

# **A randomized clinical trial for the treatment of refractory status epilepticus.**

## **Study protocol.** **(Version December 9, 2006)**

### **I. Background and significance:**

Status epilepticus (SE) occurs when seizures continue beyond their usual duration, likely due to failure of mechanisms allowing their natural termination (Lowenstein 1998). Its yearly cumulative incidence has been estimated at 10-41 / 100,000 population (DeLorenzo 1996, Coeytaux 2000).

Refractory status epilepticus is commonly defined as SE resistant to treatment with one first-line (benzodiazepines, BDZ) and one second-line (phenytoin, phenobarbital, or valproic acid) antiepileptic drug (AED) (Mayer 2002). Since SE tends to become more refractory to conventional treatment with time and the number of AED used (Treiman 1999), coma induction with an appropriate AED, including barbiturates (BBT), propofol (PRO) or midazolam, is advocated after failure of second-line treatment (Lowenstein 1998). Treatment resistance has been postulated to result from a shift from inadequate GABA-ergic inhibition towards glutamate (NMDA-mediated) excitotoxicity (Bleck 2001). Interestingly, however, pure NMDA antagonists bear the risk of neuronal damage; as a result, the combination with GABA-ergic activity has been proposed as a method to avoid this risk (Jevtovic-Todorovic 2001).

Refractory SE develops in 31%-44% of patients with status epilepticus (SE) and has a mortality of 16%-23% (Mayer 2002, Holtkamp 2005, Rossetti 2005). Despite this clinical impact, relatively few studies have investigated this entity and its treatment. Of note, the few comparative prospective trials focusing on SE treatment assessed only first-line therapy (Leppik 1983, Treiman 1998, Alldredge 2001). Technical difficulties related to patient recruitment, problems in defining SE, and the lack of consensus among clinicians at different centers in the United States and Europe as regards the optimal therapeutic protocol (Claassen 2003, Holtkamp 2003) may possibly account for the paucity of relevant investigations and the low level of evidence for the treatment of refractory SE..

Most of the existing studies of refractory SE deal with case series of patients receiving a single coma-inducing AED (Stecker 1998, Prasad 2001, Parviainen 2002, Rossetti 2004). This may not accurately reflect clinical practice, in which treatments may be combined. Considering barbiturates, mortality within the first 4 days of refractory SE treatment or treatment failures was 0/10 (0%, Parviainen 2002), and 3/8 (38%, Stecker 1998). Considering propofol, corresponding proportions were 13/31 (45%, Rossetti 2004), 3/6 (50%, Stecker 1998) and 8/14 (57%, Prasad 2001). However, a meta-analysis did not disclose any significant difference of short-term mortality (48% for barbiturates vs. 52% for propofol); acute failure (within the first 6 hours of drug administration) was 8% vs. 27%; breakthrough seizures (during drug administration) were 12% vs. 15%; withdrawal seizures (within 48h of discontinuation of the treating agent) were 43% for barbiturates vs. 46% for propofol. In this analysis, though, patients with nonconvulsive SE and coma (which is more treatment resistant) were more prevalent in the propofol group, and an unclear number of anoxic subjects were included (Claassen 2002). Furthermore, a retrospective survey of refractory SE treatment, taking into account several strategies (drugs combinations or monotherapy), did not show any statistical difference in outcome (Rossetti 2005). There is also uncertainty for the optimal extent of EEG suppression in this context (Krishnamurthy 1999, Rossetti 2005).

There are three classes of medications currently in use for treatment of refractory SE barbiturates (BBT), propofol (PRO), and midazolam (MDZ). Each has particular advantages and disadvantages

Propofol has been used since more than 25 years for induction and maintenance of anesthesia (Rogers 1980). It has a short half-life of about 140 minutes after prolonged perfusion (Wessen 1994), allowing a rapid titration and withdrawal, with practically no risk of accumulation. Its main mechanism is an agonistic action on GABA<sub>A</sub> receptors, but modulation of Ca and Na channels has also been described (Marik 2004). Its effect on NMDA glutamate receptors is controversial, since some found an inhibitory action in vitro (Hans 1994, Orser 1995), while others describe a potentiation of NMDA mediated neuronal damage (Zhu 1997, Zhan 2001). Propofol has bronchodilatory and anti-inflammatory properties (Marik 2004), but may induce the so-called “infusion syndrome”, a potentially fatal cardio-circulatory collapse with hypertriglyceridemia and rhabdomyolysis, which however has been only exceptionally described in patients with SE (Vasile 2003).

Barbiturates prescribed to induce coma in refractory SE, such as thiopental (THP) in use in Europe, or its metabolite pentobarbital (PTB) in use in North America, after prolonged administration have an at least seven times longer elimination half-life as compared to propofol (THP 14-36 hours; PTB 15-22 hours) (Bayliff 1985, Cordato 1999), although higher values have been reported earlier (THP 38-86h, PTB 26h) (Piatt 1984). There is a considerable tendency to accumulation, thus prolonging the need for mechanical ventilation with potential risks of associated morbidity. Their main action is also GABA-ergic (GABA<sub>A</sub> receptors), with possible action also on calcium channels (Zhan 1998, Rogawski 2004). Both THP (Zhu 1997, Zhan 1998, Zhan 2001) and PTB (Charlesworth 1996) are NMDA antagonists in vitro. On the other hand, barbiturates may exert immunological inhibition (Kress 1987). A hypotensive action has been described for barbiturates and propofol (Claassen 2002), and both agents reduce intracranial pressure and brain metabolic requirements (Jevtovic-Todorovic 2001, Marik 2004). Although PTB has been claimed to be less hypotensive than THP (Van Ness 1990), the issue remains controversial.

The third agent used for refractory SE, midazolam, appears somewhat less popular among clinicians (Holtkamp 2003), probably because of the important tachyphylaxia that may develop within 24-48h (Beyenburg 2000). Furthermore, benzodiazepines do not act on NMDA receptors.

The previous points suggest that the optimal agent for refractory SE should exert a GABA-ergic and NMDA antagonistic action, be fast acting, with a short half-life, and have a favorable risk profile. So far, no single drug may be considered gold standard: PRO has a controversial action on NMDA receptors and the possibility of inducing the “infusion syndrome”, whereas barbiturates have a very long half-life. A comparison between these drugs should help understanding whether potential pharmacokinetic advantages (PRO) or a potential more complete pharmacodynamic profile (BBT) are more important in this setting.

To date, no controlled comparative study has been conducted to investigate the use of these agents. In consideration of the unclear relative effectiveness despite several retrospective case series and meta-analysis, a prospective investigation is needed (Schor 2005). Previous descriptions included patients with cerebral anoxia/hypoxia. However, since these have invariably a dismal prognosis, it seems appropriate to exclude them from an investigational treatment assessment.

## **II. Specific aims:**

This study is designed to assess the effectiveness (SE control, adverse events) of a first course of propofol versus barbiturates in the treatment of refractory SE.

## **III. Subject selection:**

### **Inclusion criteria:**

- Patients with refractory SE not due to cerebral anoxia. Refractory SE will be defined as ongoing clinical or electrographical seizure activity or repetitive seizure activity without intercurrent return to the baseline for at least 30 minutes despite administration of at least 1 first-line AED (benzodiazepine), and at least one second-line AED (phenytoin, valproate, phenobarbital, other), in adequate doses, needing coma induction for clinical management.
- Note: patients intubated for airway protection and sedated with a small dose of benzodiazepines (<0.02mg/kg.h midazolam or equivalent), propofol (<1mg/kg.h) or receiving opiates are eligible.

Exclusion criteria:

- Age < 16yo.
- Known pregnancy.
- Post-anoxic SE.
- Epilepsia partialis continua (simple partial SE).
- Known intolerance to the study drugs.
- Known mitochondrial disorder, hypertriglyceridemia (>5 mmol/l), or significant rhabdomyolysis (CK>1500 U/l).
- Known allergy to egg lecithin.

Source of subjects and method of recruitment:

Patients presenting in the participating centers with RSE during the study period and requiring coma-induction for their clinical management will be randomized to one of the study treatments.

**IV. Subject enrollment:**

All eligible patients should be recruited for randomization. In fact, both study drugs classes are routinely used for this indication worldwide, but in an uncontrolled manner. As discussed under section I., there is no evidence than one agent is more safe or efficacious than the other.

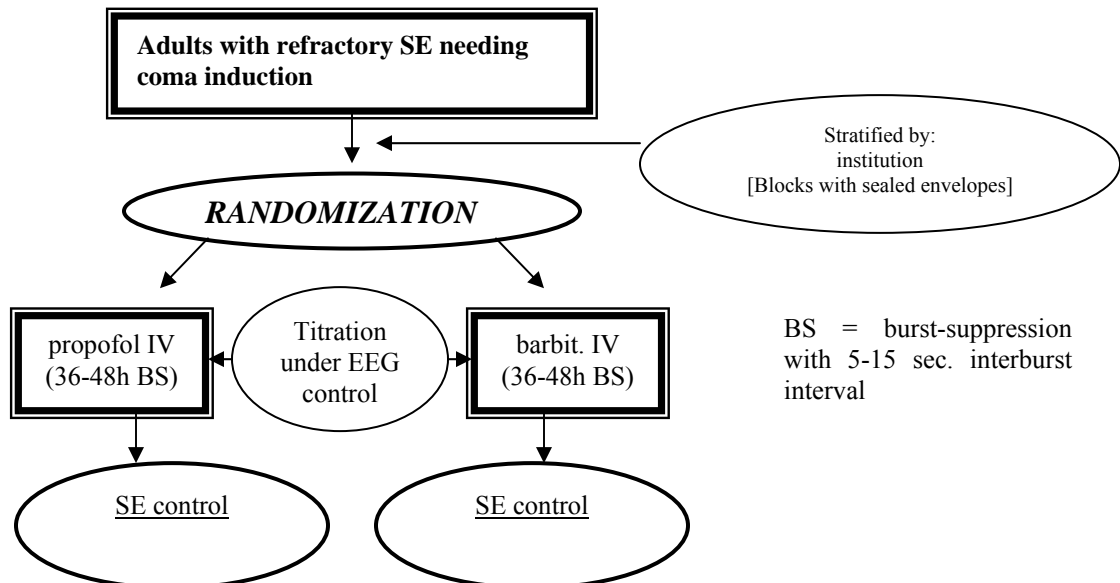
Confidentiality of study data:

Each participant will be linked to a code; he/she will be directly identifiable only by the PI and his co-investigators of the center where he was recruited. Five years after publication of the data, the cross linking information will be destroyed.

**V. Study procedures:**

Design and schema:

This will be a pragmatic, randomized, single blind (markedly different pharmacokinetics and side effects profiles implying targeted monitoring), multi-center, bi-national two arms clinical trial comparing propofol with barbiturates for the treatment of refractory SE. An electroencephalographer blinded to the study treatment will perform outcome assessment.



#### Baseline work-up (standardized form):

- Demographics: age, gender.
- History: previous seizures/SE, concurrent medical treatment, presumed time to treatment (SE beginning to administration of first-line AED).
- Functional Score before SE episode (0-2): 0 = completely independent; 1 = partially dependent; 2 = completely dependent.
- Consciousness impairment at presentation (before 1<sup>st</sup> treatment) (alert, somnolent/confused, stupor, coma).
- Assessment of seizure type (simple partial, complex partial, generalized convulsive, nonconvulsive status in coma).
- Blood tests: creatinine, ASAT, ALAT,  $\gamma$ GT, triglycerides, CK, CRP.
- Drug blood levels (if applicable), particularly PHT, PB, VPA, CBZ.
- Urine pregnancy test in women 18-50 yo.
- During the first 24h: Simplified acute physiological score (SAPS2).

SE is primarily a clinical diagnosis, and this will be sufficient when that diagnosis can be made (e.g., in presence of abnormal movements, myoclonus); in other cases, such as complex partial and nonconvulsive SE, EEG will be needed.

#### Randomization:

Randomization will be stratified by institution, using blocks with sealed envelopes.

#### Intervention:

The patient is in an ICU setting, intubated and ventilated according to standard practices for ventilated brain-injured patients. The second-line AED(s) is (are) administered in usual daily doses. EEG monitoring must be available at least within 12h of the beginning of the intervention.

- PTB (USA and Basel, Switzerland): Loading of 5 mg/kg IV, then titration towards burst-suppression (5-15 seconds interburst intervals) and/or (especially if no EEG available) towards clinical seizure control. Titration towards 2mg/kg/h until EEG is available (within 12 h) (Van Ness 1990, Beyenburg 2000).
- THP (rest of Switzerland): bolus of 2mg/kg IV, then titration towards burst-suppression (5-15 seconds interburst intervals) and/or (especially if no EEG available) towards clinical seizure control. Titration towards 4mg/kg/h until EEG is available (within 12 h) (Turcant 1985, Beyenburg 2000).
- PRO (USA & Switzerland): bolus of 2 mg/kg, then titration towards burst-suppression (5-15 seconds interburst intervals) and/or (especially if no EEG available) towards clinical seizure control. Titration towards 5mg/kg/h until EEG is available (within 12 h) (Beyenburg 2000, Rossetti 2004).
- In each arm, a benzodiazepine is administered at low dose (lorazepam: 4mg/24h) throughout the study period (Rossetti 2004).

The pharmacological equivalence, for the aim of this study, of THP and PTB has been independently confirmed (Perucca 2005).

Burst-suppression is continued for 36-48 hours under EEG control, then the study drug administration is reduced to 50%, for at least 24h. If the treating clinicians believe that the patient has been clinically and

electroencephalographically treated (seizure have been controlled), the drug is then withdrawn over maximally 24h (Parviainen 2002, Rossetti 2004). If not, the clinicians choose to pursue the best treatment according to their experience (they may decide to retry the study drug, to switch it, or to combine it). The controlled application of the study drug ends at that point.

Daily assessment (during the controlled study drug application, until 48hrs after treatment evaluation has been performed, standardized form):

- Clinical seizure activity.
- EEG (long-term monitoring, LTM): extension of burst-suppression/complete suppression, intercurrent seizure activity. LTM needs to be carried out at least until 2h after the moment the record begins to be continuous (i.e., without suppressions, see VI.). (Thereafter, EEGs will be performed according to the clinical judgment).
- Body temperature.
- Triglycerides, CK, CRP, glucose, blood gas analysis, lactate (twice a day).
- Episodes of oxygen desaturation <90%.
- Episodes of cardiac arrhythmia (sustained supraventricular or ventricular tachycardia, bradycardia < 50 bpm, new heart blocks) associated with hemodynamic instability and requiring treatment.
- Intercurrent infections: (pneumonia, defined as new infiltrate on chest X-ray, fever, leucocytosis > 10.000 or >10% band-formed neutrophils; sepsis, defined as leucocytosis or leucopenia, acidosis, positive blood culture; urinary infection, defined as fever, leucocytosis, positive urine culture).
- Doppler/duplex confirmed deep vein thrombosis, scintigraphy or CT confirmed pulmonary embolism.
- Severe hypotension, defined as systolic BP < 90 mmHg refractory to volume expansion and requiring vasopressors (epinephrine, norepinephrine, dopamine > 5µg/kg.min).
- Administered dose of study drug.
- Class of administered antibiotics.
- Blood levels and dosage of other administered AED, particularly PHT, PB, VPA, CBZ.

Long-term assessment (standardized form):

- SE Etiology (classified according to Commission Epilepsia, 1993).
- Functional Score (0-3; 3 = death): at hospital discharge, at 21 days (+/- 2 days), at 3 months (+/- 4 days).

Note: the further etiological work-up (complementary examinations, neuroimaging, lumbar tap, etc) is up to the treating clinician. The same is true for the management of drug-related systemic complications (hypotension), and infections.

Interruption criteria:

- PRO: infusion syndrome with CK>2000 U/l (Vasile 2003), triglycerides > 5.3 mmol/l (=500mg/dl), progressive lactic acidosis > 6hrs. after treatment initiation (>2.5 mmol/l with bicarbonate <20 mmol/l), not due to sepsis, and after lactate normalization (lactate may be elevated due to prolonged seizures).
- BBT: hypersensitivity reaction with rash, fever, lymphadenopathy.
- PRO or BBT: Refractory hypotension (as judged necessary to reverse by the attending physician).

## **VI. Biostatistical analysis:**

### **Primary outcome measure and statistical method:**

The primary endpoint will be the assessment of the proportion of patients in whom control of SE has been achieved, as defined below.

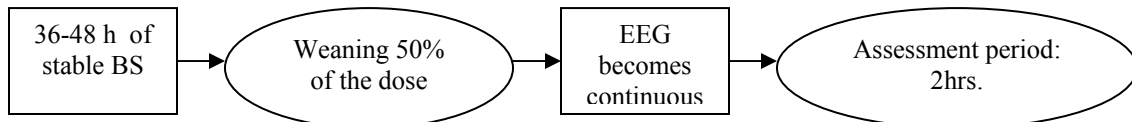
The primary analysis for this study will be the comparison of SE control between the two treatment groups (Mantel-Haenszel  $\chi^2$  test and logistic regression model). This analysis will be stratified for potential confounders (i.e., age [dichotomous, cut-off 65], SE etiology [dichotomous], seizure type at the beginning of treatment [ordinal], consciousness impairment at the beginning of treatment [ordinal], history of previous SE episodes [dichotomous], time to first-line treatment initiation [dichotomous, cut-off 1h]).

The assessment, performed by the same clinician blinded to the study treatment, occurs by inspecting the EEG recording for 2 consecutive hours (“assessment period”), beginning at the time when the record becomes continuous (i.e., no suppressions >1 second), after weaning of the study drug. This biological threshold should allow a fair comparison between the two agents, since, in consideration of the markedly variable elimination half-lives between and among the study drugs (see section I.), a correct *a priori* time prediction appears unlikely.

### **Specific criteria for SE control (all must be met):**

- Patient alive 4 days after having reached a stable burst-suppression pattern.
- No clinical need to re-titrate the study drug to a higher dose after weaning.
- $\leq 1$  discrete seizure (defined electrographically as evolving focal or generalized pattern for more than 5 sec. and less than 2 min.) per hour. A single seizure lasting more than 2 min. is sufficient for a failure. If presence of PLEDs (periodic lateralized epileptiform discharges), average interdischarge interval > 1 sec.

Interictal EEG activity is compatible with SE control.



### **Secondary outcome measures (and statistical methods):**

- Clinical outcome at day 21, assessed by the functional score (Wilcoxon rank-sum test),
- Time (days) of ventilator treatment in survivors (if censoring: log rank test; if no censoring: t-test). Ventilator weaning will be managed according to standardized ICU practices (ACCP Task Force),
- Incidence of thromboembolism (comparison of proportions).
- Incidence of infectious complications requiring specific treatment (comparison of proportions).
- Incidence of hypotension requiring specific treatment (comparison of proportions).
- Incidence of PRO infusion syndrome, defined as CK>2000 U/l (Vasile 2003) or triglycerides > 3 mmol/l (=280mg/dl) (Cramer 2001) (simple proportion).

### **Sample size:**

The primary objective is to compare the proportion of patients with control of SE after 36-48h of a stable burst-suppression pattern (interburst interval 5sec. – 15sec.) and subsequent weaning of the study drug by at least 50%.

Previous case series suggest a success proportion between 43% and 100% (see section I.); this range is extremely wide. With the described criteria, a postulated success of 75% for the best treatment seems reasonable; it would be important to determine an absolute difference of 22% (relative difference = 30%) towards the worse treatment, with  $\alpha=0.05$  (two-sided), and  $\beta = 0.2$ . The lower limit of this difference lies

10% above the lower margin of the range described above. The postulated difference between the treatments should represent a critical value for clinical practice, in consideration of the present uncertainty.

(<http://www.health.ucalgary.ca/~rollin/stats/ssize/b2.html>, accessed 8.10.2005)

A **total of 150 patients** older than 16 years old, 75 in each treatment arm, will be needed to detect a relative difference of 30% in the proportion of subjects reaching a control of their refractory SE episode after 48 h of coma induction with burst-suppression on EEG between these 2 treatment groups, with a power of 0.8, using a two-sided  $p = 0.05$  level test.

In practice, considering of the rarity of the condition, the sample size is limited (+10%). With  $p = 0.05$ , and a total sample of 150, following **power** is predicted for different proportions of success of the best treatment and relative differences:

Relative Difference		Success of best treatment				
		85%	80%	75%	70%	65%
Relative Difference	40%	1.00	0.99	0.97	0.94	0.90
	30%	0.94	0.89	0.80	0.75	0.65
	25%	0.85	0.77	0.69	0.57	0.51
	20%	0.69	0.59	0.50	0.43	0.36

With a total sample of 166 subjects (corresponding to a recruitment of 10% higher than planned), leaving the other parameters unchanged, following **power** is predicted:

Relative Difference		Success of best treatment				
		85%	80%	75%	70%	65%
Relative Difference	40%	1.00	1.00	0.99	0.97	0.94
	30%	0.97	0.93	0.83	0.82	0.72
	25%	0.90	0.83	0.76	0.64	0.57
	20%	0.76	0.66	0.57	0.49	0.42

If the success of the best treatment will be higher, the total sample size of 150 patients allows a reasonable power to detect smaller relative differences. For the opposite scenario, a higher sample size would be needed: if the best treatment will show an efficacy of only 65%, a reasonable power to detect a 30% difference could be reached with about 170 randomized patients.

A conservative estimation of ten centers recruiting each 5 patients per year for three years will be needed for completion of this study. The follow-up per patient is going to be 1 month; therefore the total duration of the study should be about 3-4 years.

As a representative example, the Brigham and Women's hospital, whose size corresponds to the average size of the other potentially participating centers, treated in the period July 2004-June 2005 (12 months) 10 patients eligible for this study.

One interim analysis after randomization of 100 patients will be performed using the Haybittle-Peto stopping rules ( $p < 0.001$ ) by the Data Safety Monitoring.

**VII. Risks and discomforts:**

The participating patients should not experience additional risks or discomfort as compared to patients in the same clinical condition not participating in the study.

Drug-determined adverse effects:

- Propofol: PRO infusion syndrome (potentially fatal cardiocirculatory and metabolic breakdown, uncommon); hypotension, transitory extrapyramidal movements (common) (Claassen 2002, Vasile 2003, Rossetti 2004).
- Barbiturates: hypersensitivity reaction (uncommon), hypotension (common) (Claassen 2002).

Adverse effects related to coma-induction (uncommon):

- Pulmonary infection, sepsis.
- Vein thrombosis, embolism.
- Decubitus.

**VIII. Potential benefits:**

No additional benefits other than careful monitoring of side effects may be expected for participating as compared to non-participating patients.

This study, being the first prospective one in this field, may represent an important step in clinical research of SE, leading to the optimization of the treatment of refractory SE.

**IX. Monitoring and quality assurance**

It is extremely unlikely that one or the other study drug will show an unexpected side effect, since all drugs have been used at least for more than 15 years for this indication.

Informed consent should be administered to surrogates (proxy), since both investigation drugs represent to date standard treatments in the investigated clinical condition; furthermore, they have to be administered in an emergency setting to mostly unconscious patients.

A Data Safety Monitoring will receive monthly data updates and will be notified within 24 hours of serious adverse events. Dr. Malin Maeder-Ingvar, Child Epileptologist at the University Hospital of Lausanne (CHUV), Switzerland, has been designated for this task. She is not an investigator for this study. She will be working together with a certified ICU specialist. Since the study is unblinded for the PIs, the role of the Data Safety Monitoring is to quickly provide them with summary data (i.e., primary endpoint, mortality) justifying an early interruption of the study.

**X. References**

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**Refractory Status epilepticus study** Patient's form

<b>Center #</b>	<b>Pt. Initials</b>	<b>D.o.B</b>	<b>Gender</b>	<b>Pregnancy test</b>

**Historical data**

<b>Known for previous seizures</b> (circle the right answer)	Yes	No
If yes, <b>AED used regularly</b> at the beginning of this SE episode	Level known	Level unknown
•		
•		
•		
•		
•		
<b>Estimated latency SE beginning – SE treatment institution</b> (hr.)		
<b>Functional score before SE episode</b> (0 = completely independent; 1 = partially dependent; 2 = dependent)		

**Day 0 (date: \_\_\_\_\_), before study treatment institution**

<b>SAPS2 score</b>		
<b>Worst seizure type before SE treatment institution</b> (SP, CP, GC, NCSEC)		
<b>Level of consciousness before SE treatment institution</b> (alert, somnolent, stuporous, comatose)		
<b>AED co-medication</b>	Level known	Level unknown
1.		
2.		
3.		
4.		
5.		
<b>Glucose</b> (mmol/l)		
<b>CK</b> (U/l)		
<b>Triglycerides</b> (mmol/l)		
<b>Lactate</b> (mmol/l)		
<b>CRP</b> (specify units)		
<b>Study drug elected by randomization</b>		
<b>Instituted at (time)</b>		
<b>Initial dosage (mg/kg/h, after the bolus)</b>		

Center #	Pt. Initials	D.o.B	Gender

**Days +1 - +9 (fill in until 48hr after treatment evaluation has been performed):**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Average dosage of study drug (mg/kg/h)									
50% weaning of the study drug (give time)									
AED co-medication (with level, if known)									
1.									
2.									
3.									
4.									
5.									
6.									
7.									
Central temperature > 37 °C (mark if yes)									
Desaturation <90% (mark if yes)									
Cardiac arrhythmia requiring treatment									
Glucose (mmol/l)									
CK (U/l)									
Triglycerides (mmol/l)									
Lactate (mmol/l), AM									
Lactate (mmol/l), PM									
CRP (mg/l)									
Proven Infection (mark what kind)									
Class of administered Antibiotics									
Proven Deep Vein Thrombosis									
Proven Pulmonary Embolism									
Severe Hypotension requiring treatment									
Mechanical ventilation									
SE untreated									
SE treated (decisive AED, hr.)									
Interruption of study drug (reason)									
Death, cause									

**Intermediate assessment (21 days after treatment institution)**

Mechanical ventilation until day after treatment institution	
SE etiology: description	
SE etiology: defined after ILAE	
Functional score (0=completely independent; 1=partially dependent; 2=dependent; 3=dead)	
Date of death, cause	

**Final assessment (3 months after treatment institution)**

Functional score (0=completely independent; 1=partially dependent; 2=dependent; 3=dead)	
Date of death, cause	

<b>Centers in USA</b>	<b>Investigator</b>	<b>email</b>	<b>#</b>	<b>IRB</b>	<b>Open</b>	<b>Recr.</b>
Brigham and Women's Hospital, Boston MA	Dr. E. Bromfield (PI USA)	ebromfield@partners.org	11	yes	07/06	4
Massachusetts General Hospital, Boston MA	Dr. A. Cole	acole1@partners.org	12	yes	11/06	3
Beth Israel & Deaconess Medical Center, Boston MA	Dr. F. Drislane	fdrislan@bidmc.harvard.edu				
U-Mass. Medical Center, Worcester MA	Dr. C. Phillips Dr. J. Narayanan	PhillipC@ummhc.org; narayanj@ummhc.org	13	yes	04/07	
Brown University Medical Center, Providence, RI	Dr. A. Blum	ABlum@Lifespan.org				
Dartmouth-Hitchcock Medical Center, Lebanon, NH	Dr. B. Jobst	Barbara.C.Jobst@Hitchcock.org	14	yes	02/08	
<b>Centers in Switzerland (CH)</b>	<b>Investigator</b>	<b>email</b>				
Centre Hospitalier Universitaire Vaudois, Lausanne	Dr. A. Rossetti (PI CH)	andrea.rossetti@chuv.ch	1	yes	06/06	8
Hôpital Cantonal et Universitaire, Genève	Dr. M. Seeck	Margitta.Seeck@hcuge.ch	4	yes	11/06	2
Kantonsspital Sankt Gallen	Dr. B. Tettenborn	barbara.tettenborn@kssg.ch dominique.fluegel@kssg.ch	3	yes	05/07	
Universitätsspital Basel	Dr. S. Rüegg	srueegg@uhbs.ch	2	yes	10/06	
Inselspital Bern	Dr. J. Mathis	mathis@insel.ch	6	yes	08/07	4
Ospedale Regionale Lugano	Dr. C. Städler	claudio.staedler@eoc.ch	7			
Spitalzentrum Biel/Centre hospitalier Bienne	Dr. F. Donati	filippo.donati@szb-chb.ch	5	yes	08/07	