be.

10. I have been informed that the results of the study will be made known to the scientific community, that my identity and that of my child or minor will not be mentioned in any report of the study, and that all of the information obtained during the trial will be treated as strictly confidential (Art. 13 of Leg. Dec. 30 June 2003, no. 196).

I therefore freely consent that my child or minor participate in the study.

                               FIRST AND LAST NAME OF THE PARENT ______________________ SIGNATURE
                               __________________________
                               FIRST AND LAST NAME OF THE PARENT ______________________ SIGNATURE
                               __________________________
                               FIRST AND LAST NAME OF THE LEGAL GUARDIAN ______________________
                               SIGNATURE __________________
                               DATE:....................................

The undersigned Dr. ............................................................... confirms to have duly informed, offering the opportunity to ask clarifying questions, Mr./Ms. .............................................. with regard to the nature, purposes, expected benefits, and possible risks and drawbacks of the study in question, as well as with regard to his/her rights and those of the child or minor that he/she represents.
SIGNATURE OF THE INVESTIGATOR

_____________________________________

Date ________________
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Addressed on page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative information</td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
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<tr>
<td>Trial registration</td>
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<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
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<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>3</td>
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<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>17</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>No profit study, the sponsor is Meyer Children Hospital, Florence</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>17</td>
</tr>
<tr>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

### Introduction

**Background and rationale**

- **6a** Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
- **6b** Explanation for choice of comparators

**Objectives**

- **7** Specific objectives or hypotheses

**Trial design**

- **8** Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

### Methods: Participants, interventions, and outcomes

**Study setting**

- **9** Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

**Eligibility criteria**

- **10** Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

**Interventions**

- **11a** Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
- **11b** Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
- **11c** Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
- **11d** Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes 12
Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

Participant timeline 13
Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). Table 1, Figure 1

Sample size 14
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

Recruitment 15
Strategies for achieving adequate participant enrolment to reach target sample size N/A

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a
Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Allocation concealment mechanism 16b
Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Implementation 16c
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Blinding (masking) 17a
Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how.

17b
If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial N/A

Methods: Data collection, management, and analysis
Data collection methods

18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring

21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page(s)</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Research ethics approval</td>
<td>24</td>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>25</td>
<td>Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
</tr>
<tr>
<td>Consent or assent</td>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
</tr>
<tr>
<td></td>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>27</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
</tr>
<tr>
<td>Declaration of interests</td>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
</tr>
<tr>
<td>Access to data</td>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
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<td></td>
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<td>Authorship eligibility guidelines and any intended use of professional writers</td>
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<tr>
<td></td>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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**Appendices**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent materials</td>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
</tr>
</tbody>
</table>

IC model in attachment
Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported license.
Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01)

Anna Rosati, Lucrezia Ilvento, Manuela L'Erario, Salvatore De Masi, Annibale Biggeri, Giancarlo Fabbro, Roberto Bianchi, Francesca Stoppa, Lucia Fusco, Silvia Pulitani, Domenica Battaglia, Andrea Pettenazzo, Stefano Sartori, Paolo Biban, Elena Fontana, Elisabetta Cesaroni, Donatella Mora, Paola Costa, Rosanna Meleleo, Roberta Vittorini, Alessandra Conio, Andrea Wolfier, Massimo Mastrangelo, Maria Cristina Mondardini, Emilio Franzoni, Kathleen S McGreevy, Lorena Di Simone, Alessandra Pugi, Lorenzo Mirabile, Federico Vigevano and Renzo Guerrini

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