PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessment of the Effectiveness and Safety of Ethosuximide in the Treatment of Abdominal Pain related to Irritable Bowel Syndrome – IBSET: protocol of a randomised, parallel, controlled, double-blind and multicentre trial
AUTHORS	Kerckhove, Nicolas; SCANZI, Julien; Pereira, Bruno; ARDID, Denis; DAPOIGNY, Michel

VERSION 1 - REVIEW

REVIEWER	Dr. Marco Daniel Gulewitsch University of Tübingen, Germany Department of Psychology Clinical Psychology and Psychotherapy
REVIEW RETURNED	09-Jan-2017

GENERAL COMMENTS	Thank you for the assignment of this interesting manuscript to me. Mr. Kerckhove and colleagues present a well-written and methologically sound study protocol regarding the effectiveness of Ethosuximide in abdominal pain related to irritable bowel syndrome (IBS). Ethosuximide, a T-type calcium channel blocker, is a substance that is used to treat epilepsy. To my knowledge this is the first study on the use of Ethosuximide in IBS. There are other current studies on its use in pain disorders. Since the trial protocol itself can't be changed (ongoing study), I refer mainly to the text which was submitted as a manuscript for BMJ Open (and not the design or the attached check list according to the SPIRIT guidelines). The title of the study includes "biomedical". This is not explained. I don't understand why it is included. In the abstract and in the manuscript itself you state that "no treatment has shown a real efficiency". In my opinion, this is not correct. I agree that a proportion of patients do not respond to available therapies but well-done studies in the field of psychosocial treatment approaches show rather good response rates (CBT, hypnotherapy). But yes, pharmacological therapies are in need of improvement. Abstract, Introduction: Please insert "abdominal" ahead of "chronic pain". Abstract, Methods and analysis: "SGA" is not defined at first appearance. Abstract, Methods and analysis: not clear what you mean by "tolerance".

	Strengths and limitations: Another limitation you should add is the short follow-up period. Introduction: The proposed mechanism of action and the rationale for the study becomes clear. Maybe you could add some information about assumed long-term efficacy. Although not investigated in your trial, the reader certainly asks himself whether this substance has a positive effect in the long-term (since IBS is a chronic condition). Methods and analysis: Are all types of analgesics allowed for the participants? How is the use of additional medication (analgetics and transit regulators) documented? It is done by the participants in their log or asked by the investigators on the phone (there is a danger of retrospective bias). Please clarify this in your manscript. Inclusion criteria: “Abdominal pain for at least 3 months.” -> Continuous pain / how often per week? Is this defined? Exclusion criteria: I did not understand the exclusion of patients with a history of depression or current depression. What is the reason for this? Since depression is a very frequent comorbidity of IBS, this criterion excludes a considerable portion of potential patients. How do you assess depression prior to inclusion/exclusion? Exclusion criteria: Do you exclude patients with epilepsy? Investigational medicinal product: Can you report the dosage for the approved use of Ethosuximide (epilepsy)? Is the placebo also produced by Pfizer? Study endpoints: This is well done and more or less in accordance with guidelines. A baseline of 7 days is rather short, but this can’t be changed anymore. Study endpoints, HRQoL: “These assessments are done every planned visit”. It would be easier for the reader if you would write the number of assessments. Methodology and study design, enrolment: I miss some recruitment details. By which aspects are the potential patients “pre-selected”? In what kind of institutions are you recruiting? How are the Rome IV criteria examined prior to inclusion/exclusion? Methodology and study design, line 33: I did not understand “the median abdominal pain score experienced …” – The median score is not calculated by the participants, right? Methodology and study design: What is the maximum of days allowed between the end of the baseline and visit 2? What happens according to your protocol if a participants can make an appointment directly after the baseline? Methodology and study design: Can you describe the blinding of study staff in more detail? Methodology and study design: Is the log book returned at the end of the trial or separately at every visit? Do you have measures to prevent later changes / compliance problems (e.g. digital log book)? If so, please describe. I would prefer a more detailed description of

	the log since the primary outcomes are derived from it. I have no major ethical considerations. I am not an expert in this field: Can the administration of Ethosuximide be stopped or does it have to be successively dosed down to zero. The German leaflet of Ethosuximide warns against an immediate discontinuation. Has the placebo group the chance to obtain the verum after study completion?

REVIEWER	Kittiyod Poovorawan Gastroenterology Unit, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Thailand
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	The manuscript entitled “Assessment of the Effectiveness and Safety of Ethosuximide in the Treatment of Abdominal Pain related to Irritable Bowel Syndrome – IBSET: protocol of a biomedical, randomised, parallel, controlled, double-blinded and multicentre trial” is a protocol for phase 2 clinical study on IBS treatment. Although, IBS is benign disease, effective treatment can improve patients’ quality of life. The overall protocol was well written. There are sufficient details in the protocol for the reader to understand the study. There are some comments for the authors to consider. 1. Introduction part, authors should include some more data on previous drug dosing and safety data in human. 2. Methods part, most of primary and secondary outcomes are subjective data and will be determined by many questionnaires. Authors should provide methods of data acquisition in detail to ensure that these data will accurate and participants will able to do all those questionnaires. Minor comments 1.In abstract, abbreviation should be defined at the first appearance, eg. SGA, IBS.

REVIEWER	Lifeng Lin Division of Biostatistics, University of Minnesota, USA
REVIEW RETURNED	22-Apr-2017

GENERAL COMMENTS	This manuscript describes the protocol of the IBSET trial, which will be the first in the literature to evaluate efficacy and safety of ethosuximide for IBS patients. I focused on reviewing the part of statistical analysis. I think the protocol is well written, and it contains all information to conduct the trial and perform statistical analysis when data are collected. My main concern is about the sample size estimation on page 9. The authors cited a previous meta-analysis on IBS to estimate the sample size as 130 per group. I wonder how this number is estimated. The meta-analysis investigated the effect of antidepressants and psychological therapies, not ethosuximide, on

	IBS. Therefore, I think it's impossible to get an estimated power (90% used in this manuscript) for detecting the difference between ethosuximide and placebo based on that meta-analysis. Also, even if 130 per group is a reliable estimated sample size, accounting for a loss of follow-up rate of 10%, the trial requires at least 145 patients per group (130/0.9 = 144.44), not 143. By the way, I suggest the authors to explain some abbreviations in the abstract, such as IBS, NRS, SGA, etc. As I'm not familiar with the clinical background, it's a bit hard to follow the abstract until I read the main text.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr. Marco Daniel Gulewitsch Institution and Country: University of Tübingen, Germany, Department of Psychology, Clinical Psychology and Psychotherapy Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for the assignment of this interesting manuscript to me. Mr. Kerckhove and colleagues present a well-written and methologically sound study protocol regarding the effectiveness of Ethosuximide in abdominal pain related to irritable bowel syndrome (IBS). Ethosuximide, a T-type calcium channel blocker, is a substance that is used to treat epilepsy.

To my knowledge this is the first study on the use of Ethosuximide in IBS. There are other current studies on its use in pain disorders.

1) Since the trial protocol itself can't be changed (ongoing study), I refer mainly to the text which was submitted as a manuscript for BMJ Open (and not the design or the attached check list according to the SPIRIT guidelines).

Unless we make a mistake on our part, the protocol does not appear in "ongoing" on clinicaltrial.gov but in "Not yet recruiting". Therefore, we still have the opportunity to modify the study protocol.

2) The title of the study includes "biomedical". This is not explained. I don't understand why it is included.

Since this clarification is unnecessary and unclear, it has been deleted from the title.

3) In the abstract and in the manuscript itself you state that "no treatment has shown a real efficiency". In my opinion, this is not correct. I agree that a proportion of patients do not respond to available therapies but well-done studies in the field of psychosocial treatment approaches show rather good response rates (CBT, hypnotherapy). But yes, pharmacological therapies are in need of improvement.

We agree with this remark. We have replaced the sentence "no treatment has shown a real efficiency" by "medical treatments, mainly antispastic drugs and transit regulators, are poorly efficient in IBS abdominal pain".

4) Abstract, Introduction: Please insert "abdominal" ahead of "chronic pain". Revised
Abstract, Methods and analysis: "SGA" is not defined at first appearance. Abbreviation defined.
Abstract, Methods and analysis: not clear what you mean by "tolerance". The more adequate sentence would be "safety". We have replaced the word "tolerance" by "safety" and the details are

described in the study endpoints part.

5) Strengths and limitations: Another limitation you should add is the short follow-up period.

Limitation added.

6) Introduction: The proposed mechanism of action and the rationale for the study becomes clear. Maybe you could add some information about assumed long-term efficacy. Although not investigated in your trial, the reader certainly asks himself whether this substance has a positive effect in the long-term (since IBS is a chronic condition).

We agree with this remark. There is no evidence to suggest that the treatment will be effective in the long term. But, since this is a pilot study that wants to demonstrate that ETX is effective and safe, it seems risky to stretch this trial with longer-term follow-up. If efficacy is proven and associated with good tolerance, a second study evaluating long-term effects will be considered.

Methods and analysis:

7) Are all types of analgesics allowed for the participants? How is the use of additional medication (analgetics and transit regulators) documented? It is done by the participants in their log or asked by the investigators on the phone (there is a danger of retrospective bias). Please clarify this in your manscript.

Details added: “Only weak analgesics will be allowed (eg paracetamol, NSAIDs). Use of concomitant medications will be indicated by the patient on his logbook and during scheduled visits to the investigator. If the patient uses unauthorized treatment or changes his background treatment without prior authorization, the patient will be excluded from the analysis because of a major deviation from the protocol.”

8) Inclusion criteria: “Abdominal pain for at least 3 months.” -> Continuous pain / how often per week? Is this defined?

According to ROME IV criteria: recurrent abdominal pain on average at least 1 day a week in the last 3 months.

9) Exclusion criteria: I did not understand the exclusion of patients with a history of depression or current depression. What is the reason for this? Since depression is a very frequent comorbidity of IBS, this criterion excludes a considerable portion of potential patients. How do you assess depression prior to inclusion/exclusion?

The reason why depressive patients are not eligible for study is that ethosuximide may, in rare cases according to the SmPC, aggravate depressive disorders or make them reappear, with the risk of suicidal thoughts. To limit the portion of non-includable patient, only patients reported a current severe depression or a history of severe depression requiring hospitalization and / or attempted suicide is cons-indicated for the study. This assessment will be carried out by the investigators on their own assessment and experience.

10) Exclusion criteria: Do you exclude patients with epilepsy?

Yes, epileptic patients are excluded from the study to avoid possible interactions with other antiepileptic drugs and any adverse effects resulting from them.
We have added this in exclusion criteria.

11) Investigational medicinal product: Can you report the dosage for the approved use of Ethosuximide (epilepsy)?

Details added:
“It is recommended to start with 10ml (500mg) of syrup from the age of 6 years. Depending on the response, the dosage should be increased very gradually by 5ml (250mg) of syrup every 4 to 7 days until complete control of the seizures. In adults, the effective dosage is 20 mg / kg / day, ie 30 ml of syrup (1500 mg). The maximum dosage is 2000 mg per day (40 ml of syrup). In children, the effective dosage varies between 20 and 30 mg / kg / day, and the maximum dosage is 1000 mg per day.”

“The choice of this dosage is based on a study currently conducted by our team (EDONOT study: NCT02100046) showing that ethosuximide doses greater than or equal to 750 mg/day (15 ml) are poorly tolerated, whereas the 500 mg/day (10 ml) exhibits a clinically relevant analgesic effect associated with good tolerance in patients with neuropathic pain.”

12) Is the placebo also produced by Pfizer?

No, the placebo will be produced by the pharmacy of the coordinating center of the study.

13) Study endpoints: This is well done and more or less in accordance with guidelines. A baseline of 7 days is rather short, but this can’t be changed anymore.

We agree with this remark, but this choice of 7 days baseline was made for 2 reasons:
- Our pain assessments are always done on the 7 days before each visit.
- The patients included will be a priori, the most severe (NRS average pain on last week ≥4/10) and should present sufficient pain symptoms over a week.

14) Study endpoints, HRQoL: “These assessments are done every planned visit”. It would be easier for the reader if you would write the number of assessments.

Changes made:
“These assessments are done 4 times at visit 2, 3, 4 and 5.”

15) Methodology and study design, enrolment: I miss some recruitment details. By which aspects are the potential patients “pre-selected”? In what kind of institutions are you recruiting? How are the Rome IV criteria examined prior to inclusion/exclusion?

Patients will be recruited in referent centers that are mainly university hospitals. The investigators will recruit IBS patients from their clinical practice using the Rome IV criteria.

16) Methodology and study design, line 33: I did not understand “the median abdominal pain score experienced …” – The median score is not calculated by the participants, right?

Only the average pain experienced during the day (last 24 hours) will be indicated by the patient on his logbook. The maximum pain felt is not required. During each visit, the mean score is not calculated by the patient but by the investigator from the daily scores indicated by the patient on his logbook. We have changed “median” by “average” in the text.

17) Methodology and study design: What is the maximum of days allowed between the end of the baseline and visit 2? What happens according to your protocol if a participants can make an appointment directly after the baseline?

No delay between baseline and visit 2 is allowed. All the appointments of the study should be taken during the visit 1.
As soon as the run-in period ends, the patient makes his second visit to get his average pain over the past week. If the average of the pain is greater or equal to 4/10 then the patient is included and leaves with his treatment for a period of one month (until the next visit).

18) Methodology and study design: Can you describe the blinding of study staff in more detail?

Details added on Investigational Medicinal Product part: “The staff of the investigation center will not be allowed to open the boxes containing the therapeutic units. Only pharmacists from each center will be able to deliver and recover therapeutic units for each visit. The therapeutic units will be packaged in similar bottles and in identical opaque boxes in order to preserve the double blind.”

19) Methodology and study design: Is the log book returned at the end of the trial or separately at every visit? Do you have measures to prevent later changes / compliance problems (e.g. digital log book)? If so, please describe. I would prefer a more detailed description of the log since the primary outcomes are derived from it.

Details added: “The logbook is returned to the patient at each visit. The filled parts will be detached from the logbook and kept on the investigator site in a dedicated binder. The data will then be transcribed as soon as possible on the electronic case report form (e-CRF). The data indicated in the e-CRF will not be modifiable and will be confronted with the data indicated in the logbook.”

20) I have no major ethical considerations. I am not an expert in this field: Can the administration of Ethosuximide be stopped or does it have to be successively dosed down to zero. The German leaflet of Ethosuximide warns against an immediate discontinuation.

The recommendations on the risks of a sudden cessation of ethosuximide are only to be taken into account for epileptic patients (risk of provoking epileptic seizures). In the case of non-epileptic patients, and following our other ongoing studies with ethosuximide, there is no risk of discontinuing ethosuximide without a dose reduction.

21) Has the placebo group the chance to obtain the verum after study completion?

Indeed, patients in the placebo group may be offered ethosuximide by the investigator, if both the investigator and the patient deem it necessary. Nevertheless, no follow-up is foreseen by the protocol in this case.

Reviewer: 2
Reviewer Name: Kittiyod Poovorawan
Institution and Country: Gastroenterology Unit, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Thailand Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The manuscript entitled “Assessment of the Effectiveness and Safety of Ethosuximide in the Treatment of Abdominal Pain related to Irritable Bowel Syndrome – IBSET: protocol of a biomedical, randomised, parallel, controlled, double-blinded and multicentre trial” is a protocol for phase 2 clinical study on IBS treatment. Although, IBS is benign disease, effective treatment can improve patients’ quality of life. The overall protocol was well written. There are sufficient details in the protocol for the reader to understand the study.

There are some comments for the authors to consider.

1. Introduction part, authors should include some more data on previous drug dosing and safety data in human.

Details added on investigational medicinal product part: “It is recommended by the SmPC to start with 10ml (500mg) of syrup from the age of 6 years. Depending on the response, the dosage should be increased very gradually by 5ml (250mg) of syrup every 4 to 7 days until complete control of the seizures. In adults, the effective dosage is 20 mg/kg/day, ie 30 ml of syrup (1500 mg). The maximum dosage is 2000 mg per day (40 ml of syrup). In children, the effective dosage varies between 20 and 30 mg/kg/day, and the maximum dosage is 1000 mg per day.”

Concerning safety in the patient, due to the age of ethosuximide, only a few studies exist [Pourcher, E. et al. 1992; Pisani F. et al. 1984; Gullet JR. et al. 1976; Kästner I. et al. 1976]. These are pharmacokinetic studies, but none mention specific adverse effects. In animals, many studies on ethosuximide, especially on pain, exist and none have identified disorders suggestive of particular adverse effects.

Details added on introduction part:
“Safety of ethosuximide in humans:
According to SmPC, the safety profile of ethosuximide is similar with other antiepileptic drugs (AEDs). Frequently listed side effects are dyspepsia (nausea, epigastric pain, bloating, and loss of appetite), dizziness, headache, ataxia, skin rash and vomiting. In adults, the effective dosage is 20 mg/kg/day, ie 30 ml of syrup (1500 mg).”

2. Methods part, most of primary and secondary outcomes are subjective data and will be determined by many questionnaires. Authors should provide methods of data acquisition in detail to ensure that these data will accurate and participants will able to do all those questionnaires.

Details added on study endpoints part:
“Data acquisition:
The questionnaires will be completed, during each visit, by the patients in the investigating centres. Patients can be assisted in the event of problems understanding the questions. Data collected from the logbook and questionnaires should be verified and indicated on the day of each visit in the electronic case report form (e-CRF). This procedure will allow patients to complete the entire questionnaire and avoid the risk of missing data as much as possible.”

Minor comments

1.In abstract, abbreviation should be defined at the first appearance, eg. SGA, IBS.

Abbreviation defined.

Reviewer: 3
Reviewer Name: Lifeng Lin
Institution and Country: Division of Biostatistics, University of Minnesota, USA Please state any competing interests or state ‘None declared’: None.

Please leave your comments for the authors below This manuscript describes the protocol of the IBSET trial, which will be the first in the literature to evaluate efficacy and safety of ethosuximide for IBS patients. I focused on reviewing the part of statistical analysis. I think the protocol is well written, and it contains all information to conduct the trial and perform statistical analysis when data are

collected.

1) My main concern is about the sample size estimation on page 9. The authors cited a previous meta-analysis on IBS to estimate the sample size as 130 per group. I wonder how this number is estimated. The meta-analysis investigated the effect of antidepressants and psychological therapies, not ethosuximide, on IBS.

Since no clinical study has evaluated the analgesic effect of ethosuximide in IBS and more broadly in chronic pain, we used a meta-analysis that evaluated treatments for the same symptoms (IBS-related pain) and target population in this study. We estimated that the placebo effect observed in this meta-analysis should not change significantly with ethosuximide. Finally, in order to reduce the risk of underestimation of the placebo effect, we have taken a high estimate of 35% of responders in the placebo arm, which corresponds to the rates conventionally observed in similar studies evaluating analgesic treatments in patients with IBS or chronic pain.

2) Therefore, I think it's impossible to get an estimated power (90% used in this manuscript) for detecting the difference between ethosuximide and placebo based on that meta-analysis. Also, even if 130 per group is a reliable estimated sample size, accounting for a loss of follow-up rate of 10%, the trial requires at least 145 patients per group (130/0.9 = 144.44), not 143.

Thank you for the comment. We agree with this remark. We have amended the protocol to that effect.

3) By the way, I suggest the authors to explain some abbreviations in the abstract, such as IBS, NRS, SGA, etc. As I'm not familiar with the clinical background, it's a bit hard to follow the abstract until I read the main text.

Abbreviation defined.

VERSION 2 – REVIEW

REVIEWER	Dr. Marco Daniel Gulewitsch University of Tübingen, Germany, Department of Psychology, Clinical Psychology and Psychotherapy
REVIEW RETURNED	15-May-2017

GENERAL COMMENTS	All my remarks were answered adequately

REVIEWER	Lifeng Lin Division of Biostatistics, University of Minnesota
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	I appreciate that the authors have incorporated my previous comments in the revised manuscript. I still have a minor question regarding to the sample size estimation. If I understand correctly, the authors just use the rates of responders (35% for placebo and 55% for ethosuximide) to estimate the sample size. However, these rates were not directly informed by the meta-analysis of Ford et al. The authors may report the estimated rate of responders in the placebo group in that meta-analysis, and specify that a higher rate (35%) is used for sample size estimation in this manuscript to avoid underestimating placebo effect.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Lifeng Lin
Institution and Country: Division of Biostatistics, University of Minnesota, USA Please state any competing interests or state 'None declared': None.

1) I appreciate that the authors have incorporated my previous comments in the revised manuscript. I still have a minor question regarding to the sample size estimation. If I understand correctly, the authors just use the rates of responders (35% for placebo and 55% for ethosuximide) to estimate the sample size. However, these rates were not directly informed by the meta-analysis of Ford et al. The authors may report the estimated rate of responders in the placebo group in that meta-analysis, and specify that a higher rate (35%) is used for sample size estimation in this manuscript to avoid underestimating placebo effect.

We have added the following sentences in statistical section: "Based on the meta-analysis of Ford et al., The estimated median responder rate in the placebo group was 35%. A slightly higher rate than the previously mentioned meta-analysis (32% of responders under drug therapies), in order to avoid underestimating the placebo effect."