PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol: A Double Blind, Placebo-Controlled, Randomized, Multicenter, Proof of Concept and Dose-finding Phase II Clinical Trial to Investigate the Safety, Tolerability and Efficacy of Adrecizumab in Patients with Septic Shock and Elevated Adrenomedullin concentration (AdrenOSS-2)
AUTHORS	Geven, Christopher; Blet, Alice; Kox, Matthijs; Hartmann, Oliver; Scigalla, Paul; Zimmermann, Jens; Marx, Gernot; Laterre, Pierre-François; Mebazaa, Alexandre; Pickkers, Peter

VERSION 1 – REVIEW

REVIEWER	Reviewer name: David Klein Institution and Country: University of Toronto, Canada Competing interests: None
REVIEW RETURNED	20-Jun-2018

GENERAL COMMENTS	Expand on choice of SIS as outcome measure Add clinicaltrials.gov registration number

REVIEWER	Reviewer name: Anthony Gordon Institution and Country: Imperial College London, UK Competing interests: None
REVIEW RETURNED	05-Jul-2018

GENERAL COMMENTS	In this manuscript the authors describe a double-blind placebo controlled RCT of Adrecizumab in septic shock. This is an early phase trial to test mainly the safety and tolerability of the drug but has been powered on an efficacy signal. It appears to be an important and methodological robust trial and generally a well written manuscript. My main comments focus on the efficacy outcome, sample size and power calculations. The “Sepsis Support Index” over 14 days is the primary efficacy outcome. This is novel but makes sense. It is essentially equivalent (or inverse) to “Days alive and free of ventilation, vasopressor support and renal failure”. However, death or organ failure are scored as a point, and so a high score is a bad outcome. It is the reverse of “Days alive and free…” The power calculation was based on simulation which seems appropriate given that the distribution of the SSI is unlikely to be normally distributed. A non-parametric test is planned for the final analysis.

	However, the authors do not state what the SSI in the control group is expected to be. This should be given. Also an effect size of 10% is expected. What does that mean; that the SSI in the treatment group(s) is expected to be 10% lower? Or that each of the composite outcomes that make up SSI are 10% improved? Where does the 80% probability of improvement of SSI >0 fit in the power calculation? I am not a statistician but the analysis plan is slightly confusing. The first analysis is to check if there is an 80% probability that improvement in SSI is >0. This sounds like a Bayesian analysis. But then a p-value will be calculated and combined with the power calculation discussed above this sounds like a frequentist design. I think this is confusing and should be clarified. As an early phase trial many exploratory analyses are planned and this is therefore justified. But the planned analyses should be more clearly defined a priori. For instance, in line 288 which "potential confounders" will be included? If they are not pre-specified then how they are to be selected must be pre-specified. Similarly, in the planned subgroup analyses what are the pre-specified subgroup definitions, ie which disease severity markers, other clinical data will be used. Again, if the actual values for defining subgroups can't be given then the criteria to be used must be given a priori, such as dichotomising using the median value or split into quartiles. At the moment these descriptions are too vague and could allow post-hoc data mining. The pre-planned futility stopping rule may be overruled if other data are supportive, which is sensible. But who will be responsible for making the final stop / go decisions. Is there a trial steering committee or is it the sponsor? I don't think the trial sponsor is stated in the manuscript and this should be added (if not there already). In the introduction (line 104-5) I think it would be useful to state how many healthy volunteers were studied in the phase I studies.

REVIEWER	Reviewer name: Michelle Chew Institution and Country: Professor, Department of Anaesthesia and Intensive Care, Medical and Health Sciences Linköping University, Sweden 58185 Competing interests: None declared
REVIEW RETURNED	07-Jul-2018

GENERAL COMMENTS	In this manuscript Geven and colleagues present their study protocol for AdrenOSS-2, a randomized, multicenter study designed to test the safety and tolerability of Adrecizumab in patients with septic shock. The study has been prospectively registered in clinicaltrials. gov and is ongoing. Rationale: The study is relevant insofar as septic shock is still a major health problem associated with high morbidity, mortality and resource use. It is also a logical continuation of the group's preclinical experiments and a Phase I study in healthy volunteers. The rationale behind the investigation makes sense. ADM is a pleiotropic molecule that may exert variable effects on the vascular system – on the one hand restoring vascular endothelial function and thereby reducing some of the undesired effects of sepsis,

	and on the other hand inducing hypotension and further aggravating hypotension in septic shock. The study drug, Adrecizumab, which is a non-neutralizing antibody, acts by modulating (rather than blocking) ADM which the authors hope will preserve its beneficial effects while minimizing any adverse effects. Choice of subjects: Stratification according to biomarker level makes sense in an attempt to delineate subgroups that may benefit from therapy. The authors refer to a few key studies some of which are as yet unpublished. There are a number of other studies (albeit using MR-pro-ADM) that support the use of adrenomedullin as a biomarker. Examples include Elke et al. (Crit Care 2018;22:79), Lundberg et al. (Crit Care 2016;20:178) and Andaluz-Ojeda et al. (Ann Int Care 2017;7:15). Given that this is a novel study with largely unknown effects of the study drug, I think that it is important for the authors to demonstrate that they have taken into account all available information on ADM and sepsis prior to planning of the study. Screening and eligibility: Please provide a statement on eligibility criteria, how patients will be screened, and if a screening and eligibility log will be kept. Figure 1 requires modification for the screening process. As it stands now it begins when patients have already been included so it is impossible to assess the proportion of patients that were eligible but not included in the study. Inclusion and exclusion criteria: Are explicitly stated. A minor query regarding inclusion criteria #6 'Women of childbearing potential……have to use a highly effective method of contraception'. What is meant by a 'highly effective method' and for what time period? Exposure: Measurement of bio-ADM appears logical since it reflects biologically active levels, as opposed to the measurement MR-pro-ADM which measures an inactive prohormone. I cannot comment on the accuracy of this assertion and have accepted the author's expertise in this area. The choice of cut-off (bio-ADM of 70pg/ml) is difficult to evaluate. Of the 3 references given only one is published and that study contained a sample size of 956 patients where a cut-off of 110pg/ml was used for evaluating 90-day mortality outcome (ie. different cut-off and different outcome). Who will measure bio-ADM? Is this a bedside test? How reliable are the measurements? Does it require calibration? Please provide a statement regarding assay variability and laboratory quality control. Outcome reporting: Primary and secondary outcomes are clearly reported and defined. There are a number of secondary efficacy-related outcomes. I support the use of a composite end-point because this allows a more nuanced assessment of both morbidity and mortality. The use of composite end-points is common in other specialities (eg. cardiology) but is rare within intensive care medicine and may be relevant in reducing type II errors. I also support the choice of 14 days in this type of preliminary study in order to reduce the risk of confounding by random events unrelated to the treatment when more distant end points are chosen.

	I appreciate and support the SSI and its use as an endpoint. However, I note that single organ dysfunction is rated equally as multiorgan dysfunction. Thus, the SSI does not provide enough granularity to assess the degree of 'organ dysfunction', although this information may be provided by the SOFA score that is also a secondary outcome parameter. The use of vasopressor therapy may be related to sedation alone and the authors may like to consider this in their SSI definition. Since this treatment targets vascular tone, the authors may also wish to consider vasopressor inotrope score or inotropic index as a secondary outcome. Blinding of study personnel: All study personnel are adequately blinded and breaking of the blinding code is strictly regulated. Therefore, performance bias is extremely unlikely. Data collection and management: Data will be entered into electronic case report forms. Will source documentation be photocopied, or stored in any other way? Please also state where the data will be kept, for how long and if the data will be pseudonymized. Where will the key-codes be stored? Please also include a statement on patient data confidentiality and compliance to current regulatory requirements (eg. GDPR since the study sites are all within the EU). Statistical analysis: The sample size calculation was based on simulation analyses based on data from a subgroup of another unrelated study in patients with sepsis (ALBIOS, ref #15) as well as the AdrenOSS-1 study. The calculation was made for the primary efficacy endpoint, SSI at day14. Although this approach seems reasonable, the authors may wish to clarify why the sample size calculation was made for a secondary endpoint instead of the primary, safety endpoint. In Heyland et al (ref#26) the incidence of SSI (=death + persistent organ dysfunction) was 53% on Day 14. In ref#15, which the sample size calculation was partially based on, only 90-day mortality data are reported. I wonder how information on organ dysfunction and death at 14 days were extracted, and I would appreciate a description of the assumed values used for sample size calculation. It is not clear how the primary end-point will be analyzed statistically. There are multiple secondary end-points. It may be helpful to the reader if the variables, outcome measures and planned statistical tests are outlined in a table. Please outline how multiple testing will be handled. I note the intention-to-treat analysis, as well as the planned per-protocol analysis. Interim analysis is planned for futility, and there is a prespecified decision rule. I wonder why there will be stopping rules for futility and not for harm, which is reflected by the primary end point? Are there different stopping rules for harm that do not employ a statistical criterion?

	The statistical analysis planned is marred by the fact that the interim analysis will be unblinded. What is the reason for this? The authors may wish to consider conducting a blinded interim analysis, with unblinding to DSMB if safety issues exist. The authors should also state who will conduct the interim analysis eg. independent statistician; and who has the ultimate authority to stop the study. Missing data: How will the authors handle data where there is a decision to withdraw or withhold therapy or to withdraw from the study? And how will other missing data be handled? Data monitoring and audits: These are clearly specified. A DSMB has been established and meets monthly. I am not entirely sure that the study monitors should 'discuss the conduct of the study'. Rather, the role of monitors is to review source documents if required, and to determine if the reported data are accurate and complete. Ethics and dissemination: Please state how consent will be acquired, and who will be conducting this process, including any training given. Please also state whether a biobank will be used, and if the samples will be stored for future use. Will there be any secondary studies, and if so, will the patients' informed consents encompass these? Who will have access to the data, and will individual patient data be made available after the study has been published? Finally, please be explicit regarding the role of the sponsor (although some detail is already given) and state if this is an investigator- or industry-initiated study. Summary: In general, this is a well-considered and well-written manuscript describing the protocol for a double blind, randomized, controlled multicentre study investigating a novel drug for the treatment of septic shock. Recruitment has started but the planned interim analysis has not been conducted. The study has several notable strengths – the use of an appropriate randomization procedure with random (block) sequence generation and excellent allocation concealment; and blinding of treating and research personnel. The use of a biomarker to isolate a more homogeneous group of patients is also a strength. The end-points are well defined and appropriate. A few additional details are required regarding recruitment and screening, as well as the conduct of the statistical analysis including interim analysis. Specifically, I believe that a statistical analysis plan for the primary outcome should be included and the interim analysis should be blinded. Thank you for the opportunity to read and comment this protocol. Professor Michelle S Chew Department of Anaesthesia and Intensive Care Medical and Health Sciences Linköping University Hospital S-58185 Sweden

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 1. Expand on the choice of SIS as outcome measure.

Authors' response

Traditionally, survival was often used as a primary efficacy endpoint in major sepsis trials. However, because of the large number of failed trials, it is now thought that this endpoint may not be sensitive enough to demonstrate beneficial effects of novel interventions in sepsis patients. The use of composite endpoints allows for a more nuanced assessment of morbidity and mortality. The Sepsis Support Index (SSI) combines hemodynamic/pulmonary organ support, renal organ dysfunction and all-cause mortality. These organ systems were improved by Adrecizumab administration in preclinical models, and support of these organ systems defines ICU care, indicating that a therapeutic effect is of clinical relevance. The SSI is thought to allow for earlier and more sensitive observations of possible clinically relevant beneficial effects of Adrecizumab compared to more traditional primary efficacy endpoints. Our study is not the first to incorporate a composite endpoint, for example, the SEPSIS-act study used a primary endpoint of pressor- and ventilator-free days, with penalization if the patient died within 30 days (Lewis et al. Ann Am Thorac Soc; 2018).

The above explanation is also described in the discussion of the article on page 20, lines 554-565.

Authors' actions

We added an additional sentence to the relevant section of the discussion:

"The use of composite endpoints allows for more a nuanced assessment of morbidity and mortality".

2. Add clinicaltrials.gov registration number.

Authors' response

This was mentioned after the abstract as "Trial registration number: NCT03085758".

Author's actions

To make it clear that the registration number refers to a clinicaltrials.gov registration number we changed the sentence into: "ClinicalTrials.gov registration number: NCT03085758".

Reviewer 2

In this manuscript the authors describe a double-blind placebo controlled RCT of Adrecizumab in septic shock. This is an early phase trial to test mainly the safety and tolerability of the drug but has been powered on an efficacy signal. It appears to be an important and methodological robust trial and generally a well written manuscript.

1. My main comments focus on the efficacy outcome, sample size and power calculations.

The "Sepsis Support Index" over 14 days is the primary efficacy outcome. This is novel but makes sense. It is essentially equivalent (or inverse) to "Days alive and free of ventilation, vasopressor support and renal failure". However, death or organ failure are scored as a point, and so a high score is a bad outcome. It is the reverse of "Days alive and free…"

Authors' response

Indeed, a high score reflects a higher need of organ support and/or mortality, and thus indicates a more adverse disease course for the patient. The reviewer is correct to point out that it essentially is the reverse of days alive and free of ventilation, vasopressor support and renal failure.

2. The power calculation was based on simulation which seems appropriate given that the distribution of the SSI is unlikely to be normally distributed. A non-parametric test is planned for the final analysis. However, the authors do not state what the SSI in the control group is expected to be. This should be given.

Authors' response

In the previously conducted (and as of yet unpublished) observational AdrenOSS-1 study performed in septic patients, the median SSI for patients with septic shock and bio-ADM larger than 70 pg/mL was 4 (IQR 2-11), while in ALBIOS (Caironi et al., Chest 2017; 152(2): 312-320), median SSI for patients with septic shock and bio-ADM larger than 70 pg/mL was 7 (IQR 4-14).

Authors' actions

We added the following sentence to the "Sample size calculations" section of the manuscript:

"Based on the previously conducted (yet unpublished) observational AdrenOSS-1 study performed in septic patients, we anticipate a median SSI in the control group of 4 [IQR 2-11], while in the ALBIOS study the median was 7 (IQR 4-14) (these medians reflect a selection of patients with septic shock and bio-ADM larger 70 pg/mL). However, due to the non-normal distribution of the SSI, the median is still highly volatile (the majority of patients have either a low SSI (1-3 days, if improving and discharged early), or a high SSI (14 days, as patients that die within the first 14 days are usually on organ support while alive and in ICU))."

3. Also an effect size of 10% is expected. What does that mean; that the SSI in the treatment group(s) is expected to be 10% lower? Or that each of the composite outcomes that make up SSI are 10% improved? Where does the 80% probability of improvement of SSI >0 fit in the power calculation?

Authors' response

The SSI for each patient in the Adrecizumab-treated group was reduced, such that, given the restraints of the SSI (cannot be below 1 (=as vasopressors on day 1 is mandatory for inclusion) or larger than 14), the resulting simulated delta translated into an approx. 10%

lower SSI score compared to the simulated pseudo-median score in the control group. Note that the Wilcoxon test, and therefore the estimated delta between treatment groups, is not based on the difference in medians but rather the median of the difference between a sample from the treatment group and a sample from the control group. Individual components of the SSI were not simulated.

Power was defined as the probability of rejecting the null hypothesis (of no difference between groups), i.e. delta SSI > 0. The 80% probability corresponds to the lower limit of the 60%-confidence interval of the estimated difference in location, the delta SSI. In simulations, if the lower limit was >0 the simulation run reached the endpoint.

Authors' actions

We rewrote the "sample size calculation" section for improved clarity:

"For the simulations, a sample size of n=150 per group (treatment or placebo), and an effect size resulting in an approximately 10% decrease in SSI in the Adrecizumab-treatment group (compared to the simulated control group) resulted in a power of the study of more than 80% to demonstrate an improvement of SSI of > 0 with at least 80% probability. The 80% probability corresponds to the lower limit of the 60%-confidence interval of the effect estimate, delta SSI, which is based on the estimated difference of location from the Wilcoxon test. If the simulated lower limit of delta SSI was > 0, the simulation run reached the endpoint."

4. I am not a statistician but the analysis plan is slightly confusing. The first analysis is to check if there is an 80% probability that improvement in SSI is >0. This sounds like a Bayesian analysis. But then a p-value will be calculated and combined with the power calculation discussed above this sounds like a frequentist design. I think this is confusing and should be clarified.

Authors' response

Both calculations are based on the probabilities derived from the confidence interval for the estimate of location difference from the Wilcoxon test. The first goal is to reach a delta SSI >0 with 80% probability, i.e. the lower limit of the (one sided) 80% confidence interval needs to be >0. Second, we evaluate whether the (two sided) lower limit of the 95% confidence interval is also >0.

Authors' actions

We rewrote a section of the statistical analyses (page 10) to improve clarity:

"The primary efficacy endpoint, 14-day SSI, will be analyzed using the non-parametric Wilcoxon test, to estimate the treatment effects (based on the Wilcoxon estimate for difference in location) as well as its confidence interval. First, it will be determined whether the improvement in SSI due to treatment is > 0 with at least 80% probability (based on the lower limit of the one-sided confidence interval of the effect estimate of the Wilcoxon test). If this is achieved, the classical p-value from the Wilcoxon test will also be calculated."

5. As an early phase trial many exploratory analyses are planned and this is therefore justified. But the planned analyses should be more clearly defined a priori. For instance, in line 288 which "potential confounders" will be included? If they are not pre-specified then how they are to be selected must be pre-specified.

Authors' response

We agree with the reviewer and have now described this more clearly.

Authors' actions

We have added the following sentences to the statistical analysis section:

"Potential confounders include age, gender, MAP, HR, source of infection, blood culture, comorbidities and initial SOFA score, as well as variables showing significant between-group differences (despite randomization).".

and

"Statistical analysis of secondary endpoints is exploratory, and will be specified in a separate statistical analysis plan, which is to be finished before conclusion of the study."

6. Similarly, in the planned subgroup analyses what are the pre-specified subgroup definitions, ie which disease severity markers, other clinical data will be used. Again, if the actual values for defining subgroups can't be given then the criteria to be used must be given a priori, such as dichotomising using the median value or split into quartiles. At the moment these descriptions are too vague and could allow post-hoc data mining.

Authors' response and actions

We agree with the reviewer and have added the following to the statistical analyses:

“The subgroup analyses are nevertheless purely exploratory. Subgroups will be defined by tertiles for continuous variables. For categorical variables, categories will be summarized such that they best represent tertiles if more than 3 categories are available.”

7. The pre-planned futility stopping rule may be overruled if other data are supportive, which is sensible. But who will be responsible for making the final stop / go decisions. Is there a trial steering committee or is it the sponsor? I don’t think the trial sponsor is stated in the manuscript and this should be added (if not there already).

Authors’ response

An independent statistician will do the futility analysis, and provide the stop/go result to the steering committee, which will remain blinded as long as the trial is running.

Regarding the sponsor of the trial: Correct, this was not literally stated in the manuscript. In the “Funding” section of the manuscript, it was stated that the work was supported by Adrenomed AG.

Authors’ actions

We added the following sentence to the section “Interim analysis with futility stop”:

“An independent statistician is responsible for analysing the data at interim analysis, and the steering committee, as well as the sponsor will remain blinded until the end of the study.”

We added “(the study sponsor)” to the sentence in the “funding” section of the manuscript.

8. In the introduction (line 104-5) I think it would be useful to state how many healthy volunteers were studied in the phase I studies.

Authors’ response and actions

We added the numbers to the relevant sentence in the introduction.

“Importantly, Adrecizumab administration was not associated with any safety concerns in the first-in-human phase I study in healthy volunteers (n=24) and in a follow-up study in healthy volunteers which were intravenously challenged with lipopolysaccharide (LPS) to induce systemic inflammation (also n=24).”

Reviewer 3

In this manuscript Geven and colleagues present their study protocol for AdrenOSS-2, a

randomized, multicenter study designed to test the safety and tolerability of Adrecizumab in patients with septic shock. The study has been prospectively registered in clinicaltrials.Gov and is ongoing.

Rationale: The study is relevant insofar as septic shock is still a major health problem

associated with high morbidity, mortality and resource use. It is also a logical continuation of the group’s preclinical experiments and a Phase I study in healthy volunteers.

The rationale behind the investigation makes sense. ADM is a pleiotropic molecule that may exert variable effects on the vascular system – on the one hand restoring vascular

endothelial function and thereby reducing some of the undesired effects of sepsis, and on

the other hand inducing hypotension and further aggravating hypotension in septic shock.

The study drug, Adrecizumab, which is a non-neutralizing antibody, acts by modulating

(rather than blocking) ADM which the authors hope will preserve its beneficial effects while minimizing any adverse effects.

1. Choice of subjects: Stratification according to biomarker level makes sense in an attempt to delineate subgroups that may benefit from therapy. The authors refer to a few key studies some of which are as yet unpublished. There are a number of other studies (albeit using MRpro- ADM) that support the use of adrenomedullin as a biomarker. Examples include Elke et al. (Crit Care 2018;22:79), Lundberg et al. (Crit Care 2016;20:178) and Andaluz-Ojeda et al. (Ann Int Care 2017;7:15).

Authors' response

It is true that there are a great number of observational studies that investigated the ADM system in sepsis, often by measuring the surrogate marker MR-proADM. However, in the AdrenOSS-2 study, C-terminally amidated ADM (the 'bioactive form' of ADM, hence referred to as 'bio-ADM') is used for patient inclusion. Both biomarkers have prognostic value for sepsis and correlate with need for organ support (vasopressors, RRT), positive fluid balance, organ dysfunction, length of stay and mortality. However, even although MR-proADM is derived from the same precursor in a similar ratio, it is a peptide with no biologically active effects, and in theory, has 2 limitations:

1) MR-proADM measurements do not take into account that a significant amount of adrenomedullin is circulating in its 'inactive' glycine-extended form, and only a limited amount is circulating in bio-active form.

2) Clearance kinetics of MR-proADM and bio-ADM likely differ. Thus, bio-ADM measurements may better reflect the activity of the ADM system and may correlate better with the clinical status of the patient.

So far, MR-proADM and bio-ADM were only compared head-to-head in a subgroup of patients in a single study (Marino et al. Crit Care; 2014). In this study, bio-ADM correlated better with 28-day mortality (AUC 0.74 versus 0.60).

Because the bio-ADM assay is relatively new, naturally, the available body of literature is less extensive. We do refer to two 'unpublished studies', which are currently both under review elsewhere, because we consider them relevant for the present manuscript. If these are not accepted prior to acceptance of this manuscript, we could remove them or refer to them as (yet unpublished data) in the text.

Please see the following publication for more information regarding the bio-ADM assay:

Weber J, Sachse J, Bergmann S, et al. Sandwich Immunoassay for Bioactive Plasma Adrenomedullin. J Appl Lab Med 2017;2:222-233.

2. Given that this is a novel study with largely unknown effects of the study drug, I think that it is important for the authors to demonstrate that they have taken into account all available information on ADM and sepsis prior to planning of the study.

Authors' response

We agree that this is important. The reviewer might appreciate that the sponsor (Adrenomed AG) and steering committee of the study have spent a long time preparing for such a study, and before deciding to expose patients to a new drug. Many years of development and research by Adrenomed AG and collaborators were necessary before this step could be taken.

Previous research includes extensive evaluation of preclinical safety in animals (including mice, rats, dogs and cynomolgus monkeys, submitted), clinical safety in humans (first-in-human phase I studies, published and referred to in our manuscript, ref: Geven et al. British Journal of Clinical Pharmacology, 2018), as well as efficacy studies in a wide range of animals and models (of which only a few studies have been published so far, multiple are currently submitted).

In addition, institutional review boards and independent ethics committees studied the study protocol and other relevant information (such as the investigator brochure [IB] and investigational medical product dossier, which contain all previous research), before approving the study protocol. Patient safety was an important consideration for these boards and committees.

Data is reviewed and extensively discussed in 2 review articles (Geven et al. Frontiers in Immunology 2018; Geven et al. Shock 2018). We also refer to these publications in the manuscript.

3. Screening and eligibility: Please provide a statement on eligibility criteria, how patients will be screened, and if a screening and eligibility log will be kept. Figure 1 requires modification for the screening process. As it stands now it begins when patients have already been included so it is impossible to assess the proportion of patients that were eligible but not included in the study.

Authors' response

Screening and enrolment logs will be maintained for all patients. For patients not enrolled in the study, the reason for non-enrolment is documented. Therefore, it will be possible to assess the proportion of patients that were eligible but not included in the study.

Regarding the screening process: patients will undergo various screening assessments, including recording of information on hospital and ICU admission (date, time, location before admission, diagnosis, origin of sepsis), documenting of relevant ongoing conditions, relevant medical history and comorbidities present or treated within the last year (cardiovascular and non-cardiovascular), concomitant medication use, age, gender, ethnic origin, physical examination including weight and height, blood sampling for laboratory examinations and bio-ADM measurement, pregnancy test (urine or serum), recording of 12-lead ECG, and calculation of APACHE II and SOFA score. Eligibility criteria are currently presented in Table 1.

Authors' actions

Added the following section to "Patient selection":

"Screening and enrolment logs will be maintained for all patients. For patients not enrolled in the study, the reason for non-enrolment is documented. Patients will undergo various screening assessments, including recording of information on hospital and ICU admission (date, time, location before admission, diagnosis, origin of sepsis), documenting of relevant ongoing conditions, relevant medical history and comorbidities present or treated within the last year (cardiovascular and non-cardiovascular), concomitant medication use, age, gender, ethnic origin, physical examination including weight and height, blood sampling for laboratory examinations and bio-ADM measurement, pregnancy test (urine or serum), recording of 12-lead ECG, and calculation of APACHE II and SOFA score."

Also, Figure 1 was altered to include more information regarding the screening process.

4. Inclusion and exclusion criteria: Are explicitly stated. A minor query regarding inclusion

criteria #6 'Women of childbearing potential……have to use a highly effective method of

contraception'. What is meant by a 'highly effective method' and for what time period?

Authors' response:

The following contraception methods are considered highly effective and have to be used until 6 months after the end of infusion. These were specified in the study protocol:

 Hormonal (estrogen and progesterone) contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation.

 Progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.

 Intrauterine deviced (IUD) or intrauterine hormone releasing systems (IUS)

 Bilateral tubal occlusion

 Vasectomy

We felt that this information was too extensive to include in the published protocol in BMJ open, but if the editor/reviewer wishes, we are willing to include this information in the manuscript.

5. Exposure: Measurement of bio-ADM appears logical since it reflects biologically active levels, as opposed to the measurement MR-pro-ADM which measures an inactive prohormone. I cannot comment on the accuracy of this assertion and have accepted the author's expertise in this area. The choice of cut-off (bio-ADM of 70pg/ml) is difficult to evaluate. Of the 3 references given only one is published and that study contained a sample size of 956 patients where a cut-off of 110 pg/ml was used for evaluating 90-day mortality outcome (ie. different cut-off and different outcome).

Authors' response

For details on the assay, please refer to our answers to question 1 and 6. Regarding the cut-off value, all data available at the time was re-evaluated for the specific needs and purpose of the planned intervention study in patients with septic shock. Per patient data available for this evaluation included data from ALBIOS, Frog-ICU and AdrenOSS-1, to name the largest and most relevant, as well as data from healthy normals. Specific needs to be met for the first phase 2 study included that patients with normal bio-ADM, as well as low severity and low expected mortality were to be excluded, to maximise the observable treatment effect, while keeping the eligible population as large as possible. That the

selected cut off was 70 pg/ml was identical to the one used in Marino et al. was coincidental.

Authors' actions

We have added the following to the manuscript:

"The cut-off point for bio-ADM of 70 pg/mL was selected based on the specific needs and purpose of this study. Per patient data available for this evaluation included data from the ALBIOS, Frog-ICU and AdrenOSS-1 studies, to name the largest and most relevant, as well as data from healthy normal individuals. Specific needs to be met for the study were that patients with normal bio-ADM, as well as low severity and low expected mortality were to be excluded, to maximise the observable treatment effect, while keeping the eligible population as large as possible."

6. Who will measure bio-ADM? Is this a bedside test? How reliable are the measurements?

Does it require calibration? Please provide a statement regarding assay variability and

laboratory quality control.

Authors' response

The bio-ADM assay used (sphingotest® bio-ADM®, sphingotec GmbH, Hennigsdorf, Germany) is a fully validated CE-marked, commercially available IVD, quality-controlled by the manufacturer and thus reliable. Basic characteristics of the assay have been published (Weber et al., 2017). It will be performed locally by trained personnel. Each patient sample will be measured in duplicate, and in parallel two calibrators (one with a concentration around the decision making point (70 pg/mL)) will be run in triplicate along with each patient sample. The functionality of the measuring system will be checked on a monthly basis at each site. Finally, bio-ADM will be re-measured from banked aliquots in batch at a central lab to verify locally gained results.

Authors' actions

Added new section 'Measuring bio-ADM':

"For measurement of bio-ADM, 5 mL EDTA blood will be collected after written informed consent is obtained. After centrifugation (2500G, 15 minutes, 20°C), bio-ADM levels are determined using a fully validated, CE-marked, commercially available immunoluminometric assay (sphingotest® bio-ADM assay, sphingotec GmbH, Hennigsdorf, Germany). This assay is performed locally by trained personnel. The assay is highly specific for C-terminally amidated adrenomedullin (the biologically active form of adrenomedullin, hence named bio-ADM). Each patient sample will be measured in duplicate, and in parallel two calibrators (one with a concentration around the decision-making point (70 pg/mL)) will be run in triplicate along with each patient sample. The functionality of the measuring system will be checked on a monthly basis at each site. Finally, bio-ADM will be re-measured from banked aliquots in batch at a central lab to verify locally gained results. Further details about the assay are described elsewhere.25"

7. Outcome reporting: Primary and secondary outcomes are clearly reported and defined. There are a number of secondary efficacy-related outcomes. I support the use of a composite end-point because this allows a more nuanced assessment of both morbidity and

mortality. The use of composite end-points is common in other specialities (eg. cardiology)

but is rare within intensive care medicine and may be relevant in reducing type II errors. I also support the choice of 14 days in this type of preliminary study in order to reduce the risk of confounding by random events unrelated to the treatment when more distant end points are chosen. I appreciate and support the SSI and its use as an endpoint. However, I

note that single organ dysfunction is rated equally as multiorgan dysfunction. Thus, the SSI does not provide enough granularity to assess the degree of 'organ dysfunction', although this information may be provided by the SOFA score that is also a secondary outcome parameter.

Authors' response

Indeed, SSI does not assess the degree of organ dysfunction. The SOFA score does, and is assessed daily during ICU stay. We had to choose one version of the SSI as the primary efficacy endpoint, other versions are of course possible. In addition, we had to choose between rating single organ failures, multiple organ failures or death either equally for each day, or differently – which leaves the problem of defining weights for death vs. multi-organ failure vs. single organ failure.

8. The use of vasopressor therapy may be related to sedation alone and the authors may like to consider this in their SSI definition.

Authors' response

Indeed, patients with hypotension clearly related to infusion of sedatives (e.g. for intubation/surgery)/clearly not directly related to sepsis, should not be eligible for the study. Such patients will however not be meeting the other required inclusion criteria, and therefore such a patient would not be enrolled. Vasopressor therapy during ICU stay is relevant for primary and secondary efficacy endpoints. For simplicity, generalizability and practical reasons, we believe any treatment with vasopressors should be counted, even if it should be solely related to sedation during follow up on the ICU.

9. Since this treatment targets vascular tone, the authors may also wish to consider

vasopressor inotrope score or inotropic index as a secondary outcome.

Authors' response

Although this was not yet specified in the manuscript, vasopressor use is recorded daily (drug names, highest/lowest dose, starting time, duration) and will be analysed as an exploratory endpoint. We have the cardiac SOFA component as a secondary endpoint, as well as total duration of vasopressor therapy. The same is true for infusion policy and fluid balance, as ADM and the intervention influenced capillary leakage in preclinical studies.

We added this to the secondary objectives section of the manuscript:

"Total duration of vasopressor/catecholamine use"

10. Blinding of study personnel: All study personnel are adequately blinded and breaking of the blinding code is strictly regulated. Therefore, performance bias is extremely unlikely. Data collection and management: Data will be entered into electronic case report forms. Will source documentation be photocopied, or stored in any other way?

Please also state where the data will be kept, for how long and if the data will be pseudonymized. Where will the key-codes be stored? Please also include a statement on

patient data confidentiality and compliance to current regulatory requirements (eg. GDPR

since the study sites are all within the EU).

Authors' response

Source data archiving:

The clinical center is responsible for the secure and restrictive archiving of source data (both paper and electronic) for at least 15 years or until the written notification from the

sponsor that the documents are no longer required. During the required period, the clinical center will ensure that archived data and documents will be undamaged, legible and accessible to the sponsor and/or for regulatory purposes, if required. The study master file, the ECRFs, code envelopes and other material supplied for the performance of the study will be retained by the sponsor according to applicable regulations and laws.

Pseudonymization:

Patients are pseudonymized via a unique 6-digit patient identification number in ascending order at inclusion which will include country (1 digit), site number (2 digits), patient number (3 digits). For example 1-01-001, 1-01-002, etc. The pseudonymization list is only stored locally at the participating sites.

Source data are transcribed to and reported through the eCRF. It is to be ensured by the investigator that documents that are given to the sponsor or its representatives (this also includes the eCRF) do not contain the name or address of the patient, or other information that would affect the anonymity of the patient. Possible addenda to the eCRF (i.e. clinical laboratory reports, ECG printouts) should bear the patient identification number, allocated randomization code, study day and time, and signature of the investigator.

The code list with treatment allocations (randomization list) is stored separately from the Sponsor at the data management vendor during the course of the study (see also section “Blinding”). These data management vendors will provide all relevant data (pseudonymized) to the sponsor after the end of the study. In addition, sets of sealed envelopes with the randomization codes will be prepared containing information about treatment and the dose the patient had received (dose of Adrecizumab or placebo) for each patient: One is kept at the clinical study site to be used in case of emergency (during the entire study period). One is kept with the secretary of the DSMB (pharmacovigilance expert). One is kept with the party responsible for reporting of a suspected unexpected SUSAR as required by the regulatory agencies. The evaluation and decision to whether a SAE qualifies as SUSAR is the responsibility of the sponsor or designee.

Confidentiality

The investigators, designated CRO and Adrenomed AG and all other involved parties will preserve the confidentiality of all patients taking part in the study, in accordance with ICH-GCP and local regulations. The confidentiality of all patient identities will be maintained, except during source data verification, when monitors, auditors and other authorized agents of the sponsor or its designee, the IECs approving this research, as well as any other applicable regulatory authorities will be granted direct access to the study patients’ original medical records. No material bearing a patient’s name will be kept on file by designated CRO or Adrenomed AG. The data retained from this study will be protected in accordance with all applicable legal requirements. Information about study patients will be kept confidential and managed according to the requirements of the EU-Directives 2001/20/EC, 2005/28/EC, and 2003/63/EC and relevant national and local legislations. All ongoing subjects signed the ICF (including the data protection part) and additionally the “Information letter for ongoing Patients” regarding the new GDPR/ (DSGVO, Germany). All patients have been informed by investigators before they signed these documents.

Authors’ actions

Added to section ‘Data quality assurance’:

“The clinical center is responsible for the secure and restrictive archiving of source data for at least 15 years or until the written notification from the sponsor that the documents are no longer required. During the required period, the clinical center will ensure that

archived data and documents will be undamaged, legible and accessible to the sponsor and/or for regulatory purposes, if required. The study master file, the ECRFs, code envelopes and other material supplied for the performance of the study will be retained by the sponsor according to applicable regulations and laws, including the new GDPR (see also the section on confidentiality).”

Added to section confidentiality:

“The investigators, designated CRO and sponsor and all other involved parties will preserve the confidentiality of all patients taking part in the study, in accordance with ICH-GCP and local regulations.”

“The code list with treatment allocations (randomization list) is stored separately from the Sponsor at the data management vendor during the course of the study.

These data management vendors will provide all relevant data (pseudonymized) to the sponsor after the end of the study. In addition, sets of sealed envelopes with randomization codes are kept at the site for emergency unblinding, with the DSMB, and with the party responsible for reporting SUSARs as required by regulatory agencies."

"Data retained from this study will be protected in accordance with all applicable legal requirements. Information about study patients will be kept confidential and managed according to the requirements of EU-directives 2001/20/EC, 2005/28/EC and 2003/63/EC, and relevant national and local legislation. All ongoing subjects signed the ICF (including the data protection part) and additionally the "Information letter for ongoing Patients" regarding the new GDPR/(DSGVO, Germany). All patients and/or their legal representatives will be informed by investigators before they signed these documents."

11. Statistical analysis:

The sample size calculation was based on simulation analyses based on data from a

subgroup of another unrelated study in patients with sepsis (ALBIOS, ref #15) as well as the AdrenOSS-1 study. The calculation was made for the primary efficacy endpoint, SSI at day 14. Although this approach seems reasonable, the authors may wish to clarify why the sample size calculation was made for a secondary endpoint instead of the primary, safety endpoint.

Authors' response

Power was based on the primary efficacy endpoint, because a good estimation of efficacy is needed in order to plan a phase III study. The sample size used is typical for phase II studies and regarded as sufficient for evaluation of safety.

12. In Heyland et al (ref#26) the incidence of SSI (=death + persistent organ dysfunction) was 53% on Day 14. In ref#15, which the sample size calculation was partially based on, only 90-day mortality data are reported. I wonder how information on organ dysfunction and death at 14 days were extracted, and I would appreciate a description of the assumed values used for sample size calculation.

Authors' response

The authors of ref#15 provided us with the individual patient data (without which the simulation would not have worked). To answer the second question, in the previously conducted (and as of yet unpublished) observational AdrenOSS-1 study performed in septic patients, the median SSI for patients with septic shock and bio-ADM larger 70

pg/mL was 4 (IQR 2-11), while it was 7 (IQR 4-14) in the ALBIOS study (also in patients with septic shock and bio-ADM > 70 pg/mL).

Authors' actions

We added a sentence to the "Sample size calculations" section of the manuscript:

"Based on the previously conducted (yet unpublished) observational AdrenOSS-1 study performed in septic patients, we anticipate a median SSI in the control group of 4 [IQR 2-11], while in the ALBIOS study the median was 7 (IQR 4-14) (these medians reflect a selection of patients with septic shock and bio-ADM larger 70 pg/mL). However, due to the non-normal distribution of the SSI, the median is still highly volatile (the majority of patients have either a low SSI (1-3 days, if improving and discharged early), or a high SSI (14 days, as patients that die within the first 14 days are usually on organ support while alive and in ICU))."

13. It is not clear how the primary end-point will be analyzed statistically. There are multiple secondary end-points. It may be helpful to the reader if the variables, outcome measures and planned statistical tests are outlined in a table. Please outline how multiple testing will be handled.

Authors' response

The primary endpoint is safety and tolerability. As usual for phase 2 trials, the study is not powered on safety but on efficacy. Safety data will be presented descriptively in tables (with numbers, percentages, etc.), but are not analysed statistically.

Correction for multiple testing is not performed as a primary effect estimate is defined and all secondary effect estimates are exploratory (and will be therefore also be labelled exploratory in future publications of the study). The Statistical Analysis Plan is currently being drafted, but will not ready to be submitted with the design paper. However, the key elements of the statistical analysis are well described in the paper.

Authors' actions

Added to statistical analysis section of manuscript:

"Regarding the primary endpoint (safety), all adverse events (AEs) will be listed. The number and percent of patients experiencing 1 or more AEs will be summarized by treatment arm / control group, relationship to study drug and severity/grade. Serious adverse event (SAE) specific listings for each patient population will be generated on reported SAEs. The same will be made for related severe AEs. Mortality analysis is described below.

...

All-cause mortality will be evaluated using Kaplan-Meier plots comparing treatment (separate for each dose, as well as a comparison combining both doses into one group) versus placebo (log-rank test) and Cox regression modelling including covariates to adjust for potential confounders. Potential confounders include age, gender and initial SOFA score, as well as variables showing significant between-group differences (despite randomization)."

"Statistical analysis of secondary endpoints is exploratory, and will be specified in a separate statistical analysis plan, which is to be finished before conclusion of the study."

14. I note the intention-to-treat analysis, as well as the planned per-protocol analysis. Interim analysis is planned for futility, and there is a prespecified decision rule. I wonder

why there will be stopping rules for futility and not for harm, which is reflected by the primary end point? Are there different stopping rules for harm that do not employ a statistical criterion?

Authors' response

The interim analysis focuses on futility only. Analysis for harm (both SAE and mortality) will be conducted regularly by the DSMB anyway. The DSMB can recommend to modify or stop the conduct of the study if continuation may pose a substantial risk to subjects at any time.

Authors' actions

Added to "interim analysis with futility stop" section:

"Note that the interim analysis focuses on futility only, potential termination of the trial based on harm is based on the reviewing and evaluation of unblinded data on safety and mortality by the DSMB (described further below)."

15. The statistical analysis planned is marred by the fact that the interim analysis will be

unblinded. What is the reason for this? The authors may wish to consider conducting a

blinded interim analysis, with unblinding to DSMB if safety issues exist. The authors should also state who will conduct the interim analysis eg. independent statistician; and who has the ultimate authority to stop the study.

Authors' response

An independent statistician will do the futility analysis, and the steering committee, as well as the sponsor, will remain blinded until the end of the study.

Added to section "Interim analysis with futility stop":

"An independent statistician is responsible for analysing data at interim analysis, and the steering committee, as well as the sponsor, will remain blinded until the end of the study."

16. Missing data: How will the authors handle data where there is a decision to withdraw or withhold therapy or to withdraw from the study? And how will other missing data be

handled?

Authors' response and actions

The primary analysis for efficacy will be performed as an intention-to-treat analysis (as described in the manuscript). We added the following sentences to the statistical section:

"Patients that were randomized, but did not receive any treatment, will be reported separately, and excluded from the primary analysis."

The following has been changed in the section "Withdrawal":

"No study specific data or patient material will be collected after withdrawal of consent. No data obtained after withdrawal of consent will be recorded on eCRFs, unless the patient consents to the use thereof. For safety analysis, the patient's outcome status (dead or alive) at day 90 (if dead, day of death) will be collected. For the main efficacy analysis, these patients will be excluded. In order to rule out that patient withdrawal is linked to treatment, a sensitivity analysis will be conducted assigning missing endpoint data with the worst possible value (i.e. worst possible value for patients in the treatment group, the best possible value for patients in the control group). In addition, an analysis will be conducted where missing data points will be imputed using inter- or extrapolation, if applicable."

Created new section "missing data", under "data quality assurance":

"Missing data: In general, missing data in clinical variables will not be replaced or imputed. If missing data should occur in variables required for secondary efficacy endpoints (e.g. SOFA score or other secondary efficacy endpoints), a sensitivity analysis will be conducted assigning missing endpoint data with the worst possible value (as defined for withdrawals), in addition to the analysis based on valid data only. In addition, an analysis will be conducted where missing data points will be imputed using inter- or extrapolation, with the exception that missing Bilirubin will be set to normal (liver SOFA component = 0). Missing follow up time information will not be replaced for mortality analysis, but rather treated as respective methods for survival analysis intend."

17. Data monitoring and audits:

These are clearly specified. A DSMB has been established and meets monthly. I am not entirely sure that the study monitors should 'discuss the conduct of the study'.

Rather, the role of monitors is to review source documents if required, and to determine if the reported data are accurate and complete.

Authors' response

What was meant was: Any practical issues or problems related to the conduct of the study could be discussed, However, we agree with the reviewer and we changed the wording in the "Study monitoring" section:

"... , and will determine if the reported data are accurate and complete."

18. Ethics and dissemination:

Please state how consent will be acquired, and who will be conducting this process,

including any training given. Please also state whether a biobank will be used, and if the samples will be stored for future use. Will there be any secondary studies, and if so, will the patients' informed consents encompass these? Who will have access to the data, and will individual patient data be made available after the study has been published? Finally, please be explicit regarding the role of the sponsor (although some detail is already given) and state if this is an investigator- or industry-initiated study.

Authors' response

Informed consent by the patient is obtained according to local requirements in Belgium, France, Germany and the Netherlands. During site initiation visits all investigators were trained for consenting procedures and documentation. Only study investigators are allowed to inform patients and to sign the ICFs. The documentation (source) of the consenting process can be done by investigators and study nurses or coordinators. The investigator will provide sufficient information about the study orally and with the patient information, to enable the patient to understand the study and any risks it details. Upon receiving this information, the patient will be given opportunity to ask any questions he/she might have and will be given appropriate time to decide on the participation in the study. The voluntary agreement to study participation by the patient will be documented by his personally dated signature on the informed consent form. The written informed consent must be co-signed and personally dated by the person who obtained the informed consent on the Informed Consent Form (ICF). The patient will be provided with copy or second original of the signed ICF. It will be guaranteed that personal data are kept confidential and will be used only for study related purposes.

For patients unable to give consent due to the emergency nature of the patient's condition the investigator will provide sufficient information about the study to the legal representative of the patient, designated according to the applicable national law, local

regulations in the involved countries to enable the patient's legal representative to understand the study and any risks in detail. Upon receiving this information, the patient's representative will be given opportunity to ask any questions he/she might have and will be given appropriate time to decide on the participation in the study on the patient's behalf. Once the patient has recovered and is able to understand the nature of this study a consent will be obtained retrospectively after the patient has been provided information about the study by the investigator in detail and after the patient has been given ample time to consider his/her further participation in the study to take a voluntary decision. After his/her decision in favor to further participation the patient will confirm his/her willingness to continue in this study by personally dated signature on the informed consent form, co-signed and dated by the informing investigator. The patient will be provided with copy or second original of the signed ICF. Patient and / or the patient's legal representatives can withdraw their consent on study participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

A biobank for biomarkers is implemented and samples are stored for potential future use. However, prior to analyses of these biomarker samples (e.g. for secondary studies), the protocol and the ICF for patients will be amended regarding their consent to use these samples.

The following parties have access to the data: sponsor, sites and selected vendors (CRO, data management, pharmacovigilance). Individual patient data may be used by site investigators for publication in agreement with the sponsor. The sponsor recognizes the investigator's and the institution's rights and obligations, as an academic partner, to publish the study results. The study results will be published in accordance with the good publication practice guideline of the international society for medical publication professionals. The sponsor and the investigator and other individuals who have expertise in the area and who are willing to interpret the data and write or review articles and presentations will form a publication Steering Committee to oversee the preparation of articles and presentations from this study.

Authors' actions

Added to section "Informed consent":

"Informed consent is obtained according to local requirements in Belgium, France, Germany and the Netherlands. Written informed consent is obtained by trained investigators after providing adequate verbal and written information about the study (in order to fully understand the study and any risks it entails), and giving the patient opportunity to ask questions and appropriate time to decide on participation in the study."

Added new section "Sample storage":

"A biobank for biomarkers is implemented and samples are stored for potential future use."

Added to "Dissemination policy":

The data of the study will be reported at scientific meetings and published in a peer-reviewed scientific journal, regardless of the results on outcome...

"... in accordance with the good publication practice guideline of the international society for medical publication professionals. The sponsor and the investigator and other individuals who have expertise in the area and who are willing to interpret the data and write or review articles and presentations will form a publication Steering Committee to oversee the preparation of articles and presentations from this study."

Added new section "Data access":

"The following parties have access to the data: sponsor, sites and selected vendors (data management, pharmacovigilance). Individual patient data may be used by site investigators for publication in agreement with the sponsor. Please note that the confidentiality section also specifies some external parties that may access data (regulatory authorities, etc.)."

19. Summary:

In general, this is a well-considered and well-written manuscript describing the protocol for a double blind, randomized, controlled multicentre study investigating a novel drug for the

treatment of septic shock. Recruitment has started but the planned interim analysis has not

been conducted.

The study has several notable strengths – the use of an appropriate randomization procedure with random (block) sequence generation and excellent allocation

concealment; and blinding of treating and research personnel. The use of a biomarker to isolate a more homogeneous group of patients is also a strength. The end-points are well defined and appropriate. A few additional details are required regarding recruitment and screening, as well as the conduct of the statistical analysis including interim analysis. Specifically, I believe that a statistical analysis plan for the primary outcome should be included and the interim analysis should be blinded.

Authors' response

We have added information about recruitment, screening, as well as statistical analysis. The interim analysis will be conducted by an independent statistician in unblinded fashion in order to perform the futility analysis. However, both steering committee and sponsor will remain blinded during the course of the study.

We thank the reviewers for their constructive comments. We believe that the quality of our manuscript has improved considerably thanks to the review process and hope our manuscript is now acceptable for publication in BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Anthony Gordon Institution and Country: Professor of Anaesthesia and Critical Care, Imperial College London, UK. Competing interests: None declared
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	I have no further comments

REVIEWER	Reviewer name: Michelle S Chew Institution and Country: Department of Anaethesia and Intensive Care, Medicine and Health, Linköping University, Sweden Competing interests: None declared
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	I appreciate the authors efforts in revising this manuscript. All my concerns have been adequately addressed.