PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a non-inferiority double-blind randomised controlled trial comparing gabapentin versus tramadol for the treatment of chronic neuropathic or mixed pain in children and adolescents: the GABA-1 trial.
AUTHORS	Kaguelidou, Florentia; Le Roux, Enora; Mangiarini, Laura; Lundin, Rebecca; de Leeuw, Thomas; Della Pasqua, Oscar; Felisi, Mariagrazia; Bonifazi, Donato; Tibboel, Dick; Ceci, Adriana; de Wildt, Saskia; Alberti, Corinne

VERSION 1 – REVIEW

REVIEWER	Pablo Ingelmo Montreal Children's Hospital
REVIEW RETURNED	30-Aug-2018

GENERAL COMMENTS	Six countries involving 19 academic pediatric hospital centers will be recruiting eligible children and adolescents. How many patients per center you're expecting to recruit? "Patient enrolment will begin in 2018 and is expected to end in 2019." It is not evident in the text that you already started the recruitment in July 2018 in at least four centers. Please clarify. The main limitation of this an others studies on neuropathic pain (NP) in children are the use of an "adult" grading system of NP the lack of validated PEDIATRIC tools for the diagnoses of NP. Screening tools like the Pediatric-modified Total Neuropathy Score (peds-mTNS) or the Fabry Pain Questionnaire (FPQ), are focused on specific conditions. Moreover, there is no validated NP screening tool for children younger than 6 years. Furthermore, there is no consistent recommendation regarding the optimal tool for use with pediatric patients experiencing mixed chronic of general chronic pain. Given the scarcity of resources, we all rely on the history and physical examination and relevant studies to screen and assess for NP and mixed pain. You used the NeuPSIG definition of NP (ref 2) and a more recent grading system of NP (Ref 23). However, the paper of Treede et al., proposing a second version of the neuPSIG NP grading system, established "the level of certainty with which the presence or absence of neuropathic pain can be determined in an individual patient." That grading system defined three levels of probability: definite, probable and possible. The levels definite and probable "indicate that the presence of NP has been established. The level possible indicates that the presence of this condition has not yet been established". Based on four main criterions (distribution, relevant lesion, neurologic signs and diagnostic test confirming the lesion), they consider as having "definite neuropathic pain" a patient with all four criterions. A patient with a "probable" neuropathic pain should have neuroanatomically plausible distribution and a history suggestive of

	a relevant lesion or disease affecting the peripheral or central somatosensory system, and either the distribution or the lesion confirmed by one test. Your definition of neuropathic included two criterions for children older than three years and only one for children younger than three years. Those patients would be considered as having “possible neuropathic pain” using both the grading system of Treede et al. or “unconfirmed” neuropathic pain using the grading system of the neuPSIG. Seems to me that your definition of NP put your study at risk of critical selection bias and may shift your population towards a “mixed pain” population. The IASP grading system could be particularly beneficial as a reliable screening tool for NP in children as it only requires the patient’s cooperation to explain the anatomic location of the pain (provided the medical history is known or can be given by a caregiver). “Primary endpoint: Average pain score at the end of the treatment period (average of two measures each day for three days before the end of study visit, V10) as assessed by age-appropriate pain scales.” Who will apply the scales when and if the patients are not in the hospital? Were the parents been trained for the study? Did you select any time of the day to control the evaluations of the primary endpoint? Will older patients be enquiring about the maximum or average pain? Does the pain evaluation correspond to pain at rest or during/after physical activity? Secondary en-points: Daily pain intensity assessed by age-appropriate scale (FLACC, FPS-R or NRS-11) during dose optimization (V3 to V6): you mean average pain intensity at different time points or the mean value of multiples evaluations around the time points? I would suggest using the same model than for the primary outcome measures of pain intensity. “Observational assessment using the NRS-11 completed by parents and Investigator (or caregiver) at each visit.” Do you think this endpoint is relevant at all? If yes, I would suggest using validated tools to compare the “impressions” of parents an healthcare professionals. NRS-11 is typically a self-evaluation scale and in general parent visual analogue scale ratings of children's pain do not reliably reflect pain reported by child (Kelly AM, Powell CV, Williams A.. Pediatr Emerg Care. 2002 Jun;18(3):159-62., Chambers C. The Clinical Journal of Pain: December 1998 - Volume 14 - Issue 4 - p 336-342) Reasons include but are not limited to the following: … “lack of efficacy (efficacy is defined as pain intensity of less than 4/10 in all pain assessments in the last 48 hours during the maintenance period)”: do you mean a patient that just reach the steady state “ideal” will be excluded from the trial after two days. This may introduce two confounding factor in the study: first, the efficacy of gabapentin is significantly related with the absorption. Second, some patients need two to four weeks to stabilize the effect of gabapentin, especially in patients with neuromas or small fiver lesions. Excluding those patients, you may lose valuable information regarding the association between the pharmacokinetics of gabapentin and it’s efficacy. You may also lose patients that may have benefits with gabapentin, shifting the proportion of patients with effective treatment towards tramadol. Reasons include but are not limited to the following: … “continuous use of rescue medication (defined as the use of the maximum daily dose of paracetamol and/or ibuprofen for 12 days in 15 continuous days)…” I assume that’s this applies only to the time points between V6 and V10. Please clarify.

REVIEWER	James Paul McMaster University, Canada
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	This is a well written protocol covering an important clinical question. It is reported very clearly and the methodology addresses all the methodological and statistical steps necessary for the trial to be repeated. The methods as described minimize bias. Kaguelidou 2018 Study protocol for non-inferiority double-blind randomised controlled trial comparing gabapentin versus tramadol for the treatment of chronic neuropathic or mixed pain in shildren and adolescents. BMJ Open July 2018 Objective: To compare the safety and efficacy of gabapentin versus tramadol in the treatment of chronic pain in pediatric patients. Population: Participants are aged 3 months to <18 years and have moderate to severe neuropathic or mixed pain. Design: Multi-centre, double blind, double-dummy randomized, active-controlled, non-inferiority trial Randomization: Computer random number generator, random permuted blocks of varying sizes Sample size: 94 Intervention: 1. Gabapentin 2. Tramadol placebo 3. Gabapentin placebo 4. Tramadol and Gabapentin 16-19 weeks treatment period Outcome(s): Primary: 1. Difference in average pain scores between treatment groups after 15 weeks. Secondary: 2. Safety 3. Quality of life 4. Global satisfaction 5. Pharmacokineitic pharmacodynamic relationship Setting: 19 clinical sites in 10 European countries. Comments: The introduction is well written and covers the background nicely. The methods are very detailed and cover all the required elements recommended by the CONSORT Guidelines. Page 22, line 47. What is that “Error! Reference”. This needs to be resolved.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Pablo Ingelmo
Institution and Country: Montreal Children's Hospital

Six countries involving 19 academic pediatric hospital centers will be recruiting eligible children and adolescents. How many patients per center you're expecting to recruit?
Currently, the trial involves the participation of 14 centers in 8 countries because while the protocol manuscript was reviewed, the trial was not accepted by the Ukrainian Competent Authority and by the Ethics Committee of the Institute for Health Protection of Children and Youth of Vojvodina, Novi Sad, Serbia. Therefore, a total of 5 sites from 2 countries were withdrawn. Corrections have been made accordingly in 'The members of the GAPP consortium' section (page 2), the abstract (pages 5-6 of the manuscript), 'the strengths and limitations of the study' section (page 7) and in the 'GABA-1 trial design and setting' paragraph (age 14).
Moreover, estimations of patient recruitment by center have been assessed during pre-study qualification visit performed by the Sponsor ('Monitoring' paragraph, page 34). Every selected center reported a capacity of recruitment varying between 3 and 10 potentially eligible patients in accordance with each center's activity and resources. Thus, not all centers will recruit the same number of patients.

"Patient enrolment will begin in 2018 and is expected to end in 2019." It is not evident in the text that you already started the recruitment in July 2018 in at least four centers. Please clarify.
We have now added the following sentence to clarify this point lines 10-11, page 14, second paragraph of the 'GABA-1 trial design and setting' section : 'Patient enrolment begun in July 2018 (7 centres open to recruitment at that date) and is expected to end in 2019.'

The main limitation of this and others studies on neuropathic pain (NP) in children are the use of an "adult" grading system of NP the lack of validated PEDIATRIC tools for the diagnoses of NP. Screening tools like the Pediatric-modified Total Neuropathy Score (peds-mTNS) or the Fabry Pain Questionnaire (FPQ), are focused on specific conditions. Moreover, there is no validated NP screening tool for children younger than 6 years.
Furthermore, there is no consistent recommendation regarding the optimal tool for use with pediatric patients experiencing mixed chronic of general chronic pain. Given the scarcity of resources, we all rely on the history and physical examination and relevant studies to screen and assess for NP and mixed pain.
We fully agree that current guidelines for assessment and diagnosis of neuropathic pain are designed for adults and may be less valid in children. Since no validated tools exist to assess the presence of neuropathic pain in children, diagnosis is mainly based on clinical indicators. This is subject to the well described problems of pain assessment especially in young children. Pain history is the mainstay of diagnosis. Physical examination verifies and locates the lesion of the somatosensory system and documents associated neurological signs. Sensory abnormalities are more difficult to elicit in infants and young children. Several tests can be indicated like quantitative sensory testing, electroneuromyography, microneurography, functional brain imaging and skin biopsy but are not always performed in routine medical practice. Main role of radiological investigations is to rule out other underlying pathology.
Taking into consideration the above, we also propose to base diagnosis on medical history (underlying disease, quality and temporal aspects of pain, plausible neurological distribution, and response to previous treatment) and clinical examination (positive and negative sensory criteria) for eligibility in the GABA-1 trial.

You used the NeuPSIG definition of NP (ref 2) and a more recent grading system of NP (Ref 23). However, the paper of Treede et al., proposing a second version of the neuPSIG NP grading system, established "the level of certainty with which the presence or absence of neuropathic pain can be determined in an individual patient." That grading system defined three levels of probability: definite, probable and possible. The levels definite and probable "indicate that the presence of NP has been established. The level possible indicates that the presence of this condition has not yet been established". Based on four main criterions (distribution, relevant lesion, neurologic signs and

diagnostic test confirming the lesion), they consider as having “definite neuropathic pain” a patient with all four criterions. A patient with a “probable” neuropathic pain should have neuroanatomically plausible distribution and a history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system, and either the distribution or the lesion confirmed by one test. Your definition of neuropathic included two criterions for children older than three years and only one for children younger than three years. Those patients would be considered as having “possible neuropathic pain” using both the grading system of Treede et al. or “unconfirmed” neuropathic pain using the grading system of the neuPSIG.
Seems to me that your definition of NP put your study at risk of critical selection bias and may shift your population towards a “mixed pain” population. The IASP grading system could be particularly beneficial as a reliable screening tool for NP in children as it only requires the patient’s cooperation to explain the anatomic location of the pain (provided the medical history is known or can be given by a caregiver).

We fully agree that diagnosis of neuropathic pain in children is mostly based on medical history, neuro-anatomical distribution of pain and clinical examination. Diagnosis remains very challenging in the youngest. However, because of the multicenter and multinational nature of the GABA-1 trial, we needed to standardize as much as possible the diagnosis of NP for study inclusion. We also needed to help clinicians with different training backgrounds to identify neuropathic pain. This is why we proposed the 4 criteria described by Treede et al. For use in children, we limited the number of criteria that are necessary to include a child in the GABA-1 study as we acknowledge that: 1) a diagnostic test confirming lesion or disease explaining neuropathic pain and/or 2) a confirmatory tests for the anatomically plausible distribution and/or 3) screening questionnaires are often missing in children and 4) defining neuroanatomical pain distribution can be imprecise therefore, diagnosis will be based essentially on medical history and clinical examination. In the youngest, <3 years of age, clinical examination may also be challenging or unspecific, therefore 1 criterion out of 4 was required and a list of neuromuscular diseases (Appendix 2) potentially associated with neuropathic pain will be provided to clinicians.
Regarding the IASP grading system, the reviewer is probably referring to the article by Finnerup N. et al., ‘Neuropathic pain: an updated grading system for research and clinical practice’ published on 2016 (http://dx.doi.org/10.1097/j.pain.0000000000000492). We are aware of this publication but we had finalized the features of the trial for approval by the different regulatory authorities before it was published.
Thus, although we share your concerns about including a potentially ‘heterogeneous’ population with regards to pain, we tried to standardize as much as possible the selection of patients taking into account that a trial with very ‘homogenous’ population would be unfeasible in terms of attaining adequate sample size. We also feel that this heterogeneous population better reflects ‘real’ patients taken care of in pediatric pain management units.

“Primary endpoint: Average pain score at the end of the treatment period (average of two measures each day for three days before the end of study visit, V10) as assessed by age-appropriate pain scales.”
Who will apply the scales when and if the patients are not in the hospital? Were the parents been trained for the study?
Indeed, we will be using 3 different pain measurement scales: one observational (parent or principal caregiver will be using) for children under 3 years of age and two self-assessment scales (patient will be assessing his own pain intensity) for children above 3 years of age (see ‘Outcome measures’ paragraph, page 24). Parents (principal caregiver) and patients will be trained to adequately use these scales at the screening visit and will also be provided with an individual patient diary that includes instructions for use. This information has now been added to the manuscript, last paragraph before the end of page 26 and first lines of page 27.

Did you select any time of the day to control the evaluations of the primary endpoint?
Patients will be instructed to measure their pain intensity in the morning and in the evening, if possible always at the same moment of the day. For example, in the morning, when they wake up and in the evening, before they go to bed. These instructions are provided in the patient diary. This information has now been added to the manuscript, last paragraph before the end of page 26 and first lines of page 27.

Will older patients be enquiring about the maximum or average pain?
Older patients will not be asked to provide an average daily pain. However, they are instructed to report episodes of breakthrough pain and this information will be assessed for all patients in the trial.

Does the pain evaluation correspond to pain at rest or during/after physical activity?
Patients will be instructed to provide daily pain level at the same moment of the day every day and episodes of breakthrough pain during the day. They are not requested to provide pain during rest or physical activity as the latter may be very variable among trials participants.

Secondary endpoints: Daily pain intensity assessed by age-appropriate scale (FLACC, FPS-R or NRS-11) during dose optimization (V3 to V6): you mean average pain intensity at different time points or the mean value of multiples evaluations around the time points? I would suggest using the same model than for the primary outcome measures of pain intensity.
They will be instructed to provide daily pain level (pain intensity experienced at the moment of assessment) at their convenience but preferably at the same time of the day and before drug administration.

“Observational assessment using the NRS-11 completed by parents and Investigator (or caregiver) at each visit.” Do you think this endpoint is relevant at all? If yes, I would suggest using validated tools to compare the “impressions” of parents an healthcare professionals. NRS-11 is typically a self-evaluation scale and in general parent visual analogue scale ratings of children's pain do not reliably reflect pain reported by child (Kelly AM, Powell CV, Williams A.. Pediatr Emerg Care. 2002 Jun;18(3):159-62., Chambers C. The Clinical Journal of Pain: December 1998 - Volume 14 - Issue 4 - p 336-342)
Thank you for your comment and we agree that observational pain assessment using NRS-11 completed by parents and Investigator is of limited interest. We decided to include this as a secondary outcome essentially to evaluate correlations between the pain intensity as determined using a self-assessment pain scale and the observational assessments of the child’s pain using the NRS-11 scale by parents and by clinicians at different moment of the trial.

Reasons include but are not limited to the following: … “lack of efficacy (efficacy is defined as pain intensity of less than 4/10 in all pain assessments in the last 48 hours during the maintenance period)”: do you mean a patient that just reach the steady state “ideal” will be excluded from the trial after two days? This may introduce two confounding factor in the study: first, the efficacy of gabapentin is significantly related with the absorption. Second, some patients need two to four weeks to stabilize the effect of gabapentin, especially in patients with neuromas or small fiver lesions. Excluding those patients, you may lose valuable information regarding the association between the pharmacokinetics of gabapentin and it’s efficacy. You may also lose patients that may have benefits with gabapentin, shifting the proportion of patients with effective treatment towards tramadol.
Thank you for this comment. Removal of patients from the trial is at the discretion of the investigator and the patient/family and will be evaluated on a case-by-case basis. Patients entering the maintenance period and after V7 should have reached an optimal dosing level with regards to pain relief. This criterion was added to indicate that we can remove a patient during maintenance period if he is poorly relieved and that in this case, no patient should be maintained provided also that rescue medication has been optimally managed.

Reasons include but are not limited to the following: … “continuous use of rescue medication (defined as the use of the maximum daily dose of paracetamol and/or ibuprofen for 12 days in 15 continuous days)…” I assume that’s this applies only to the time points between V6 and V10. Please clarify.
We confirm that this applies to the maintenance period and this precision has been added now in the first paragraph of the ‘Removal or withdrawal of trial participants’ section, line 6 before the end of page 31.

Reviewer: 2
Reviewer Name: James Paul
Institution and Country: McMaster University, Canada

This is a well written protocol covering an important clinical question. It is reported very clearly and the methodology addresses all the methodological and statistical steps necessary for the trial to be repeated. The methods as described minimize bias.
Thank you for your comments.

Objective: To compare the safety and efficacy of gabapentin versus tramadol in the treatment of chronic pain in pediatric patients.
Population: Participants are aged 3 months to <18 years and have moderate to severe neuropathic or mixed pain.
Design: Multi-centre, double blind, double-dummy randomized, active-controlled, non-inferiority trial
Randomization: Computer random number generator, random permuted blocks of varying sizes
Sample size: 94
Intervention: 1.Gabapentin
2. Tramadol placebo
3. Gabapentin placebo
4. Tramadol and Gabapentin
16-19 weeks treatment period
We just wish to clarify that patients will be randomized in two intervention arms to receive: 1) gabapentin and a placebo of tramadol or 2) tramadol and a placebo of gabapentin. This information is provided in the ‘random sequence generation’ paragraph, page 21 of the manuscript.

Comments:
The introduction is well written and covers the background nicely.
The methods are very detailed and cover all the required elements recommended by the CONSORT Guidelines.
Page 22, line 47. What is that “Error! Reference”. This needs to be resolved.
We have now corrected this typing error and you can read ‘Table 1’ instead of “Error! Reference” on line 21, page 22.

Additional changes in the manuscript
We have added sentences to clarify:
1) Where list of study sites can be found : page 14, lines 22-23
2) Insurance to ensure post-trial care and compensation to those who suffer harm from trial participation: page 36, lines 12-13
3) Processing, storage and shipment of biological specimens, paragraph ‘Data collection’, page 29.
4) That ‘No interim analysis is planned.’ in the ‘Analysis of efficacy variables’, page 35 of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Pablo Ingelmo Montreal Children's Hospital. Canada
REVIEW RETURNED	28-Oct-2018

GENERAL COMMENTS	Good luck.