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TITLE PAGE

Assessment of the Effectiveness of Ethosuximide in the Treatment of Peripheral Neuropathic Pain – EDONOT: protocol of a biomedical, randomised, controlled, double-blinded and multicentre trial

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Contributors

NK, AE, CC, CM, CD and CD led and contributed to the conceptualisation, design and implementation of this research protocol. BP led the development of the statistical analysis plan. NK participated in the design of the protocol for interventions and assessments. All the authors have read and approved the final manuscript.

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Competing interests

The authors declare they have no competing interests.

Ethics approval

The approval of the medical ethics committee (CPP Sud Est VI, Clermont-Ferrand, France) was obtained on 14 February 2014. The protocol was declared to the competent French authority (Agence Nationale de Sécurité du Médicament et des produits de santé) and registered under the number 131567A-32. Authorisation was obtained on 26 March 2014.

ABSTRACT

Introduction: Currently available analgesics are ineffective in 30 to 50% of patients suffering from neuropathic pain and often induce deleterious side-effects. T-type calcium channel blockers (mibefradil, ethosuximide, TTA-A2, NNC 55-0396) are of great interest for the development of new symptomatic treatments of neuropathic pain, due to their various effects on pain perception. Interestingly, ethosuximide (Zarontin®), which has already been approved for treating epilepsy, is available on the European market for clinical use. Despite numerous preclinical data demonstrating an antinociceptive effect of ethosuximide in various animal models of neuropathic pain, no clinical studies have been published to date on the analgesic efficacy of ethosuximide in patients with neuropathic pain.

Methods and analysis: The EDONOT trial is a randomised, controlled, double-blinded, multicentre study. It is the first clinical trial to evaluate the efficacy and safety of ethosuximide in the treatment of peripheral neuropathic pain. Adult patients exhibiting peripheral neuropathic pain (NRS ≥ 4 and DN4 ≥ 4) for at least 3 months and under stable analgesic treatment for at least 1 month will be included. Patients (n=110 per arm) will be randomly assigned to receive either ethosuximide or control treatment for 6 weeks following a 1 week run-in period. The primary endpoint is the intensity of neuropathic pain, assessed by NRS (0-10) before and after 6 weeks of treatment. The secondary endpoints are treatment safety, the intensity and features of neuropathic pain (assessed by BPI and NPSI questionnaires) and health related quality of life (HRQoL assessed by MOS-SF-12 and Leeds questionnaires).

Ethics and communication: The study was approved by an independent medical ethics committee (CPP Sud-Est VI, Clermont-Ferrand, France, IRB00008526) and registered by the French competent authority (French Medicine Agency, ANSM). The results will be communicated in a peer-review journal and presented at international congresses.

Trial registration number: NCT02100046

INTRODUCTION

Currently, there is evidence that voltage gated calcium channels (VGCCs) modulate pain perception due to their influence on neuronal transmission and excitability. In the past, attention was focused on the modulation of High Voltage Activated calcium channels (HVA; Cav1 and Cav2 families). More recently, scientific interest has turned to Low Voltage Activated calcium channels (LVA; Cav3 family), so-called T-type channels. Since this change of direction, the literature has emphasised significant involvement of these channels in the physiology of nociception and chronic pain processes (for a review see ref [1]).

The analgesics currently available often lack efficacy in the treatment of neuropathic pain and have fairly poor tolerability (for a review see refs [2,3]). Thus the clinical use of inhibitors of T-type calcium channels would not only help the development of new therapies for the treatment of neuropathic pain, whose prevalence is estimated at 7-8% in Europe (5% for moderate and severe pain)[4–10], but it would also have an economic impact due to the low sales price of the currently available inhibitor, Zarontin® (200 ml syrup; 250 mg / 5 ml).

T-type calcium channels and pain:

Cloning the alpha-1 subunit of T-type channels revealed at least three subtypes: alpha-1G (Cav3.1) [11], alpha-1H (Cav3.2) [12] and alpha 1I (Cav3.3) [13]. T-type calcium channels possess a unique property in neuronal excitability processes [14,15]: activation by weak depolarization of the cell membrane. This makes them capable of playing a role in different neurophysiological processes in neurons: the initiation of action potentials or spike trains, intracellular calcium influx, the release of neurotransmitters and the amplification of weak dendritic signals (inhibitory and excitatory postsynaptic potentials) (for a review see ref [1]).

Several *in vitro* and *in vivo* studies have identified various functions of T-type calcium channels, including their involvement in nociception and their contribution in the development of acute and chronic pain (neuropathic, visceral and inflammatory) [16–20]. T-type channel inhibition achieved by various experimental approaches (genetic and pharmacological) induces an analgesic effect in different types of painful conditions and in various pathological contexts. The main pharmacological compounds used to assess the analgesic properties of T-type channels are ethosuximide [21] and mibefradil [22].

Ethosuximide and peripheral neuropathic pain:

Ethosuximide is currently used in children and adults to treat absence seizures but it has no indication for pain relief. Considering the role of T-type calcium channels in nociceptive processes, several preclinical studies have investigated the effect of ethosuximide on pain, especially in the context of neuropathic pain. According to these studies, ethosuximide exhibited a relevant analgesic and antihyperalgesic effect and reduced painful symptoms related to neuropathic syndrome, suggesting the role of T-type calcium channels in the initiation and maintenance of neuropathic pain.

Ethosuximide possesses a moderate analgesic property in healthy rats [23] but completely removes painful neuropathic symptoms induced by sciatic and spinal nerve ligation [24].

Several cytotoxic chemotherapies may induce neuropathic syndrome (including neuropathic pain), thus limiting their use in patients. Flatters and Bennett showed that systemic injection of ethosuximide relieved mechanical and thermal cold allodynia in rats after receiving anticancer therapy (paclitaxel or vincristine) [25]. Similar results were found in a model of oxaliplatin-induced

peripheral neuropathy [26]. In addition, the chronic use of ethosuximide in these animal models does not induce tolerance.

No preclinical studies have evaluated the potential benefit of the use of ethosuximide in the context of diabetic neuropathy, but two preclinical studies have shown a relationship between T-type channels (Cav3.2 member) and diabetic neuropathy: the knock-out animals for Cav3.2 channels [27] and receiving Cav3.2 antisense RNA [28] do not develop allodynia or hyperalgesia induced by diabetic neuropathy.

Rationale for this pilot study

Due to their various involvements in the development and maintenance of chronic pain, T-type calcium channels are of great interest for the development of new symptomatic treatments of neuropathic pain. Analgesics available in our *pharmacopoeia* are ineffective and poorly tolerated in many patients with neuropathic pain. Interestingly, Zarontin®, which contains the active substance ethosuximide (T-type calcium blocker), is available on the European market for epilepsy. Despite this and numerous preclinical data demonstrating the antinociceptive effect of ethosuximide in various models of neuropathic pain, no clinical studies have been published to date on the therapeutic efficacy of ethosuximide in patients with neuropathic pain. Preclinical arguments and the absence of clinical evaluation provide the rationale for conducting the first pilot clinical trial to assess the potential benefit of using ethosuximide in the treatment of neuropathic pain.

METHODS AND ANALYSIS

The present study is a randomised, controlled, double-blinded and multicentre phase II trial to evaluate the efficacy and safety of ethosuximide in patients with peripheral neuropathic pain. Two hundred and twenty patients from 19 clinical sites in France are planned for inclusion. The study duration for each patient included will be 7 weeks, including a one week run-in period and 6 weeks of treatment.

Study objectives

The primary objective of this study is to evaluate the analgesic efficacy of ethosuximide administered in addition to background therapy to patients with peripheral neuropathic pain, versus inactive control.

Secondary objectives will be to study the effects of ethosuximide on:

- the intensity of daily pain (average and maximum pain experienced) throughout the study,
- the characteristics of neuropathic pain at the end of 6 weeks treatment,
- the HRQoL (physical and mental) at the end of 6 weeks treatment,
- the patient's quality of sleep throughout the study,
- the patient's global impression of change at the end of 6 weeks treatment.

Inclusion and exclusion criteria

Participants will be patients with peripheral neuropathic pain diagnosed for more than 3 months and not relieved by the usual treatments (see details in Box 1).

Box 1 Inclusion and exclusion criteria of the study

Inclusion criteria

- Man or woman aged 18 or over.
- Negative pregnancy test and effective contraception.
- Peripheral neuropathic pain diagnosis (DN4 ≥ 4)[29].
- Treatment failure (NRS Pain ≥ 4) for at least 3 months despite stable analgesic treatment for one month.
- Normal liver function (ALT, AST, ALP, GGT <3N).
- Normal renal function (creatininemia <133 µmol/L).
- Haematocrit >38% (men) and >34% (women).
- Patients affiliated with the French Social Security system.
- Patients able to provide free and informed consent.

Exclusion criteria

- Breastfeeding.
- Central neuropathic pain (spinal or supraspinal), stroke type or spinal cord injury, phantom limb pain, fibromyalgia.
- Medical and surgical history incompatible with the study.
- Addiction to alcohol and / or drugs.
- Taking antiepileptics (carboxamide family).
- Patient treated with ethosuximide.
- Allergy to succinimide (ethosuximide, methsuximide, phensuximide).
- Psychotic disorders.
- Epilepsy.

- Malabsorption of glucose and galactose.
- Glucose / fructose intolerance.
- Sucrase / isomaltase deficit.
- Participation in another clinical trial.
- Clinical trial exclusion period.
- Total amount of compensation higher than €4,500 for the 12 months preceding the start of the trial.
- Insufficient cooperation and understanding to adhere strictly to the conditions demanded by the study.
- Patients subject to legal protection.

No therapeutic change will be generated by the protocol; patients will be treated with ethosuximide or inactive control in addition to their current treatment for neuropathic pain. However, no therapeutic change for neuropathic pain will be allowed at any time during the study.
Patients can be withdrawn from the study for any of the following reasons: modification of the analgesic therapy, intolerance to ethosuximide, withdrawal of consent, breach of protocol, significant adverse events.

Investigational Medicinal Product

To ensure the double-blind condition, therapeutic units will be kept in similar bottles and labelling will be performed to mask brand names.

Zarontin® (Pfizer, ethosuximide)
The active substance is ethosuximide. This is an antiepileptic drug and a T-type calcium channel blocker. It is currently authorized in Europe for the treatment of epilepsy. It is active on absence seizures and used alone or in combination with another antiepileptic drug in the treatment of generalised epilepsies.
Ethosuximide will be administered bid, morning and evening during meals for 42 days (6 weeks). The dosage will be increased very gradually 250 mg (5 ml) every 4 days until reaching the maximum dose at 20 mg/kg (or 1500 mg) per day, which corresponds to the current Summary of Product Characteristics. However, if during the titration phase the patient reports uncomfortable adverse effects, the investigator has the option to continue treatment at the lower dose level, if well tolerated, up to the end of the study. This pragmatic attitude corresponds to current clinical practice and is aimed at reducing the risk of study discontinuation. It will also provide information on the dose with the best benefit/risk *ratio* in this indication.

Inactive control
Stodal® (Boiron Laboratories) is a homeopathic syrup indicated for the treatment of cough. The choice of this homeopathic syrup as inactive control is justified by several arguments:

- The syrup bottle packaging of Stodal® is similar to that of Zarontin®: pharmaceutical form (syrup), bottle shape, colour and volume. These similarities conform to the double blind requirements.
- It is a homeopathic treatment traditionally used in the treatment of cough, and has no indication in the treatment of pain.

- According to the recommendations of the painkiller studies mentioned in the last Cochrane review of Moore *et al.* [30] dealing with clinical studies evaluating the efficacy of analgesics on neuropathic pain, and according to good clinical practice, it is recommended that the first Phase II study should evaluate the efficacy of analgesics tested in comparison with a placebo or inactive control. In addition, current active comparators, namely pregabalin and gabapentin, are marketed in capsule or tablet form, which would require implementing a double-dummy.

Stodal® will be taken for 42 days (6 weeks) with the same administration modalities as the ethosuximide group.

Study endpoints

Study endpoints were based on the recommendation of the European Medicinal Agency (ICH guideline on neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Primary endpoint

Pain intensity (NRS, 11 points). This scale allows the patient to rate their pain from 0 to 10, with 0 for no pain and 10 for the worst possible pain. Pain intensity will be recorded daily on the logbook throughout the study, and the values will be averaged for the 7 days preceding the two time points D0 (baseline) and D0+42 (last visit). The primary endpoint is the calculated difference Δ = NRS (D0) – NRS (D0+42).

Secondary endpoints

Health Related Quality of Life (MOS SF-12). HRQoL will be evaluated by the MOS SF-12[31] questionnaire which assesses the physical and mental health of the patient using 12 questions related to eight aspects of health (physical and social activities, morale, physical and emotional strength to accomplish everyday tasks, physical pain, general mental health, vitality, perceived general health status). A score is determined for both physical and mental health (0-100).

Neuropathic pain symptom (NPSI and BPI). The Neuropathic Pain Symptom Inventory (NPSI)[32] and the Brief Pain Inventory (BPI)[33] will be used to evaluate the characteristics and impacts of neuropathic pain.

The NPSI is a self-administered questionnaire designed to assess different symptoms of neuropathic pain. It includes 12 items that can discriminate and quantify five separate clinically relevant dimensions.

The BPI is a self-administered questionnaire which includes: 1) a body scheme, 2) the maximum pain, less pain, usual pain during the last 15 days (NRS 11 points), 3) the description of the analgesic treatment in progress, 4) an evaluation of pain relief on a percentage scale (0-100%), 5) the impact of pain on mood, relationships with other people, walking, sleeping, work, joy of life, leisure activities (NRS, 0 normal to 10 impossible).

Quality of sleep (LSEQ). The Leeds sleep evaluation questionnaire (LSEQ)[34] is a standardised questionnaire composed of ten self-visual analogue scales (10 cm) that relate four aspects of sleep efficiency: 1) the quality of falling asleep and level of sleepiness, 2) sleep quality, 3) awakening quality and 4) the quality of state after awakening and performance

These evaluations will be conducted during the screening visit (D0) and at the end of the study (D0+42).
Moreover, a daily evaluation (in the morning) of the quality of falling asleep and sleep during the previous night (NRS from 0 (very poor) to 10 (excellent)) will be reported on the daily logbook.

Patient's Global Impression of Change (PGIC). PGIC[35] is aimed at assessing the general effectiveness of the treatment. This scale consists of 7 level descriptors answering the question "How are you?" distributed in three ways: (i) improved (very/medium/slightly), (ii) unchanged and (iii) aggravated (slight/medium/very).

Safety. Adverse events will be evaluated throughout the study and the study discontinuation rate will be evaluated and compared in the two treatment arms.

Methodology and study design
The study methodology was selected on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Patients will be treated for 6 weeks either by ethosuximide, according to a scheme of specific titration (maximum dose of 1500 mg/day achieved in 20 days) or an inactive control treatment administered with the same modalities (see figure 1).

Enrolment
Patients followed-up in their referral centre for the treatment of pain will be pre-selected. Patients will be contacted in order to briefly present the purpose of the study and make an appointment for the inclusion visit.

Visit 1 - Inclusion (D-7) and run-in period (D-7 to D0)
The objectives of the study, practice organisation, constraints and different questionnaires will be explained in detail to the patient by the investigator who will also collect the informed consent form. The patient must present a neuropathic pain diagnostic defined according to the DN4 questionnaire and the IASP (International Association for the Study of Pain) criteria determined during the clinical examination by the investigating physician.
A daily logbook will be given to the patient along with detailed instructions to collect every day, the median and maximum pain score experienced during the day and sleep and falling asleep quality. Possible side effects should be collected. The patient will return home with a logbook for 7 days, corresponding to the run-in period assessing the patient's ability to complete the logbook and recover the data on the intensity of neuropathic pain.

Visit 2 - Start of treatment (D0)
Daily average pain scores have to be filled-in by the patient on the logbook during the last 7 days and the average pain score should be ≥4 to include the patient in the study. The patients have to fill in four questionnaires: 1) LSEQ), 2) MOS SF-12), 3) NPSI and 4) BPI.
If all the inclusion and non-inclusion criteria are conformed to, the patient will be enrolled in the study and randomised in one of the two treatment arms (ethosuximide or inactive control). The administration dosages, according to a specific titration scheme, will be explained in detail to the

patient. At the end of the visit, the patient will receive all the therapeutic units for the duration of administration required by the study protocol (42 days).

Ambulatory period (D0 to D0+42).

Ethosuximide or inactive control treatment will be administered in two daily doses during meals, according to a scheme of specific titration for 20 days followed by a plateau at the maximum dose of 1500 mg/day for 22 days. The patient will assess and record the following daily in the logbook: the quality of falling asleep and sleep during the previous night and the median and maximum pain felt in the day.

Every 4 days (at the end of each dose escalation level), patients will be contacted by phone in order to collect information on any side effects.

Visit 3 – Study end (D0+42).

Idem visit 2. The patient must also complete the PGIC questionnaire. This visit represents the end of study.

Statistical considerations

Sample size Estimation

According to previous works [30,36], pain intensity was estimated at around 2.5. Hundred patients per group will be included to highlight a difference equals to 1 for a two-sided type I-error at 5% and a statistical power at 80%. Finally, a total of N=220 patients will be considered to take into account lost to follow-up (10%). An interim analysis is planned after enrolment of the first 110 patients using the Lan and DeMets rule (Pocock, East software, Cytel Inc, Cambridge, Massachusetts, USA). The type I error is fixed at 0.003 for this interim analysis.

Statistical analysis

Statistical analyses will be conducted using Stata software (version 13, StataCorp, College Station, US). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance (except interim analysis). Comparisons between independent groups will be analysed using the $\chi 2$ or Fisher's exact test for categorical variables (notably Patient's Global Impression of Change and safety) and Student's t-test or Mann-Whitney's test for quantitative parameters (notably pain intensity, health related quality of life scores measured by MOS SF-12, NPSI and BPI scores, sleep quality evaluated using Leeds score). Normality will be studied by the Shapiro-Wilk test and homoscedasticity using the Fisher-Snedecor test. Intention to treat (ITT) will be considered for the primary analysis. The analysis of the primary outcome will be completed by multivariate analysis using a linear mixed model to take into account: (1) fixed effects covariates chosen according to univariate results and to clinical relevance, and (2) centre as random-effects (to measure between and within centre variability).Also included will be the analysis of repeated measures and random-effect models (linear or generalised linear). Other treatments will be considered as a covariate to study the impact on patient quality of life, pain intensity and quality of sleep. According to clinical relevance and to EMA and CONSORT recommendations, sub-group analysis depending on the aetiology (diabetic neuropathy, post-herpetic, etc.) will be proposed after the study of aetiology x randomization group interaction in regression models (for repeated data or not). Finally, particular focus will be placed on lost to follow-up. A study of abandonment considered as censored data will be proposed using the Kaplan-Meier estimation. A sensitivity analysis will be performed and the

nature of missing data will be studied (missing at random or not). According to this, the most appropriate approach to the imputation of missing data will be proposed (maximum bias).

Dissemination

Approval

Any substantial modification of the protocol and of the informed consent form will be presented to the independent medical ethics committee. The latter and the competent French authority will be informed of the end of the study. In accordance with the independent medical ethics committee (CPP Sud Est VI, Clermont-Ferrand, France), no safety and data monitoring committee has been set up in view of the low risk of the ethosuximide treatment. The study is currently registered on the clinical trials website under the following number: NCT02100046. The protocol has been in V.12 since 16/12/2015.

Patient informed consent

According to the French law on biomedical research, written informed consent must be obtained from patients prior to participation in the study. Patients will voluntarily confirm their willingness to participate in the study, after having been informed (in writing and verbally) by investigators of all aspects of the study that are relevant to their decision to participate. They will be informed about requirements concerning data protection and have to agree to direct access to their individual data. The patients will be informed that they are free to withdraw from the study at any time at their own discretion without necessarily giving reasons.

Data collection and quality management

A clinical research assistant will be dedicated to data entry, coding, security and storage. Each patient included and the study data will be anonymised. The study data will be collected and managed using a Case Report Form (CRF). A clinical research assistant will be commissioned by the sponsor (University Hospital of Clermont-Ferrand) in order to monitor the progress of the study in accordance with the Standard Operating Procedures implemented in the University Hospital of Clermont-Ferrand, in accordance with Good Clinical Practices and current French laws.

Access to data and communication of results

The data set will be the property of the sponsor (University Hospital of Clermont-Ferrand). However, the principal investigator (AE) and the project manager (NK) will have full access to the final data set. The results will be communicated in a peer-reviewed journal, presented at international congresses and completed online on ClinicalTrials.gov.

DISCUSSION

This translational research project aims to demonstrate the therapeutic effect of ethosuximide on peripheral neuropathic pain.

In this study, particular emphasis has been placed on the methodology in order to provide a sufficient level of evidence. Indeed, we relied on the recommendation of the EMA (ICH guideline on neuropathic pain: CPMP / EWP / 252/03 Rev. 1) and endeavoured to comply with them as much as possible: randomised; controlled; double-blinded; parallel groups; large patient sample (110 / arm); several weeks of treatment; mixed population and relevant evaluation criteria.

However, in this study we used a homeopathic syrup (Stodal®) as an inactive control instead of a placebo. This choice was made not only for logistical reasons but also for scientific motives. Indeed, several studies have shown that the effect of homeopathic treatment is not better than that of a placebo (for a review see ref [37]). Because of conflicting studies [38], this choice was made assuming that if homeopathy does have a therapeutic effect, and that ethosuximide has a greater effect than our inactive control group, then this will give even greater credence to the therapeutic effect observed. Moreover, no data was found when searching for links between the terms “Stodal” and all these components and “pain” on Medline. This provides further evidence of the lack of analgesic effect of Stodal® and these components.

Neuropathic pain remains an important public health issue, as its prevalence in Europe is estimated at 7-8% [4–10] and up to 40% of the patients treated are not or poorly relieved by current treatments (for review see refs [2,3]). Peripheral neuropathy symptoms can last for months and even years after surgery, chemotherapy, herpetic infection, diabetes, trauma, etc. and the lack of support induces anxiety, depression, sleep disorders and a decrease of HRQoL (for reviews see refs [39–41]). Neuropathic pain has a strong economic and social impact, as patients with neuropathic pain generate significant excess healthcare costs and resource use amounting to €10,313 per patient per year in France [42].

Therefore, innovative therapeutic strategies are now more than necessary to treat neuropathic pain. This is the first study to examine the effectiveness of ethosuximide on neuropathic pain. If the results are positive, it will be an important step forward for the pharmacopeia of this pathology.

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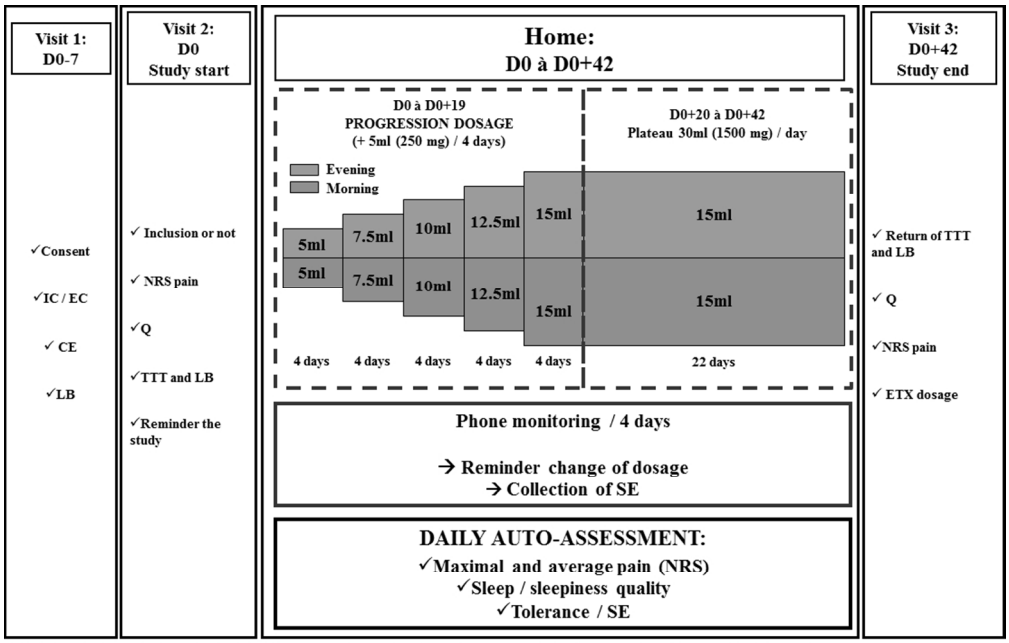

IC / EC: inclusion/exclusion criteria; CE: clinic exam; Q: questionnaires; TTT: treatment; LB: LogBook; ETX: ethosuximide; SE: side effect.

Scheme protocol design

RESEARCH CHECK LIST (SPIRIT GUIDELINES)

Administrative Information

Title: *Assessment of the Effectiveness of Ethosuximide in the Treatment of Peripheral Neuropathic Pain.*
Acronym: EDONOT

Trial registration:
Sponsor code: PHRC IR 2013 ESCHALIER
EudraCT number: 2013-004801-26
Clinical trial registration: NCT02100046

Protocol version :
Version 12 (16/12/2015)

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Introduction

Background and rationale

Currently, there is evidence that voltage gated calcium channel (VGCCs) modulate pain perception due to their influence on the neuronal transmission and excitability. In the past, the attention was focused on the modulation of High Voltage Activated calcium channels (HVA; Cav1 and Cav2 families). More recently, scientific interest proved vis-à-vis the Low Voltage Activated calcium channel (LVA; Cav3 family), so-called T-type channels. Since this interest, the literature data demonstrate significant involvement of these latter channels in the physiology of nociception and chronic pain processes (for review see ref [1]).

The available analgesics often lack efficacy in chronic pain and have a fairly poor tolerability (for review see refs [2,3]). Thus, the clinical use of inhibitors of T-type calcium channels could not only help the development of new therapies for the treatment of neuropathic pain, which prevalence is estimated at 7-8% in Europe (5% for moderate and severe pain)[4–10], but also have an economic impact due to the low selling price of their currently available inhibitor, Zarontin® (7.52 Euros per 200 ml syrup; 250 mg / 5 ml).

T-type calcium channels and pain:

Cloning of the alpha-1 subunit of T-type channels showed at least three subtypes: alpha-1G (Cav3.1)[11], alpha-1H (Cav3.2)[12] and alpha 1I (Cav3.3)[13]. T-type calcium channels possess a unique property in neuronal excitability processes[14,15]. Indeed, T-type calcium channels can be activated by a weak depolarization of the cell membrane. In neurons, this gives them the ability to be involved in different neurophysiological processes: initiation of action potentials spike train,

intracellular calcium influx, release of neurotransmitters and amplification of weak dendritic signals (inhibitory and excitatory postsynaptic potentials) (for review see ref [1]).

Several *in vitro* and *in vivo* studies have identified various functions of T-type calcium channels, including their involvement in nociception and their contribution in the development of acute and chronic pain (neuropathic, visceral and inflammatory)[16–20]. T-type channels inhibition by various experimental approaches (genetic and pharmacological) induces an analgesic effect in different types of painful conditions and in various pathological contexts. The main compounds used to assess the analgesic properties T-type channels blockers are ethosuximide[21] and mibefradil[22].

Ethosuximide and peripheral neuropathic pain:

Ethosuximide is currently used in children and adults to treat absence seizures in adults and children but, it has no indication for pain relief. Considering the role of T-type calcium channels in nociceptive processes, several studies have investigated the effect of ethosuximide on pain, especially in neuropathic pain. According to several preclinical studies this compound showed a relevant analgesic and antihyperalgesic effect and reduced the painful symptoms related to neuropathic syndrome suggesting the role of T-type calcium channels in the initiation and maintenance of neuropathic pain.

Indeed, ethosuximide has moderate analgesic property in healthy rats[23] but completely removes the painful neuropathic symptoms induced by sciatic nerve ligation[24]. In the animal model of neuropathy induced by traumatic spinal nerve, Dogrul *et al.* demonstrated that the systemic injection of ethosuximide also suppressed the painful neuropathic symptoms[24].

Several cytotoxic chemotherapies may induce neuropathic syndrome (including neuropathic pain), which limits their use in patients. Flatters and Bennett have shown that systemic injection of ethosuximide relieved the mechanical and thermal cold allodynia in rats after receiving anticancer therapy (paclitaxel or vincristine)[25]. Similar results were found in the model of neuropathy induced by oxaliplatin[26]. In addition, the chronic use of ethosuximide in these animal models does not induce tolerance phenomenon.

No preclinical studies have evaluated the potential benefit of the use of ethosuximide in the context of diabetic neuropathy, but two preclinical studies have shown a relationship between T-type channels (Cav3.2 member) and diabetic neuropathy. In fact, the knock-out animals for Cav3.2 channels[27] or receiving Cav3.2 antisense RNA[28] do not develop allodynia or hyperalgesia induced by diabetic neuropathy.

Rational for this pilot study

T-type calcium channels blockers, due to their various involvements in development and maintain of chronic pain, have a major interest for the development of new symptomatic treatments of neuropathic pain. Analgesics available in our *pharmacopoeia* are ineffective and poorly tolerated in many patients with neuropathic pain. It is interesting that the Zarontin®, containing the active substance ethosuximide (T-type calcium blocker), is available on the European market for epilepsy. Despite this and numerous preclinical data demonstrating antinociceptive effect of ethosuximide in various models of neuropathic pain, no clinical studies have been published to date on the therapeutic efficacy of ethosuximide in patients with neuropathic pain. Preclinical arguments and the absence of clinical evaluation is the rational to conduct a first pilot clinical trial to assess the potential benefit of using ethosuximide in the treatment of neuropathic pain.

Choice of comparator:

Zarontin® (Pfizer, ethosuximide)

The active substance is ethosuximide. This is an antiepileptic drug and a T-type calcium channel blocker. It aims to treat epilepsy. It is active on absence seizures and used alone or in combination with another antiepileptic drug in the treatment of generalised epilepsies.

Ethosuximide will be administered b.i.d., morning and evening during meals for 42 days. The dosage will be increased very gradually 250 mg (5 ml) every 4 days until reaching the maximum dose at 20 mg/kg (or 1500 mg) per day, which corresponds to the current Summary of Product Characteristics (SPC). However, if during the titration phase the patient reports uncomfortable side effects, the investigator has the option to continue treatment at the lower dose level, if well tolerated, and this up to the end of the study. This pragmatic attitude corresponds to the current clinical practice and aims at reducing the risk of study discontinuation. It will also provide some information about, the dose with the best benefit/risk *ratio* in this indication.

Inactive control

Stodal® (Boiron Laboratories) is homeopathic syrup which is indicated for the treatment of cough.

The choice of this homeopathic syrup as an inactive control is justified by several arguments:

- The syrup bottle packaging of Stodal® is similar to that of Zarontin®: pharmaceutical form (syrup), same bottle shape, colour and volume. These similarities respect the double blind requirements.
- It is a homeopathic treatment traditionally used in the treatment of cough, which has no indication in the treatment of pain.
- According to recommendations of the studies painkillers mentioned in the last Cochrane review of Moore *et al.* 2012[29] dealing with clinical studies evaluating the efficacy of analgesics on neuropathic pain and according to good clinical practice, it is recommended for a first Phase II study to evaluate the efficacy of analgesic tested in comparison with placebo or inactive control. In addition, current active comparators, pregabalin and gabapentin, are marketed in the form of capsule or tablet, which would require the implementation of a double-dummy of the fact that ethosuximide is in the form of syrup.

The Stodal will be taken with the same administration modalities of the ethosuximide group.

Objectives:

The main objective of this study is to evaluate the analgesic efficacy of ethosuximide administered in addition to background therapy in patients with peripheral neuropathic pain, versus inactive control.

The second objectives are:

- Evaluate daily pain patients (average and maximum pain experienced).
- Evaluate the changing characteristics of neuropathic pain.
- Evaluate the impact on patient quality of life (physical and mental).
- Evaluate sleep and asleep quality in patients.
- Evaluate the overall impression of improvement in patients.

Trial design:

Multicenter, randomized, double-blind, parallel group and controlled pilot clinical trial.

Safety and efficacy.

Methods

Study setting: Academic Hospitals

Eligibility criteria:

Inclusion criteria

- Man or woman aged 18 or more.
- Negative pregnancy test and effective contraception.
- Peripheral neuropathic pain diagnosis (DN4 ≥ 4).
- Treatment failure (NRS Pain ≥ 4) for at least 3 months despite stable analgesic treatment for a month.
- Normal liver function (ALT, AST, ALP, GGT).
- Normal renal function (creatininemia <133µmol/L).
- Haematocrit >38%.
- Patients affiliated to the regime of the French Social Security.
- Patients able to deliver a free and informed consent.

Exclusion criteria

- Breastfeeding.
- Central neuropathic pain (spinal or supraspinal) stroke type or spinal cord injury, pain phantom limb, fibromyalgia.
- Medical and surgical history incompatible with the study.
- Addiction to alcohol and / or drugs.
- Taking antiepileptic family carboxamide (carbamazepine and oxcarbazepine).
- Regular intake of St. John's wort.
- Patient treated with ethosuximide.
- Allergy to succinimide (ethosuximide, methsuximide, phensuximide).
- Psychotic disorders.
- Epilepsy.

Interventions :

Study methodology was selected on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Patients will be treated for 6 weeks either by ethosuximide, according to a scheme of specific titration (maximum dose of 1500 mg/day achieved in 20 days) or a control treatment administered with the same modalities.

Enrolment

Patients followed in their referral centre for the treatment of pain will be pre-selected. Patients will be contacted in order to present briefly the purpose of the study and make an appointment for the inclusion visit.

Visit 1 - Inclusion (D-7) and run-in period (D-7 to D0)

The objectives of the study, practice organisation, constraints and different questionnaires will be explained in detail by the investigator who also collects the inform consent form. The patient must present a neuropathic pain diagnostic defined according to the DN4 questionnaire and IASP

(International Association for the Study of Pain) criteria determined during the clinical examination by the investigating physician.
A daily logbook will be given to the patient with detailed explanations to collect every day, the median and maximum pain score experienced during the day and sleep and falling asleep quality. Possible side effects should be collected. The patient will go home with logbook for 7 days, corresponding to the run-in period assessing the patient's ability to complete the logbook and recover the data on the intensity of neuropathic pain daily.

Visit 2 - Start treatment (D0)
Daily average pain scores have to be filled by the patient on the logbook in the last 7 days and average pain score should be ≥ 4 to include the patient in the study. The patients have to fill out four questionnaires: 1) Sleep evaluation (Leeds), 2) HRQoL (MOS SF-12) and 3) neuropathic pain (NPSI and BPI).
If all the inclusion and non-inclusion criteria are respected, the patient will be enrolled in the study and randomised into one of two treatment arms (ethosuximide/inactive control). The administration dosages, according to a scheme of specific titration, will be explained in detail to the patient. At the end of the visit, the patient will receive all therapeutic units for the duration of administration required by the study protocol (42 days).

Ambulatory period (D0 to D0+42).
Ethosuximide or inactive control treatment will be administered in two daily doses during meals, according to a scheme of specific titration for 20 days followed by a plateau at the maximum dose of 1500 mg/day for 22 days. The patient will assess and record daily in the logbook: the quality of falling asleep and sleep during the last night and the median and maximum pain felt in the day.
Every 4 days (at the end of each dose escalation level), patients will be contacted by telephone in order to collect any side effects.

Visit 3 – Study end (D0+43).
Idem visit 2. The patient must also complete the PGIC questionnaire. This visit represents the end of study.

- All patients followed the same procedures (assessment of pain, filling questionnaires and taking treatment in the indicated dosage level).
- No deviation to the protocol will be allowed during the entire study.
- To verify patient compliance, accounting treatment units and a plasma dosage of active principle will be made at end of study.
- No treatment will be allowed during the test.

Outcomes:
Study endpoints were based on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Primary endpoint
Pain intensity (NRS, 11 points). This scale allows the patient to rate his pain from 0 to 10, with 0 is no pain and 10 the worst possible pain. The intensity of pain will be measured twice daily throughout the study on the logbook, and the values will averaged for the 7 days preceding the two

time points D0 (baseline) and D0+43 (last visit). The primary endpoint is the calculated difference Δ = (NRS (D0) – NRS (D0+43).

Secondary endpoints

Health Related Quality of Life (MOS SF-12 questionnaire). HRQoL will be evaluated by the MOS SF-12 questionnaire which assesses the physical and mental health of the patient using 12 questions related to eight aspects of health (physical and social activities, moral, physically and emotionally strength for accomplish everyday tasks, physical pain, general mental health, vitality, perceived general health status). A score is determined for both physical and mental health (0-100).

Neuropathic Pain Symptom (NPSI and BPI questionnaires). To evaluate characterise and assess the impact of neuropathic pain The Neuropathic Pain Symptom Inventory (NPSI) is a self-administered questionnaire designed to assess different symptoms of neuropathic pain. It includes 12 items that can discriminate and quantify five separate dimensions clinically relevant. The Brief Pain Inventory (BPI) is a self-administered questionnaire includes: 1) a body scheme, 2) the maximum pain, less pain, usual pain the last 15 days (NRS 11 points), 3) the description of analgesic treatment in progress, 4) an evaluation of the relief pain by a percentage scale (0-100%), 5) studying the impact of pain on mood, relationships with other people, walking, sleep, work, joy of life, leisure activities in general NRS, 0 (normal) to 10 (impossible).

Quality of sleep (Leeds questionnaire). The Leeds sleep evaluation questionnaire is a standardised questionnaire composed of ten self-visual analogue scales that relate to four aspects of sleep efficiency: 1) the quality of fall asleep and level of sleepiness, 2) sleep quality, 3) awakening quality and 4) the quality of the state after awakening, performance.

These evaluations will be conducted during the visit at baseline (D0) and the visit to end of study (D0+43).

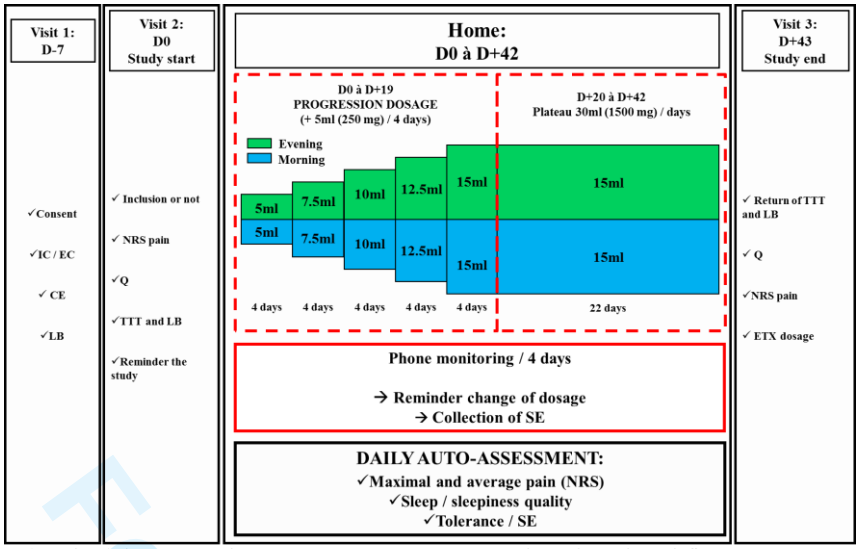
Moreover, a daily evaluation (at morning) of the quality of falling asleep and sleep during the last night (NRS from 0 (very poor) to 10 (excellent)) will be reported on the logbook.

Patient's Global Impression of Change (PGIC scale). PGIC aims to assess general effectiveness of treatment. This scale consists of 7 levels descriptors answering the question "How are you?", distributed in three ways: (i) improved (very/medium/slightly), (ii) unchanged and (iii) aggravated (slight/medium/very).

Safety. Adverse events will be evaluated throughout the study and study discontinuation rate will be evaluated and compared in the two treatment arms.

Participant timeline:

The duration of treatment is 42 days. The total duration of patient participation is maximum 50 days. The protocol includes 3 visits (Day-7, Day 0 and Day +42, see below).



IC / EC: inclusion/exclusion criteria; CE: clinic exam; Q: questionnaires; TTT: treatment; LB: LogBook; ETX: ethosuximide; SE: side effect.

Sample size:

According to previous works[29,30], pain intensity was estimated around 2.5. To highlight a difference equals 1 for a two-sided type I-error at 5% and a statistical power at 80%, n=100 patients per group will be included. Finally, a total of N=220 patients will be considered to take into account lost to follow-up (10%). An interim analysis is planned after enrolment of the first 110 patients using the Lan and DeMets rule (Pocock, East software, Cytel Inc, Cambridge, Massachusetts, USA). The type I error is fixed at 0.003 for this interim analysis.

Enrolment:

19 clinical sites in France, all specialized in the treatment of pain. The recruitment will be spread over 24 months, or 0.8 patients / month / center, which seems to be largely sufficient in the recruitment potential (prevalence of neuropathic pain = 7-8% in France).

Assignment of interventions:

Allocation Sequence generation: computer-generated random numbers. Stratification by center and 6 blocks random sequence.

Allocation concealment: sequentially numbered.

Implementation: Biostatistician generates the allocation sequence, investigators enroll participants and Clinical Research Associate (CRA) assigns participants to interventions.

Blinding:

All participants to study are blinded (double-blinded trial). Unblinding is possible only in case of serious adverse event or at the end of study if the study treatment showed a convincing therapeutic effect (Possibility of prescribing the treatment out of the study).

Data collection, management, and analysis:

Data collection methods

Data entry will be made by the investigators and CRA of each clinical center, at each visit (D-7 and D0 D0+42) and during the ambulatory period.

Data entry will be centralized in the coordinating center (CHU Clermont-Ferrand), from a paper case report form (CRF) sent by post or collected during site visits.

A duplicate of the CRF will be made (a copy to the clinical centre and a copy to the coordinating centre).
All patients will be analysed (intent to treat). However, if a major deviation from the protocol (non respect of co-occurring treatment, inclusion / exclusion criteria and the study design) only safety data will be evaluated.

Data management
Data will be entered in duplicate and a confrontation test will be performed to avoid any input errors. Finally, a consistency test will be conducted to validate compliance of data entered in accordance with the study protocol.

Statistical methods
Statistical analyses will be conducted using Stata software (version 13, StataCorp, College Station, US). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance (except interim analysis). Comparisons between independent groups will be analysed using the $\chi 2$ or Fisher's exact test for categorical variables (notably Patient's Global Impression of Change and safety) and Student t-test or Mann-Whitney's test for quantitative parameters (notably pain intensity, health related quality of life scores measured by MOS SF-12, NPSI and BPI scores, sleep quality evaluated using Leeds score). The normality will be studied by the Shapiro-Wilk test and the homoscedasticity using the Fisher-Snedecor test. Intention to treat (ITT) will be considered for the primary analysis. The analysis of the primary outcome will be completed by multivariate analysis using linear mixed model to take into account (1) fixed effects covariates retained according to univariate results and to clinical relevance, and (2) centre as random-effects (to measure between and within centre variability).The analysis of repeated measures, random-effect models (linear or generalised linear). Other treatments will be considered as a covariate to study this impact on patient quality of life, pain intensity and quality of sleep. According to the clinical relevance, to recommendations of the EMA and CONSORT, sub-group analysis according to the aetiology (diabetic neuropathy, post-herpetic, etc.) will be proposed after the study of interaction ethology x randomization group in regression models (for repeated data or not). Finally, a particular focus will be done on lost to follow-up. A study of abandonment considered as a censored data will be proposed using Kaplan-Meier estimation. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to it, the most appropriate imputation missing data approach will be proposed (maximum bias).

Monitoring:
The monitoring will be performed by CHU Clermont-Ferrand which is responsible for establishing the schedule and procedures to be followed for monitoring this study. On-site visits will be made prior to study initiation and at regular intervals during the study. Communications by telephone, telefax or mail may be used as needed to supplement site visits.

Prior to the beginning of this study, the Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the Investigator will receive reasonable notification prior to each monitoring visit during the course of the study.
The purpose of these visits is to verify:
- Adherence to the protocol,
- Availability of completed ICFs and adequate consent process

 Completeness and accuracy of the CRFs, and study related source document.

At each visit, the Investigator will be expected to cooperate with the monitor for the review and verification of all CRFs, the study drug supply and inventory records and any additional records as may have been previously arranged.

At the pre-study visit, the study monitor and/or the Sponsor representative will check that the Investigator has the technical means and the staff to carry out the study with regards to availability, subject recruitment, facilities and environment.

Prior to the start of the study, the Sponsor Study Manager will ensure that he/she has received the following information:

 Study protocol and financial agreement signed by all parts;

 Written statement of the CPP approval;

 Curriculum vitae of the investigators;

 Approval by the Competent Authority; ANSM.

As well as all other documents required for study initiation, as per GCP.

During the study, adherence to the protocol, availability of signed ICFs and conformity of the data entered in the CRF with the source documents will be checked at appropriate intervals by the study monitor.

At the end of the study, the Sponsor study manager will ensure he has received:

 The completed CRFs;

 All unused medications and remaining packaging, or that they have been destroyed in accordance with the applicable regulations.

 All documents are properly filed in the Investigator's site file as per GCP

Ethics and dissemination

Research ethics approval:

The protocol, information and consent form (ICF) and the CRF of the study will be submitted for opinion to the ethic committee (CPP VI of the Rhône-Alpes-Auvergne region) which carries the principal investigator of this trial. Notification of the approval of the CPP will be sent to the study sponsor and competent authority (ANSM). An authorization request will be made by the Promoter to ANSM before the start of the study.

When necessary, the protocol amendments will also have to be submitted to the above mentioned CPP or ANSM either for information or for formal approval. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the documented approval of the Sponsor. The IEC as well as the French Health Authorities which granted original approval for the study must be notified of all changes in the protocol and must provide documented approval for any change or deviation which may increase the risk to the subject and/or which may adversely affect the rights of the subject or validity of the investigation. This stipulation does not apply to those changes made to reduce discomfort or risk to subjects or which are purely administrative in nature.

In the event of any emergency, the Investigator shall institute any medical procedures, which he/she deems appropriate. However, all such procedures must be promptly reported to the Sponsor.

Amendments that are substantial and are likely to have an impact on the safety of trial subjects, or are otherwise significant, should receive IEC/Competent Authority approval. If the opinion of the IEC is favorable and the Competent Authorities have raised no grounds for unacceptability the study can be conducted according to the amended protocol. Non substantial amendment should only be notified.

Consent or assent:

Voluntary written ICF must be obtained from each subject prior to performing any study related procedures in compliance with the recommendations of the Declaration of Helsinki.

Subject should not be screened or treated until the subject has signed an approved ICF written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The ICF should be signed and personally dated in two originals by the subject and the person who conducted the informed consent discussion. The

Investigator, or the attending physician, will explain the nature, purpose and risks of the study. The subject will be informed that he has the right to withdraw at any time from the study, without giving reasons. In this case, the subject will not receive any indemnity. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his participation in the study.

The Investigator is responsible for assuring the appropriate content of the ICF and that informed consent is obtained from each subject in accordance with all applicable regulations and guidelines. The ICF will be reviewed and approved by the Sponsor, and then submitted to the IEC.

Each subject should receive one original of the signed and dated written ICF and any other information provided to the subject.

The second original of the signed and dated ICF should be retained in the Investigator's file.

The Investigator should maintain a log of all subjects who sign the ICF.

Confidentiality:

The information in this document and in any future information supplied contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but exclusively by an identification code.

Declaration of interests:

No competing interests.

Access to data:

The promoter is responsible for obtaining the agreement of all parties involved in research in order to guarantee direct access to all places of conduct research, source data, source documents and reports in a goal quality control and audit by the sponsor.

The investigators will make available documents and individual data strictly necessary monitoring, quality control and auditing of biomedical research, available to people with access to these

documents in accordance with legislative and regulatory provisions (Articles R.5121-13 L.1121-3 and the code of public health).

Ancillary and post-trial care:

If the patient is at the waning of the study indicates a marked improvement in his symptoms, unblinding procedure will be permitted to determine the drug to be prescribed after the study. Unblinding procedure and packaging of therapeutic units will maintain intact the double blind until the end of the study. Patients will be referred to their general practitioner or a specialist pain doctor who will be informed of the treatment received by the patient during the study. Note that the requirement in Zarontin® or Stodal® for the treatment of neuropathic pain being out of their marketing authorization framework, the sponsor does not support a continuation of treatment after the study. No patient follow-up is planned after the study.

Dissemination policy:

The data set will be propriety of the sponsor (CHU Clermont-Ferrand). However, the principal investigator (AE) and the project manager (NK) will have a full access to the final data set. The results will be disseminated in a peer-reviewed journal, presented at international congresses and completed online on ClinicalTrials.gov.

APPENDICE 1 – INFORM AND CONSENT FORM (French version)

Evaluation de l'efficacité antalgique de l'éthosuximide dans le traitement de douleur neuropathique d'origine traumatique

Promoteur

C.H.U. de Clermont-Ferrand
58 Rue de Montalembert, 63000 Clermont-Ferrand

Investigateur principal

Pr Alain ESCHALIER
UMR INSERM / UdA 1107 NEURO-DOL
CHU Gabriel-Montpied, 63000 Clermont-Ferrand

Le Docteur …….. vous a proposé de participer à un protocole de recherche clinique, dont le CHU de Clermont-Ferrand est promoteur. Toutes les consultations que vous aurez à effectuer, dans le cadre de cette étude, se feront au sein du centre de traitement de la douleur qui vous suit.

L'objectif de cette étude est d'évaluer l'efficacité de l'éthosuximide (commercialisé en France sous le nom de Zarontin®) sur le type de douleurs que vous présentez.

Comme plusieurs autres médicaments largement utilisés pour traiter les douleurs neuropathiques, l'éthosuximide, est aujourd'hui prescrit dans le traitement de l'épilepsie aussi bien chez l'enfant que chez l'adulte.

L'étude est dite faite en double aveugle, c'est-à-dire que vous recevrez, par tirage au sort, soit l'éthosuximide, soit une formulation ne contenant pas de produit actif. Le médecin et vous ne seront pas autorisés à avoir connaissance du traitement reçu.

Modalité de recrutement

Ce protocole vous est proposé ainsi qu'à 219 patients adultes souffrant de douleurs chroniques sévères. Selon un tirage au sort, vous recevrez, pendant la durée de votre participation à l'étude, soit de l'éthosuximide (sirop) soit un traitement homéopathique (sirop Stodal®) à titre de traitement contrôle. Les traitements que vous recevez habituellement seront poursuivis.

Traitements administrés dans le cadre de cette étude

Le traitement (éthosuximide ou homéopathie) sera administré de la façon suivante (qui comporte une progression des doses par paliers durant les premières semaines):

- **10 ml** (500mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours ;
- **15 ml** (750mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **20 ml** (1000mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **25 ml** (1250mg) /jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **30 ml** (1500 mg)/jour réparti en 2 prises (matin et soir) pendant 26 jours.

Les doses sont déterminées à l'aide d'une pipette en plastique graduée

Paraphe du Médecin **Paraphe du Sujet**

Evaluations réalisées

Echelle Numérique Simple (ENS)
à l'aide d'une échelle allant de 0 à 10, vous devrez, chaque jour, avant le coucher, relever sur votre carnet de suivi l'intensité douloureuse maximale et moyenne ressentie durant la journée.
Questionnaires sur les caractéristiques votre douleur et son impact sur votre vie courante :
Ils vont seront présentés et expliqués par le médecin investigateur afin que vous puissiez les remplir avec compréhension. Ces questionnaires sont au nombre de 4 : QEDN, Leeds, QCD et PGIC.
Ils devront être remplis pendant vos deux visites (J0 et J+43).

Dosages biologiques et d'éthosuximide
Un prélèvement sanguin (7,5 ml) sera effectué à chacune de vos deux visites dans le centre investigateur (J0 et J+43). Ces prélèvements seront réalisés par une infirmière.

Déroulement de l'étude

Dans le cadre de cette étude vous aurez à participer à 3 visites au centre d'investigation clinique et d'une période d'étude de 50 jours. Il vous est demandé de ne changer aucun de vos traitements habituels tout au long de l'étude. Cependant, si cela s'avérait nécessaire, il est important d'informer le médecin qui vous suit dans le cadre de cet essai, des éventuelles notifications dans les traitements que vous prenez régulièrement ou de l'introduction de nouveaux médicaments pris ou modifiés.

Recrutement
Vous serez préalablement sélectionnés par les médecins du centre d'évaluation et de traitement de la douleur et contactés par téléphone par le médecin investigateur afin de vous présenter brièvement le but de l'étude et de prendre rendez-vous pour la visite d'inclusion.

Récapitulatif de l'étude (tableau)
L'étude à laquelle vous participez se déroulera comme décrit dans le tableau ci-dessous.

Visites	Visite d'information	Inclusion	Période de traitement	Visite de fin d'étude
Jour	J-7	J0	J0 à J+42	J+43
Lieu	Centre	Centre	Domicile	Centre
Signature formulaire de consentement	+			
Examen clinique	+			
Remise du carnet de suivi	+			
Remplissage des questionnaires : - Leeds, SF12, QEDN, QCD (+PGIC)		+		+
Remise de votre traitement		+		
Contact téléphonique à votre domicile tous les 4 jours par l'ARC		+*	+*	
Evaluation journalière de votre douleur, de votre qualité de sommeil / endormissement	+	+	+	+
Ramener traitements et cahier de suivi				+
Prélèvement sanguin	+			+

* Contacts téléphoniques tous les 4 jours (à chaque augmentation de dose) à partir de J0 (inclus)

Paraphe du Médecin **Paraphe du Sujet**

Les bénéfices

Compte tenu de la durée limitée du traitement qui vous est prescrit dans le cadre de cette étude, il n'y a pas à attendre de bénéfice individuel durable résultant de la participation à l'étude. Toutefois, en cas d'amélioration sensible des épisodes douloureux durant la période de participation à l'étude, vous serez orienté vers votre médecin traitant ou éventuellement vers un centre spécialisé d'évaluation de traitement de la douleur avec un compte rendu des résultats observés pour optimiser votre traitement antalgique.

Les Risques attendus

L'éthosuximide est prescrit dans le traitement de l'épilepsie depuis 1965. La posologie retenue pour cet essai thérapeutique est celle habituellement utilisée dans cette indication. Dans cet essai, les paliers d'augmentation de dose ont été fixés à 4 jours. Comme la plupart des traitements médicamenteux, celui-ci peut générer quelques effets indésirables, à savoir principalement vertiges, céphalées et somnolence, rendant la prise de ce médicament incompatible avec la conduite sans avis préalable du médecin. Dans des cas très rares, la survenue de graves réactions cutanées (syndrome de Stevens-Johnson, lupus érythémateux disséminé, DRESS...) est possible. L'intensité de ces effets reste cependant légère à modérée et disparaissent à l'arrêt du traitement.

Afin d'éviter la survenue de ces effets indésirables, il vous est fortement recommandé de respecter l'augmentation progressive des doses par paliers pendant les quatre premières semaines jusqu'à la dose maximale. Des contacts téléphoniques tous les 4 jours (à la fin de chaque palier) seront destinés à vous rappeler les modifications de posologie et recueillir les éventuels effets indésirables que vous pourriez ressentir.
De plus, compte tenu de la mise sur le marché déjà ancienne de ce médicament, son profil de sécurité est aujourd'hui bien connu.

Le traitement contrôle (sirop Stodal) possède une forte concentration en sucre (3,75g pour 5ml) et contient un peu d'alcool (éthanol 0,069g = 1,74%). Pour ces raisons, ce médicament est déconseillé chez les personnes présentant une intolérance au fructose, un syndrome de malabsorption du glucose et du galactose ou un déficit en sucrase/isomaltase ou chez des personnes alcooliques.

Les règles d'asepsie seront rigoureusement appliquées pour les prélèvements sanguins. Le volume de sang prélevé est minime (7,5 ml deux fois, à environ 50 jours d'intervalle).

Indemnisation

Pour compenser les contraintes liées à votre participation au protocole, vous recevrez une indemnisation de 200 € pour la totalité de l'essai. Dans le cas d'un arrêt prématuré de l'essai, un calcul de l'indemnisation sera effectué au prorata des visites effectuées (arrêt en visite 2 = 50€, arrêt durant la période d'essai = 80€).

Paraphe du Médecin **Paraphe du Sujet**

Période d'exclusion pour participer à une autre recherche biomédicale

Vous n'êtes pas autorisé à participer à un autre essai clinique durant toute la durée du protocole.
De plus, la période d'exclusion définie dans le cadre de cette étude est de 30 jours, période pendant laquelle vous ne pourrez participer à un autre protocole de recherche clinique.
Le CHU de Clermont-Ferrand, qui organise cette recherche biomédicale en qualité de promoteur, a contracté une assurance conformément aux dispositions législatives, garantissant sa responsabilité civile et celle de tout intervenant auprès de la Société Hospitalière d'Assurances Mutuelles (SHAM, contrat n°135372).

Dans le cas où votre état de santé serait altéré du fait de votre participation à l'étude, conformément à la loi de Santé Publique n°2004-806 du 9 août 2004, vous seriez en droit de recevoir des dédommagements dans le cadre de ce contrat d'assurance spécifique.

Cette recherche a reçu l'avis favorable du Comité de Protection des Personnes Sud Est VI lors de la séance du 6 décembre 2013 ainsi que l'autorisation préalable de l'autorité compétente de santé datée du 26/03/2014. Il est possible que cette recherche soit interrompue, si les circonstances le nécessitent, par le promoteur ou à la demande de l'autorité de santé.

Confidentialités des données

Dans le cadre de la recherche biomédicale à laquelle le CHU de Clermont-Ferrand vous propose de participer, un traitement informatique de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté.
Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement.

En accord avec la loi Informatique et Liberté, le nom des sujets est automatiquement remplacé par un numéro de code dont la correspondance est connue des seuls médecins investigateurs.
Les données feront l'objet d'un traitement informatisé anonyme et leur consultation sera autorisée aux collaborateurs participant à la recherche, désignés par le promoteur et éventuellement au représentant des autorités de santé.
Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, vous disposez d'un droit d'accès et de rectification auprès du médecin qui vous suit dans le cadre de la recherche.
Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L. 1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.
Vous êtes libre d'accepter ou de refuser de participer à cette recherche. De plus vous pouvez exercer à tout moment votre droit de retrait de cette recherche.

Paraphe du Médecin **Paraphe du Sujet**

Par ailleurs, vous pourrez être tenu informé des résultats globaux de cette recherche à la fin de l'étude.

Si vous le souhaitez, vous pourrez à tout moment demander des informations complémentaires sur l'étude au personnel médical du Centre de Pharmacologie Clinique au 04.73.17.84.24 ou 04-73-17-84-23 du lundi au vendredi de 8h à 17h.
En cas d'urgence, et pendant toute la durée de l'étude, vous pourrez joindre à tout moment l'équipe médicale qui vous suit dans le cadre de votre participation à cette étude au N° suivant ……. Ou à défaut, le médecin d'astreinte du Centre de Pharmacologie Clinique de Clermont-Ferrand au 06-84-44-63-14.

Lorsque vous aurez lu cette note d'information et obtenu les réponses aux questions que vous vous posez en interrogeant le médecin investigateur, il vous sera proposé, si vous en êtes d'accord, de donner votre consentement écrit en signant le document préparé à cet effet.

Date : ……/……/……

Paraphe du Médecin **Signature du Sujet**
Précédée de la mention « Lu et compris »

Evaluation de l'efficacité antalgique de l'éthosuximide dans le traitement de douleur neuropathique d'origine traumatique

Investigateur principal:
Pr Alain ESCHALIER
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CHU Gabriel-Montpied, Service de Pharmacologie-Toxicologie 63000 Clermont-Ferrand
alain.eschalier@udamail.fr

Je soussigné(e) M. (*nom, prénom*)……Né(e) le _ _ / _ _ / _ _ _ _
Demeurant…….
Déclare : que le Docteur (*nom, prénom, téléphone*) ……
m'a proposé de participer à l'étude sus nommée, qu'il m'a expliqué en détail le protocole, qu'il m'a notamment fait connaître :

- l'objectif, la méthode et la durée de l'étude

- les contraintes et les risques potentiels encourus

- mon droit de refuser de participer et de retirer mon consentement à tout moment sans avoir à me justifier

- mon obligation d'inscription à un régime de sécurité sociale

- que, si je le souhaite, à son terme, je serais informé(e) par le médecin investigateur de ses résultats globaux

- que je ne serai pas autorisé(e) à participer à d'autres études cliniques pendant une durée de 3 semaines.

- que le Comité de Protection des Personnes Sud Est VI a émis un avis favorable le 06/12/2013. ainsi que l'autorisation préalable de l'autorité compétente de santé datée du 26/03/2014.

- que dans le cadre de cette étude le promoteur, le CHU de Clermont-Ferrand, a souscrit à une assurance couvrant cette recherche.

- que la période d'exclusion définie dans le cadre de cette étude est de 30 jours, période pendant laquelle vous ne pourrez participer à un autre protocole de recherche clinique.

L'étude comporte la création d'une collection d'échantillons sanguins pour le dosage de l'éthosuximide. Les échantillons seront détruits consécutivement à la fin de l'étude. J'accepte et je donne mon avis de non opposition pour le prélèvement, pour l'analyse et pour la création d'une collection d'échantillons biologiques dans le strict cadre de l'étude clinique ci-présente.

Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement.

J'accepte que ces données puissent faire l'objet d'un traitement informatisé anonyme. J'ai bien noté que le droit d'accès prévu par la loi du 6 août 2004 relative à l'informatique, aux fichiers et aux libertés s'exerce à tout moment auprès du médecin qui me suit dans le cadre de la recherche et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin, qui contactera le promoteur de la recherche.

J'accepte mon inscription dans le Fichier National des personnes qui se prêtent à des recherches biomédicales (Art. L 1121-16 du Code de la Santé Publique).

Après avoir discuté librement et obtenu réponse à toutes mes questions, j'accepte librement et volontairement de participer à cette recherche biomédicale dans les conditions précisées dans le formulaire d'information et de consentement.

Nom et prénom du sujet :……..
Date :……./……./…….
Signature *précédée de la mention « Lu et compris » :*

Nom de l'investigateur : ……
Date :……./……./…….
Signature

APPENDICE 2 – BIOLOGICAL SPECIMEN

Blood Test	**Time**
ALT	D-7 (screening)
AST	D-7 (screening)
ALP	D-7 (screening)
GGT	D-7 (screening)
Creatininemia	D-7 (screening)
Hematocrit	D-7 (screening)
Beta-HCG	D-7 (screening)
Ethosuximide	D0+42 or end of the study (compliance)

APPENDICE 3 – REFRENCES

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Assessment of the Effectiveness and Safety of Ethosuximide in the Treatment of non-Diabetic Peripheral Neuropathic Pain – EDONOT: protocol of a randomised, parallel, controlled, double-blinded and multicentre clinical trial

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TITLE PAGE

Assessment of the Effectiveness and Safety of Ethosuximide in the Treatment of non-Diabetic Peripheral Neuropathic Pain – EDONOT: protocol of a randomised, parallel, controlled, double-blinded and multicentre clinical trial

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Contributors

NK, AE, CC, CM, CD and CD led and contributed to the conceptualisation, design and implementation of this research protocol. BP led the development of the statistical analysis plan. NK participated in the design of the protocol for interventions and assessments. All the authors have read and approved the final manuscript.

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Competing interests

The authors declare they have no competing interests.

Ethics approval

The approval of the medical ethics committee (CPP Sud Est VI, Clermont-Ferrand, France) was obtained on 14 February 2014. The protocol was declared to the competent French authority (Agence Nationale de Sécurité du Médicament et des produits de santé) and registered under the number 131567A-32. Authorisation was obtained on 26 March 2014.

ABSTRACT

Introduction: Currently available analgesics are ineffective in 30 to 50% of patients suffering from neuropathic pain and often induce deleterious side-effects. T-type calcium channel blockers (mibefradil, ethosuximide, NNC 55-0396) are of great interest for the development of new symptomatic treatments of neuropathic pain, due to their various effects on pain perception. Interestingly, ethosuximide, which has already been approved for treating epilepsy, is available on the European market for clinical use. Despite numerous preclinical data demonstrating an antinociceptive effect of ethosuximide in various animal models of neuropathic pain, no clinical studies have been published to date on the analgesic efficacy of ethosuximide in patients with neuropathic pain.

Methods and analysis: The EDONOT trial is a randomised, parallel, controlled, double-blinded, multicentre clinical study. It is the first clinical trial to evaluate the efficacy and safety of ethosuximide in the treatment of non-diabetic peripheral neuropathic pain. Adult patients exhibiting peripheral neuropathic pain (NRS ≥ 4 and DN4 ≥ 4) for at least 3 months and under stable analgesic treatment for at least 1 month will be included. Patients (n=220) will be randomly assigned to receive either ethosuximide or control treatment for 6 weeks following a 1 week run-in period. The primary endpoint is the intensity of neuropathic pain, assessed by NRS (0-10) before and after 6 weeks of treatment. The secondary endpoints are safety (adverse events are collected during the study: daily by the patient on the logbook and during planned phone calls by investigators), the intensity and features of neuropathic pain (assessed by BPI and NPSI questionnaires) and health related quality of life (assessed by MOS-SF-12 and Leeds questionnaires).

Ethics and communication: The study was approved by an independent ethics committee (CPP Sud-Est VI, France, IRB00008526) and registered by the by the French competent authority (ANSM).

Trial registration number: NCT02100046

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strenghts:

- First clinical study assessing Ethosuximide on neuropathic pain,
- Randomised, double-blinded and controlled study,
- Larger study (220 patients),
- Methodology and eligible population close to clinical practices,
- Intention To Treat analyses.

Limitations:

- The treatment duration is shorter (6-weeks) than the current recommendations (≥12-weeks),
- An inactive control rather than a placebo,
- Diabetic population not considered.

INTRODUCTION

Currently, there is evidence that voltage gated calcium channels (VGCCs) modulate pain perception due to their influence on neuronal transmission and excitability. In the past, attention was focused on the modulation of High Voltage Activated calcium channels (HVA; Cav1 and Cav2 families). More recently, scientific interest has turned to Low Voltage Activated calcium channels (LVA; Cav3 family), so-called T-type channels. Since this change of direction, the literature has emphasised significant involvement of these channels in the physiology of nociception and chronic pain processes (for a review see ref [1]).

The analgesics currently available often lack efficacy in the treatment of neuropathic pain and have fairly poor tolerability (for a review see refs [2]). Thus the clinical use of inhibitors of T-type calcium channels would not only help the development of new therapies for the treatment of neuropathic pain, whose prevalence is estimated at 7-8% in Europe (5% for moderate and severe pain)[3–9], but it would also have an economic impact due to the low sales price of the currently available inhibitor, Zarontin® (200 ml syrup; 250 mg / 5 ml).

T-type calcium channels and pain:

Cloning the alpha-1 subunit of T-type channels revealed at least three subtypes: alpha-1G (Cav3.1) [10], alpha-1H (Cav3.2) [11] and alpha 1I (Cav3.3) [12]. T-type calcium channels possess a unique property in neuronal excitability processes [13,14]: activation by weak depolarization of the cell membrane. This makes them capable of playing a role in different neurophysiological processes in neurons: the initiation of action potentials or spike trains, intracellular calcium influx, the release of neurotransmitters and the amplification of weak dendritic signals (inhibitory and excitatory postsynaptic potentials) (for a review see ref [1]).

Several *in vitro* and *in vivo* studies have identified various functions of T-type calcium channels, including their involvement in nociception and their contribution in the development of acute and chronic pain (neuropathic, visceral and inflammatory) [15–19]. T-type channel inhibition achieved by various experimental approaches (genetic and pharmacological) induces an analgesic effect in different types of painful conditions and in various pathological contexts. The main pharmacological compounds used to assess the analgesic properties of T-type channels are ethosuximide [20] and mibefradil [21].

Ethosuximide and peripheral neuropathic pain:

Ethosuximide is currently used in children and adults to treat absence seizures but it has no indication for pain relief. Considering the role of T-type calcium channels in nociceptive processes, several preclinical studies have investigated the effect of ethosuximide on pain, especially in the context of neuropathic pain. According to these studies, ethosuximide exhibited a relevant analgesic and antihyperalgesic effect and reduced painful symptoms related to neuropathic syndrome, suggesting the role of T-type calcium channels in the initiation and maintenance of neuropathic pain.

Ethosuximide possesses a moderate analgesic property in healthy rats [22] but completely removes painful neuropathic symptoms induced by sciatic and spinal nerve ligation [23].

Several cytotoxic chemotherapies may induce neuropathic syndrome (including neuropathic pain), thus limiting their use in patients. Flatters and Bennett showed that systemic injection of ethosuximide relieved mechanical and thermal cold allodynia in rats after receiving anticancer therapy (paclitaxel or vincristine) [24]. Similar results were found in a model of oxaliplatin-induced

peripheral neuropathy [25]. In addition, the chronic use of ethosuximide in these animal models does not induce tolerance.

No preclinical studies have evaluated the potential benefit of the use of ethosuximide in the context of diabetic neuropathy, but two preclinical studies have shown a relationship between T-type channels (Cav3.2 member) and diabetic neuropathy: the knock-out animals for Cav3.2 channels [26] and receiving Cav3.2 antisense RNA [27] do not develop allodynia or hyperalgesia induced by diabetic neuropathy.

Ethosuximide, action mechanism and safety in humans:

Ethosuximide is a succinimide anticonvulsant, which is marketed since 1988 and is on the World Health Organization's List of Essential Medicines [28]. It is considered as the first line treatment for treatment of absence seizures, partly because it is devoid of idiosyncratic hepatotoxicity, contrary to valproic acid, the alternative treatment (Katzung 2003, Drugs used in generalized seizures. Basic and Clinical Pharmacology (9th ed.)). The mechanism by which ethosuximide affects neuronal excitability mainly includes block of T-type calcium channels, and may include effects of the drug on other classes of ion channels [29–31].

Ethosuximide is rapidly and almost completely absorbed after oral administration. Peak plasma levels of 38 µg/ml are observed on average 3-7 hours after administration of a single dose of 500 mg in children. In adults, steady state is reached in about 7 days. The residual plasma levels are at 34 µg/ml on average, for a daily intake of 500mg. Therapeutic blood levels of ethosuximide vary between 40 and 100 µg/ml. The volume of distribution of ethosuximide is about 0.7 L/kg. It does not bind to plasma proteins. It is found in the cerebrospinal fluid, saliva, tears and breast milk in concentrations similar to those of the plasma. It is extensively metabolized mainly by oxidative pathway in at least three metabolites. Only 20% of the administered dose is recovered in urine. The primary metabolite in urine and representing 60% of the total dose is 2- (1-hydroxyethyl) -2-methyl suximide.

The half-life of plasma elimination is approximately 60 hours in adults and about 30 hours in children due to a higher metabolic clearance.

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. The potential advantage of ethosuximide resides in its mode of action that is different of other antiepileptic drugs used in neuropathic pain treatment. Indeed, gabapentinoids act primarily on the alpha 2 delta subunit of calcium channel [32,33], while ethosuximide acts primarily on T-type calcium channels (having no alpha 2 delta subunit) [13]. This specific pharmacological profile could provide to ethosuximide same efficacy in patients who are not sufficiently relieved by gabapentinoids.

No clinical studies have evaluated the potential benefit of the use of ethosuximide in the context of peripheral neuropathy. If the analgesic efficacy and good safety of ethosuximide is demonstrated, a comparison with other reference AEDs in the treatment of neuropathic pain should be considered.

Rationale for this pilot study:

Due to their various involvements in the development and maintenance of chronic pain, T-type calcium channels are of great interest for the development of new symptomatic treatments of neuropathic pain. Analgesics available in our *pharmacopoeia* are ineffective and poorly tolerated in many patients with neuropathic pain. Interestingly, Zarontin®, which contains the active substance

ethosuximide (T-type calcium blocker), is available on the European market for epilepsy. Despite this and numerous preclinical data demonstrating the antinociceptive effect of ethosuximide in various models of neuropathic pain, no clinical studies have been published to date on the therapeutic efficacy of ethosuximide in patients with neuropathic pain. Preclinical arguments and the absence of clinical evaluation provide the rationale for conducting the first pilot clinical trial to assess the potential benefit of using ethosuximide in the treatment of neuropathic pain.

METHODS AND ANALYSIS

The present study is a randomised, parallel, controlled, double-blinded and multicentre phase II clinical trial to evaluate the efficacy and safety of ethosuximide in patients with non-diabetic peripheral neuropathic pain. Two hundred and twenty patients from 19 clinical sites in France are planned for inclusion. The study duration for each patient included will be 7 weeks, including a one week run-in period and 6 weeks of treatment.

Study objectives

The primary objective of this study is to evaluate the analgesic efficacy of ethosuximide administered in addition to background therapy to patients with peripheral neuropathic pain, versus inactive control.

Secondary objectives will be to study the effects of ethosuximide on:

- the intensity of daily pain (average and maximum pain experienced) throughout the study,
- the characteristics of neuropathic pain at the end of 6 weeks treatment,
- the HRQoL (physical and mental) at the end of 6 weeks treatment,
- the patient's quality of sleep throughout the study,
- the patient's global impression of change at the end of 6 weeks treatment.

Inclusion and exclusion criteria

Participants will be patients with peripheral neuropathic pain diagnosed for more than 3 months and not relieved by the usual treatments (see details in Box 1).

Box 1 Inclusion and exclusion criteria of the study

Inclusion criteria

- Man or woman aged 18 or over.
- Negative pregnancy test and effective contraception.
- Peripheral neuropathic pain diagnosis (DN4 ≥ 4)[34].
- Treatment failure (NRS Pain ≥ 4) for at least 3 months despite stable analgesic treatment for one month.
- Normal liver function (ALT, AST, ALP, GGT <3N).
- Normal renal function (creatininemia <133 µmol/L).
- Haematocrit >38% (men) and >34% (women).
- Patients affiliated with the French Social Security system.
- Patients able to provide free and informed consent.

Exclusion criteria

- Breastfeeding.
- Central neuropathic pain (spinal or supraspinal), stroke type or spinal cord injury, phantom limb pain, fibromyalgia.
- Medical and surgical history incompatible with the study.
- Addiction to alcohol and / or drugs.
- Taking antiepileptics (carboxamide family).
- Patient treated with ethosuximide.
- Allergy to succinimide (ethosuximide, methsuximide, phensuximide).
- Psychotic disorders.
- Epilepsy.

- Malabsorption of glucose and galactose.
- Diabetic patients.
- Sucrase / isomaltase deficit.
- Participation in another clinical trial.
- Clinical trial exclusion period.
- Total amount of compensation higher than €4,500 for the 12 months preceding the start of the trial.
- Insufficient cooperation and understanding to adhere strictly to the conditions demanded by the study.
- Patients subject to legal protection.

No therapeutic change will be generated by the protocol; patients will be treated with ethosuximide or inactive control in addition to their current treatment for neuropathic pain. However, no therapeutic change for neuropathic pain will be allowed at any time during the study.
Patients can be withdrawn from the study for any of the following reasons: modification of the analgesic therapy, intolerance to ethosuximide, withdrawal of consent, breach of protocol, significant adverse events.

Investigational Medicinal Product

To ensure the double-blind condition, therapeutic units will be kept in similar bottles and labelling will be performed to mask brand names.

Zarontin® (Pfizer, ethosuximide)
The active substance is ethosuximide. This is an antiepileptic drug and a T-type calcium channel blocker. It is currently authorized in Europe for the treatment of epilepsy. It is active on absence seizures and used alone or in combination with another antiepileptic drug in the treatment of generalised epilepsies.
Ethosuximide will be administered bid, morning and evening during meals for 42 days (6 weeks). The dosage will be increased very gradually 250 mg (5 ml) every 4 days until reaching the maximum dose at 20 mg/kg (or 1500 mg) per day, which corresponds to the current Summary of Product Characteristics. However, if during the titration phase the patient reports uncomfortable adverse effects, the investigator has the option to continue treatment at the lower dose level, if well tolerated, up to the end of the study. This pragmatic attitude corresponds to current clinical practice and is aimed at reducing the risk of study discontinuation. It will also provide information on the dose with the best benefit/risk *ratio* in this indication.

Inactive control
Stodal® (Boiron Laboratories) is a homeopathic syrup indicated for the treatment of cough. The choice of this homeopathic syrup as inactive control is justified by several arguments:

- The syrup bottle packaging of Stodal® is similar to that of Zarontin®: pharmaceutical form (syrup), bottle shape, colour and volume. These similarities conform to the double blind requirements.
- It is a homeopathic treatment traditionally used in the treatment of cough, and has no indication in the treatment of pain.

- According to the recommendations of the painkiller studies mentioned in the last Cochrane review of Moore *et al.* [35] dealing with clinical studies evaluating the efficacy of analgesics on neuropathic pain, and according to good clinical practice, it is recommended that the first Phase II study should evaluate the efficacy of analgesics tested in comparison with a placebo or inactive control. In addition, current active comparators, namely pregabalin and gabapentin, are marketed in capsule or tablet form, which would require implementing a double-dummy.

Stodal® will be taken for 42 days (6 weeks) with the same administration modalities as the ethosuximide group.

Study endpoints

Study endpoints were based on the recommendation of the European Medicinal Agency (ICH guideline on neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Primary endpoint

Pain intensity (NRS, 11 points). This numeric scale allows the patient to rate their pain from 0 to 10, with 0 for no pain and 10 for the worst possible pain. Average pain intensity over the past 24 hours is recorded once daily, before bedtime, on the logbook throughout the study, and the values are averaged for the 7 days preceding the two time points D0 (baseline) and D0+42 (last visit). The primary endpoint is the change in numeric rating scale at D0 and D0+42.

Secondary endpoints

Health Related Quality of Life (MOS SF-12). HRQoL will be evaluated by the MOS SF-12[36] questionnaire which assesses the physical and mental health of the patient using 12 questions related to eight aspects of health (physical and social activities, morale, physical and emotional strength to accomplish everyday tasks, physical pain, general mental health, vitality, perceived general health status). A score is determined for both physical and mental health (0-100).

Neuropathic pain symptom (NPSI and BPI). The Neuropathic Pain Symptom Inventory (NPSI)[37] and the Brief Pain Inventory (BPI)[38] will be used to evaluate the characteristics and impacts of neuropathic pain.

The NPSI is a self-administered questionnaire designed to assess different symptoms of neuropathic pain. It includes 12 items that can discriminate and quantify five separate clinically relevant dimensions.

The BPI is a self-administered questionnaire which includes: 1) a body scheme, 2) the maximum pain, less pain, usual pain during the last 15 days (NRS 11 points), 3) the description of the analgesic treatment in progress, 4) an evaluation of pain relief on a percentage scale (0-100%), 5) the impact of pain on mood, relationships with other people, walking, sleeping, work, joy of life, leisure activities (NRS, 0 normal to 10 impossible).

Quality of sleep (LSEQ). The Leeds sleep evaluation questionnaire (LSEQ)[39] is a standardised questionnaire composed of ten self-visual analogue scales (10 cm) that relate four aspects of sleep efficiency: 1) the quality of falling asleep and level of sleepiness, 2) sleep quality, 3) awakening quality and 4) the quality of state after awakening and performance

These evaluations will be conducted during the screening visit (D0) and at the end of the study (D0+42).
Moreover, a daily evaluation (in the morning) of the quality of falling asleep and sleep during the previous night (NRS from 0 (very poor) to 10 (excellent)) will be reported on the daily logbook.

Patient's Global Impression of Change (PGIC). PGIC[40] is aimed at assessing the general effectiveness of the treatment. This scale consists of 7 level descriptors answering the question "How are you?" distributed in three ways: (i) improved (very/medium/slightly), (ii) unchanged and (iii) aggravated (slight/medium/very).

Safety. Any adverse events were collected daily by the patient and during the planned phone calls by investigators (every 4 days). Adverse events are categorized according to their type, intensity and treatment related by investigators. Due to the long half-life of ethosuximide (60h), a phone call, within 2 weeks after stopping treatment, will be allowed to recover any adverse effects.

Methodology and study design

The study methodology was selected on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Patients will be treated for 6 weeks either by ethosuximide, according to a scheme of specific titration (maximum dose of 1500 mg/day achieved in 20 days) or an inactive control treatment administered with the same modalities (see figure 1).

Enrolment

Patients followed-up in their referral centre for the treatment of pain will be pre-selected. Patients will be contacted in order to briefly present the purpose of the study and make an appointment for the inclusion visit.

Visit 1 - Inclusion (D-7) and run-in period (D-7 to D0)

The objectives of the study, practice organisation, constraints and different questionnaires will be explained in detail to the patient by the investigator who will also collect the informed consent form. The patient must present a neuropathic pain diagnostic defined according to the DN4 questionnaire and the IASP (International Association for the Study of Pain) criteria determined during the clinical examination by the investigating physician.
A daily logbook will be given to the patient along with detailed instructions to collect every day, the median and maximum pain score experienced during the day and sleep and falling asleep quality. Possible side effects should be collected. The patient will return home with a logbook for 7 days, corresponding to the run-in period assessing the patient's ability to complete the logbook and recover the data on the intensity of neuropathic pain.
This run-in period, without any studied treatment, was introduced (i) to evaluate the ability of the patients to rate their pain daily in their logbook; (ii) to check the basal average pain intensity over a 1-week period. The patients received the treatment after this run-in period only if the inclusion criteria were met (NRS pain ≥ 4 and completed logbook as required by the protocol).

Visit 2 - Start of treatment (D0)

Daily average pain scores have to be filled-in by the patient on the logbook during the last 7 days and the average pain score should be ≥4 to include the patient in the study. The patients have to fill in four questionnaires: 1) LSEQ), 2) MOS SF-12), 3) NPSI and 4) BPI.

If all the inclusion and non-inclusion criteria are conformed to, the patient will be enrolled in the study and randomised in one of the two treatment arms (ethosuximide or inactive control). The administration dosages, according to a specific titration scheme, will be explained in detail to the patient. At the end of the visit, the patient will receive all the therapeutic units for the duration of administration required by the study protocol (42 days).

Ambulatory period (D0 to D0+42).

Ethosuximide or inactive control treatment will be administered in two daily doses during meals, according to a scheme of specific titration for 20 days followed by a plateau at the maximum dose of 1500 mg/day for 22 days. The patient will assess and record the following daily in the logbook: the quality of falling asleep and sleep during the previous night and the median and maximum pain felt in the day.

Every 4 days (at the end of each dose escalation level), patients will be contacted by phone in order to collect information on any side effects.

Visit 3 – Study end (D0+42).

Idem visit 2. The patient must also complete the PGIC questionnaire.

This visit represents the end of study.

Due to the long half-life of ethosuximide (60h), telephone contact, within 2 weeks after stopping treatment, will be allowed to recover any adverse effects.

Statistical considerations

Sample size estimation

According to previous works [35,41], pain intensity was estimated at around 2.5. Hundred patients per group will be included to highlight a difference equals to 1 for a two-sided type I-error at 5% and a statistical power at 80%. Finally, a total of N=220 patients will be considered to take into account lost to follow-up (10%). An interim analysis is planned after enrolment of the first 110 patients using the Lan and DeMets rule (Pocock, East software, Cytel Inc, Cambridge, Massachusetts, USA). The type I error is fixed at 0.003 for this interim analysis.

Statistical analysis

Statistical analyses will be conducted using Stata software (version 13, StataCorp, College Station, US). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance (except interim analysis). Comparisons between independent groups will be analysed using the $\chi 2$ or Fisher's exact test for categorical variables (notably Patient's Global Impression of Change and safety) and Student's t-test or Mann-Whitney's test for quantitative parameters (notably pain intensity, health related quality of life scores measured by MOS SF-12, NPSI and BPI scores, sleep quality evaluated using Leeds score). Normality will be studied by the Shapiro-Wilk test and homoscedasticity using the Fisher-Snedecor test. Intention to treat (ITT) will be considered for the primary analysis. The analysis of the primary outcome will be completed by multivariate analysis using a linear mixed model to take into account: (1) fixed effects covariates chosen according to

univariate results and to clinical relevance, and (2) centre as random-effects (to measure between and within centre variability). The two treatment groups will be compared for end of treatment data. Also included will be the analysis of repeated measures and random-effect models (linear or generalised linear). Other treatments will be considered as a covariate to study the impact on patient quality of life, pain intensity and quality of sleep. According to clinical relevance and to EMA and CONSORT recommendations, sub-group analysis depending on the aetiology (diabetic neuropathy, post-herpetic, etc.) will be proposed after the study of aetiology x randomization group interaction in regression models (for repeated data or not). Finally, particular focus will be placed on lost to follow-up. A study of abandonment considered as censored data will be proposed using the Kaplan-Meier estimation. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to this, the most appropriate approach to the imputation of missing data will be proposed (maximum bias (e.g. last observation carried forward vs. baseline observation carried forward) or estimation proposed by Verbeke and Molenberghs for repeated data).

Dissemination

Approval

Any substantial modification of the protocol and of the informed consent form will be presented to the independent medical ethics committee. The latter and the competent French authority will be informed of the end of the study. In accordance with the independent medical ethics committee (CPP Sud Est VI, Clermont-Ferrand, France), no safety and data monitoring committee has been set up in view of the low risk of the ethosuximide treatment. The study is currently registered on the clinical trials website under the following number: NCT02100046. The protocol has been in V.12 since 16/12/2015.

Patient informed consent

According to the French law on biomedical research, written informed consent must be obtained from patients prior to participation in the study. Patients will voluntarily confirm their willingness to participate in the study, after having been informed (in writing and verbally) by investigators of all aspects of the study that are relevant to their decision to participate. They will be informed about requirements concerning data protection and have to agree to direct access to their individual data. The patients will be informed that they are free to withdraw from the study at any time at their own discretion without necessarily giving reasons.

Data collection and quality management

A clinical research assistant will be dedicated to data entry, coding, security and storage. Each patient included and the study data will be anonymised. The study data will be collected and managed using a Case Report Form (CRF). A clinical research assistant will be commissioned by the sponsor (University Hospital of Clermont-Ferrand) in order to monitor the progress of the study in accordance with the Standard Operating Procedures implemented in the University Hospital of Clermont-Ferrand, in accordance with Good Clinical Practices and current French laws.

Access to data and communication of results

The data set will be the property of the sponsor (University Hospital of Clermont-Ferrand). However, the principal investigator (AE) and the project manager (NK) will have full access to the final data set.

The results will be communicated in a peer-reviewed journal, presented at international congresses and completed online on ClinicalTrials.gov.

DISCUSSION

This translational research project aims to demonstrate the therapeutic effect of ethosuximide on peripheral neuropathic pain.

In this study, particular emphasis has been placed on the methodology in order to provide a sufficient level of evidence. Indeed, we relied on the recommendation of the EMA (ICH guideline on neuropathic pain: CPMP / EWP / 252/03 Rev. 1) and endeavoured to comply with them as much as possible: randomised; controlled; double-blinded; parallel groups; large patient sample (110 / arm); several weeks of treatment; mixed population and relevant evaluation criteria.

However, the present protocol has some limitations:

i) A 6-weeks treatment period was chosen, considering that this study is a proof-of-concept aimed at providing a first look on the efficacy and the safety of ethosuximide in neuropathic pain patients. In the case of positive efficacy / tolerability ratio, a larger study with longer treatment duration (≥ 12 weeks) and an active comparator (i.e. gabapentinoid) will be undertaken.

ii) In this study we used a homeopathic syrup (Stodal®) as an inactive control. This homeopathic cough syrup may taste different than the study treatment. To lower the risk of bias as much as possible, the study design is in parallel groups and all patients included have to be naive for ethosuximide treatment. In addition, investigators are not in contact with the treatment, which is always dispensed by pharmacists.

This choice was made also for scientific motives. Indeed, several studies have shown that the effect of homeopathic treatment is not better than that of a placebo (for a review see ref [42]). Because of conflicting studies [43], this choice was made assuming that if homeopathy does have a therapeutic effect, and that ethosuximide has a greater effect than our inactive control group, then this will give even greater credence to the therapeutic effect observed. Moreover, no data was found when searching for links between the terms “Stodal” and all these components and “pain” on Medline. This provides further evidence of the lack of analgesic effect of Stodal® and these components.

Neuropathic pain remains an important public health issue, as its prevalence in Europe is estimated at 7-8% [3–9] and up to 40% of the patients treated are not or poorly relieved by current treatments (for review see refs [44,45]). Peripheral neuropathy symptoms can last for months and even years after surgery, chemotherapy, herpetic infection, diabetes, trauma, etc. and the lack of support induces anxiety, depression, sleep disorders and a decrease of HRQoL (for reviews see refs [46–48]). Neuropathic pain has a strong economic and social impact, as patients with neuropathic pain generate significant excess healthcare costs and resource use amounting to €10,313 per patient per year in France [49]. Therefore, innovative therapeutic strategies are now more than necessary to treat neuropathic pain. This is the first study to examine the effectiveness of ethosuximide on neuropathic pain. If the results are positive, it will be an important step forward for the pharmacopeia of this pathology.

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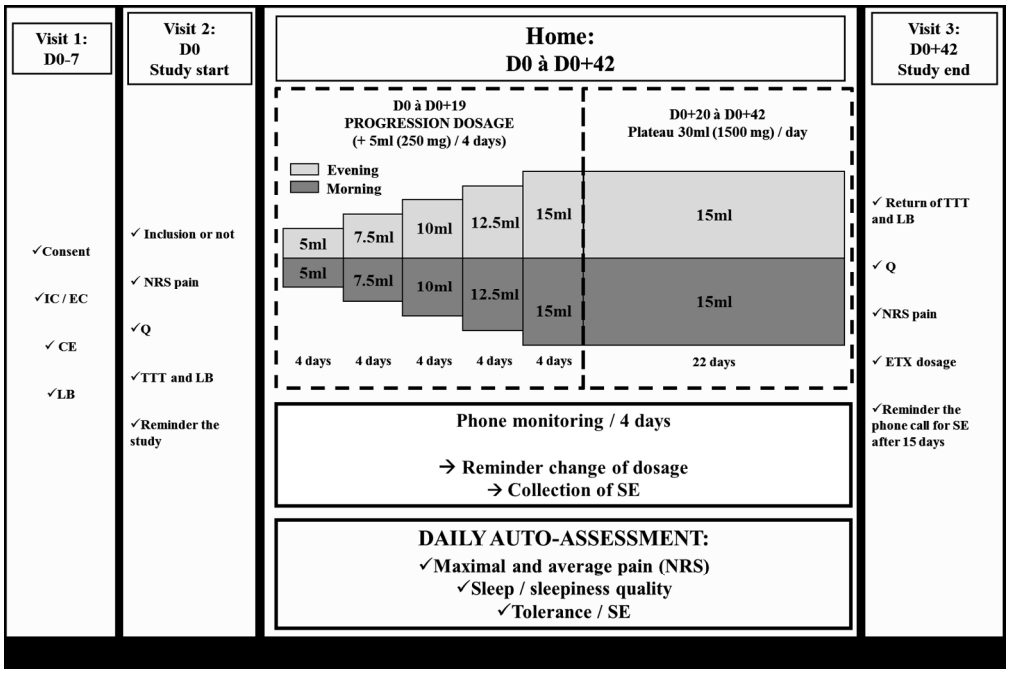

Study Design

146x97mm (300 x 300 DPI)

RESEARCH CHECK LIST (SPIRIT GUIDELINES)

Administrative Information

Title: *Assessment of the Effectiveness of Ethosuximide in the Treatment of Peripheral Neuropathic Pain.*
Acronym: EDONOT

Trial registration:
Sponsor code: PHRC IR 2013 ESCHALIER
EudraCT number: 2013-004801-26
Clinical trial registration: NCT02100046

Protocol version :
Version 12 (16/12/2015)

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Introduction

Background and rationale

Currently, there is evidence that voltage gated calcium channel (VGCCs) modulate pain perception due to their influence on the neuronal transmission and excitability. In the past, the attention was focused on the modulation of High Voltage Activated calcium channels (HVA; Cav1 and Cav2 families). More recently, scientific interest proved vis-à-vis the Low Voltage Activated calcium channel (LVA; Cav3 family), so-called T-type channels. Since this interest, the literature data demonstrate significant involvement of these latter channels in the physiology of nociception and chronic pain processes (for review see ref [1]).

The available analgesics often lack efficacy in chronic pain and have a fairly poor tolerability (for review see refs [2,3]). Thus, the clinical use of inhibitors of T-type calcium channels could not only help the development of new therapies for the treatment of neuropathic pain, which prevalence is estimated at 7-8% in Europe (5% for moderate and severe pain)[4–10], but also have an economic impact due to the low selling price of their currently available inhibitor, Zarontin® (7.52 Euros per 200 ml syrup; 250 mg / 5 ml).

T-type calcium channels and pain:

Cloning of the alpha-1 subunit of T-type channels showed at least three subtypes: alpha-1G (Cav3.1)[11], alpha-1H (Cav3.2)[12] and alpha 1I (Cav3.3)[13]. T-type calcium channels possess a unique property in neuronal excitability processes[14,15]. Indeed, T-type calcium channels can be activated by a weak depolarization of the cell membrane. In neurons, this gives them the ability to be involved in different neurophysiological processes: initiation of action potentials spike train,

intracellular calcium influx, release of neurotransmitters and amplification of weak dendritic signals (inhibitory and excitatory postsynaptic potentials) (for review see ref [1]).
Several *in vitro* and *in vivo* studies have identified various functions of T-type calcium channels, including their involvement in nociception and their contribution in the development of acute and chronic pain (neuropathic, visceral and inflammatory)[16–20]. T-type channels inhibition by various experimental approaches (genetic and pharmacological) induces an analgesic effect in different types of painful conditions and in various pathological contexts. The main compounds used to assess the analgesic properties T-type channels blockers are ethosuximide[21] and mibefradil[22].

Ethosuximide and peripheral neuropathic pain:
Ethosuximide is currently used in children and adults to treat absence seizures in adults and children but, it has no indication for pain relief. Considering the role of T-type calcium channels in nociceptive processes, several studies have investigated the effect of ethosuximide on pain, especially in neuropathic pain. According to several preclinical studies this compound showed a relevant analgesic and antihyperalgesic effect and reduced the painful symptoms related to neuropathic syndrome suggesting the role of T-type calcium channels in the initiation and maintenance of neuropathic pain.
Indeed, ethosuximide has moderate analgesic property in healthy rats[23] but completely removes the painful neuropathic symptoms induced by sciatic nerve ligation[24]. In the animal model of neuropathy induced by traumatic spinal nerve, Dogrul *et al.* demonstrated that the systemic injection of ethosuximide also suppressed the painful neuropathic symptoms[24].
Several cytotoxic chemotherapies may induce neuropathic syndrome (including neuropathic pain), which limits their use in patients. Flatters and Bennett have shown that systemic injection of ethosuximide relieved the mechanical and thermal cold allodynia in rats after receiving anticancer therapy (paclitaxel or vincristine)[25]. Similar results were found in the model of neuropathy induced by oxaliplatin[26]. In addition, the chronic use of ethosuximide in these animal models does not induce tolerance phenomenon.
No preclinical studies have evaluated the potential benefit of the use of ethosuximide in the context of diabetic neuropathy, but two preclinical studies have shown a relationship between T-type channels (Cav3.2 member) and diabetic neuropathy. In fact, the knock-out animals for Cav3.2 channels[27] or receiving Cav3.2 antisense RNA[28] do not develop allodynia or hyperalgesia induced by diabetic neuropathy.

Rational for this pilot study
T-type calcium channels blockers, due to their various involvements in development and maintain of chronic pain, have a major interest for the development of new symptomatic treatments of neuropathic pain. Analgesics available in our *pharmacopoeia* are ineffective and poorly tolerated in many patients with neuropathic pain. It is interesting that the Zarontin®, containing the active substance ethosuximide (T-type calcium blocker), is available on the European market for epilepsy. Despite this and numerous preclinical data demonstrating antinociceptive effect of ethosuximide in various models of neuropathic pain, no clinical studies have been published to date on the therapeutic efficacy of ethosuximide in patients with neuropathic pain. Preclinical arguments and the absence of clinical evaluation is the rational to conduct a first pilot clinical trial to assess the potential benefit of using ethosuximide in the treatment of neuropathic pain.

Choice of comparator:

Zarontin® (Pfizer, ethosuximide)

The active substance is ethosuximide. This is an antiepileptic drug and a T-type calcium channel blocker. It aims to treat epilepsy. It is active on absence seizures and used alone or in combination with another antiepileptic drug in the treatment of generalised epilepsies.

Ethosuximide will be administered b.i.d., morning and evening during meals for 42 days. The dosage will be increased very gradually 250 mg (5 ml) every 4 days until reaching the maximum dose at 20 mg/kg (or 1500 mg) per day, which corresponds to the current Summary of Product Characteristics (SPC). However, if during the titration phase the patient reports uncomfortable side effects, the investigator has the option to continue treatment at the lower dose level, if well tolerated, and this up to the end of the study. This pragmatic attitude corresponds to the current clinical practice and aims at reducing the risk of study discontinuation. It will also provide some information about, the dose with the best benefit/risk *ratio* in this indication.

Inactive control

Stodal® (Boiron Laboratories) is homeopathic syrup which is indicated for the treatment of cough.

The choice of this homeopathic syrup as an inactive control is justified by several arguments:

- The syrup bottle packaging of Stodal® is similar to that of Zarontin®: pharmaceutical form (syrup), same bottle shape, colour and volume. These similarities respect the double blind requirements.
- It is a homeopathic treatment traditionally used in the treatment of cough, which has no indication in the treatment of pain.
- According to recommendations of the studies painkillers mentioned in the last Cochrane review of Moore *et al.* 2012[29] dealing with clinical studies evaluating the efficacy of analgesics on neuropathic pain and according to good clinical practice, it is recommended for a first Phase II study to evaluate the efficacy of analgesic tested in comparison with placebo or inactive control. In addition, current active comparators, pregabalin and gabapentin, are marketed in the form of capsule or tablet, which would require the implementation of a double-dummy of the fact that ethosuximide is in the form of syrup.

The Stodal will be taken with the same administration modalities of the ethosuximide group.

Objectives:

The main objective of this study is to evaluate the analgesic efficacy of ethosuximide administered in addition to background therapy in patients with peripheral neuropathic pain, versus inactive control.

The second objectives are:

- Evaluate daily pain patients (average and maximum pain experienced).
- Evaluate the changing characteristics of neuropathic pain.
- Evaluate the impact on patient quality of life (physical and mental).
- Evaluate sleep and asleep quality in patients.
- Evaluate the overall impression of improvement in patients.

Trial design:

Multicenter, randomized, double-blind, parallel group and controlled pilot clinical trial.

Safety and efficacy.

Methods

Study setting: Academic Hospitals

Eligibility criteria:

Inclusion criteria

- Man or woman aged 18 or more.
- Negative pregnancy test and effective contraception.
- Peripheral neuropathic pain diagnosis (DN4 ≥ 4).
- Treatment failure (NRS Pain ≥ 4) for at least 3 months despite stable analgesic treatment for a month.
- Normal liver function (ALT, AST, ALP, GGT).
- Normal renal function (creatininemia <133µmol/L).
- Haematocrit >38%.
- Patients affiliated to the regime of the French Social Security.
- Patients able to deliver a free and informed consent.

Exclusion criteria

- Breastfeeding.
- Central neuropathic pain (spinal or supraspinal) stroke type or spinal cord injury, pain phantom limb, fibromyalgia.
- Medical and surgical history incompatible with the study.
- Addiction to alcohol and / or drugs.
- Taking antiepileptic family carboxamide (carbamazepine and oxcarbazepine).
- Regular intake of St. John's wort.
- Patient treated with ethosuximide.
- Allergy to succinimide (ethosuximide, methsuximide, phensuximide).
- Psychotic disorders.
- Epilepsy.

Interventions :

Study methodology was selected on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Patients will be treated for 6 weeks either by ethosuximide, according to a scheme of specific titration (maximum dose of 1500 mg/day achieved in 20 days) or a control treatment administered with the same modalities.

Enrolment

Patients followed in their referral centre for the treatment of pain will be pre-selected. Patients will be contacted in order to present briefly the purpose of the study and make an appointment for the inclusion visit.

Visit 1 - Inclusion (D-7) and run-in period (D-7 to D0)

The objectives of the study, practice organisation, constraints and different questionnaires will be explained in detail by the investigator who also collects the inform consent form. The patient must present a neuropathic pain diagnostic defined according to the DN4 questionnaire and IASP

(International Association for the Study of Pain) criteria determined during the clinical examination by the investigating physician.
A daily logbook will be given to the patient with detailed explanations to collect every day, the median and maximum pain score experienced during the day and sleep and falling asleep quality. Possible side effects should be collected. The patient will go home with logbook for 7 days, corresponding to the run-in period assessing the patient's ability to complete the logbook and recover the data on the intensity of neuropathic pain daily.

Visit 2 - Start treatment (D0)
Daily average pain scores have to be filled by the patient on the logbook in the last 7 days and average pain score should be ≥ 4 to include the patient in the study. The patients have to fill out four questionnaires: 1) Sleep evaluation (Leeds), 2) HRQoL (MOS SF-12) and 3) neuropathic pain (NPSI and BPI).
If all the inclusion and non-inclusion criteria are respected, the patient will be enrolled in the study and randomised into one of two treatment arms (ethosuximide/inactive control). The administration dosages, according to a scheme of specific titration, will be explained in detail to the patient. At the end of the visit, the patient will receive all therapeutic units for the duration of administration required by the study protocol (42 days).

Ambulatory period (D0 to D0+42).
Ethosuximide or inactive control treatment will be administered in two daily doses during meals, according to a scheme of specific titration for 20 days followed by a plateau at the maximum dose of 1500 mg/day for 22 days. The patient will assess and record daily in the logbook: the quality of falling asleep and sleep during the last night and the median and maximum pain felt in the day.
Every 4 days (at the end of each dose escalation level), patients will be contacted by telephone in order to collect any side effects.

Visit 3 – Study end (D0+43).
Idem visit 2. The patient must also complete the PGIC questionnaire. This visit represents the end of study.

- All patients followed the same procedures (assessment of pain, filling questionnaires and taking treatment in the indicated dosage level).
- No deviation to the protocol will be allowed during the entire study.
- To verify patient compliance, accounting treatment units and a plasma dosage of active principle will be made at end of study.
- No treatment will be allowed during the test.

Outcomes:
Study endpoints were based on the recommendation of the European Medicinal Agency (ICH guideline neuropathic pain: CPMP / EWP / 252/03 Rev. 1).

Primary endpoint
Pain intensity (NRS, 11 points). This scale allows the patient to rate his pain from 0 to 10, with 0 is no pain and 10 the worst possible pain. The intensity of pain will be measured twice daily throughout the study on the logbook, and the values will averaged for the 7 days preceding the two

time points D0 (baseline) and D0+43 (last visit). The primary endpoint is the calculated difference Δ = (NRS (D0) – NRS (D0+43).

Secondary endpoints

Health Related Quality of Life (MOS SF-12 questionnaire). HRQoL will be evaluated by the MOS SF-12 questionnaire which assesses the physical and mental health of the patient using 12 questions related to eight aspects of health (physical and social activities, moral, physically and emotionally strength for accomplish everyday tasks, physical pain, general mental health, vitality, perceived general health status). A score is determined for both physical and mental health (0-100).

Neuropathic Pain Symptom (NPSI and BPI questionnaires). To evaluate characterise and assess the impact of neuropathic pain The Neuropathic Pain Symptom Inventory (NPSI) is a self-administered questionnaire designed to assess different symptoms of neuropathic pain. It includes 12 items that can discriminate and quantify five separate dimensions clinically relevant. The Brief Pain Inventory (BPI) is a self-administered questionnaire includes: 1) a body scheme, 2) the maximum pain, less pain, usual pain the last 15 days (NRS 11 points), 3) the description of analgesic treatment in progress, 4) an evaluation of the relief pain by a percentage scale (0-100%), 5) studying the impact of pain on mood, relationships with other people, walking, sleep, work, joy of life, leisure activities in general NRS, 0 (normal) to 10 (impossible).

Quality of sleep (Leeds questionnaire). The Leeds sleep evaluation questionnaire is a standardised questionnaire composed of ten self-visual analogue scales that relate to four aspects of sleep efficiency: 1) the quality of fall asleep and level of sleepiness, 2) sleep quality, 3) awakening quality and 4) the quality of the state after awakening, performance.

These evaluations will be conducted during the visit at baseline (D0) and the visit to end of study (D0+43).

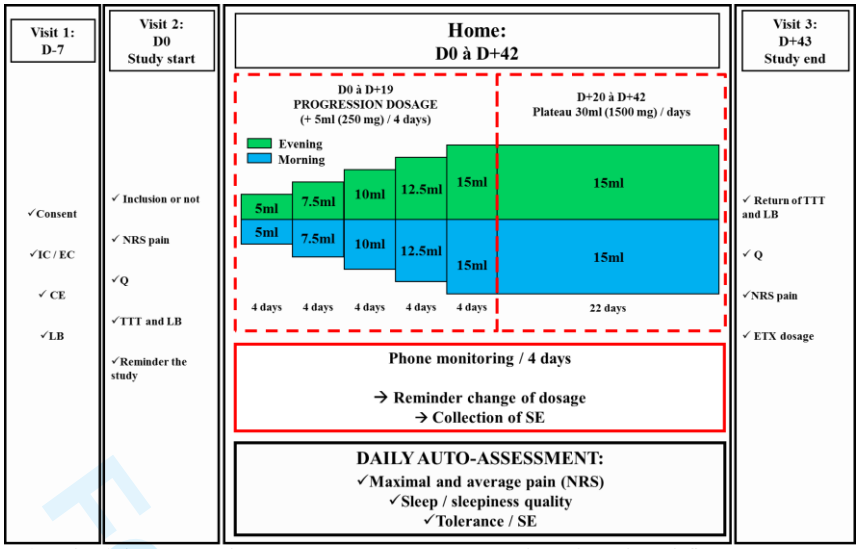
Moreover, a daily evaluation (at morning) of the quality of falling asleep and sleep during the last night (NRS from 0 (very poor) to 10 (excellent)) will be reported on the logbook.

Patient's Global Impression of Change (PGIC scale). PGIC aims to assess general effectiveness of treatment. This scale consists of 7 levels descriptors answering the question "How are you?", distributed in three ways: (i) improved (very/medium/slightly), (ii) unchanged and (iii) aggravated (slight/medium/very).

Safety. Adverse events will be evaluated throughout the study and study discontinuation rate will be evaluated and compared in the two treatment arms.

Participant timeline:

The duration of treatment is 42 days. The total duration of patient participation is maximum 50 days. The protocol includes 3 visits (Day-7, Day 0 and Day +42, see below).



IC / EC: inclusion/exclusion criteria; CE: clinic exam; Q: questionnaires; TTT: treatment; LB: LogBook; ETX: ethosuximide; SE: side effect.

Sample size:

According to previous works[29,30], pain intensity was estimated around 2.5. To highlight a difference equals 1 for a two-sided type I-error at 5% and a statistical power at 80%, n=100 patients per group will be included. Finally, a total of N=220 patients will be considered to take into account lost to follow-up (10%). An interim analysis is planned after enrolment of the first 110 patients using the Lan and DeMets rule (Pocock, East software, Cytel Inc, Cambridge, Massachusetts, USA). The type I error is fixed at 0.003 for this interim analysis.

Enrolment:

19 clinical sites in France, all specialized in the treatment of pain. The recruitment will be spread over 24 months, or 0.8 patients / month / center, which seems to be largely sufficient in the recruitment potential (prevalence of neuropathic pain = 7-8% in France).

Assignment of interventions:

Allocation Sequence generation: computer-generated random numbers. Stratification by center and 6 blocks random sequence.

Allocation concealment: sequentially numbered.

Implementation: Biostatistician generates the allocation sequence, investigators enroll participants and Clinical Research Associate (CRA) assigns participants to interventions.

Blinding:

All participants to study are blinded (double-blinded trial). Unblinding is possible only in case of serious adverse event or at the end of study if the study treatment showed a convincing therapeutic effect (Possibility of prescribing the treatment out of the study).

Data collection, management, and analysis:

Data collection methods

Data entry will be made by the investigators and CRA of each clinical center, at each visit (D-7 and D0 D0+42) and during the ambulatory period.

Data entry will be centralized in the coordinating center (CHU Clermont-Ferrand), from a paper case report form (CRF) sent by post or collected during site visits.

A duplicate of the CRF will be made (a copy to the clinical centre and a copy to the coordinating centre).
All patients will be analysed (intent to treat). However, if a major deviation from the protocol (non respect of co-occurring treatment, inclusion / exclusion criteria and the study design) only safety data will be evaluated.

Data management
Data will be entered in duplicate and a confrontation test will be performed to avoid any input errors. Finally, a consistency test will be conducted to validate compliance of data entered in accordance with the study protocol.

Statistical methods
Statistical analyses will be conducted using Stata software (version 13, StataCorp, College Station, US). A two-sided p-value of less than 0.05 will be considered to indicate statistical significance (except interim analysis). Comparisons between independent groups will be analysed using the $\chi 2$ or Fisher's exact test for categorical variables (notably Patient's Global Impression of Change and safety) and Student t-test or Mann-Whitney's test for quantitative parameters (notably pain intensity, health related quality of life scores measured by MOS SF-12, NPSI and BPI scores, sleep quality evaluated using Leeds score). The normality will be studied by the Shapiro-Wilk test and the homoscedasticity using the Fisher-Snedecor test. Intention to treat (ITT) will be considered for the primary analysis. The analysis of the primary outcome will be completed by multivariate analysis using linear mixed model to take into account (1) fixed effects covariates retained according to univariate results and to clinical relevance, and (2) centre as random-effects (to measure between and within centre variability).The analysis of repeated measures, random-effect models (linear or generalised linear). Other treatments will be considered as a covariate to study this impact on patient quality of life, pain intensity and quality of sleep. According to the clinical relevance, to recommendations of the EMA and CONSORT, sub-group analysis according to the aetiology (diabetic neuropathy, post-herpetic, etc.) will be proposed after the study of interaction ethology x randomization group in regression models (for repeated data or not). Finally, a particular focus will be done on lost to follow-up. A study of abandonment considered as a censored data will be proposed using Kaplan-Meier estimation. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to it, the most appropriate imputation missing data approach will be proposed (maximum bias).

Monitoring:
The monitoring will be performed by CHU Clermont-Ferrand which is responsible for establishing the schedule and procedures to be followed for monitoring this study. On-site visits will be made prior to study initiation and at regular intervals during the study. Communications by telephone, telefax or mail may be used as needed to supplement site visits.

Prior to the beginning of this study, the Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the Investigator will receive reasonable notification prior to each monitoring visit during the course of the study.
The purpose of these visits is to verify:
- Adherence to the protocol,
- Availability of completed ICFs and adequate consent process

 Completeness and accuracy of the CRFs, and study related source document.

At each visit, the Investigator will be expected to cooperate with the monitor for the review and verification of all CRFs, the study drug supply and inventory records and any additional records as may have been previously arranged.

At the pre-study visit, the study monitor and/or the Sponsor representative will check that the Investigator has the technical means and the staff to carry out the study with regards to availability, subject recruitment, facilities and environment.

Prior to the start of the study, the Sponsor Study Manager will ensure that he/she has received the following information:

 Study protocol and financial agreement signed by all parts;

 Written statement of the CPP approval;

 Curriculum vitae of the investigators;

 Approval by the Competent Authority; ANSM.

As well as all other documents required for study initiation, as per GCP.

During the study, adherence to the protocol, availability of signed ICFs and conformity of the data entered in the CRF with the source documents will be checked at appropriate intervals by the study monitor.

At the end of the study, the Sponsor study manager will ensure he has received:

 The completed CRFs;

 All unused medications and remaining packaging, or that they have been destroyed in accordance with the applicable regulations.

 All documents are properly filed in the Investigator's site file as per GCP

Ethics and dissemination

Research ethics approval:

The protocol, information and consent form (ICF) and the CRF of the study will be submitted for opinion to the ethic committee (CPP VI of the Rhône-Alpes-Auvergne region) which carries the principal investigator of this trial. Notification of the approval of the CPP will be sent to the study sponsor and competent authority (ANSM). An authorization request will be made by the Promoter to ANSM before the start of the study.

When necessary, the protocol amendments will also have to be submitted to the above mentioned CPP or ANSM either for information or for formal approval. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the documented approval of the Sponsor. The IEC as well as the French Health Authorities which granted original approval for the study must be notified of all changes in the protocol and must provide documented approval for any change or deviation which may increase the risk to the subject and/or which may adversely affect the rights of the subject or validity of the investigation. This stipulation does not apply to those changes made to reduce discomfort or risk to subjects or which are purely administrative in nature.

In the event of any emergency, the Investigator shall institute any medical procedures, which he/she deems appropriate. However, all such procedures must be promptly reported to the Sponsor.

Amendments that are substantial and are likely to have an impact on the safety of trial subjects, or are otherwise significant, should receive IEC/Competent Authority approval. If the opinion of the IEC is favorable and the Competent Authorities have raised no grounds for unacceptability the study can be conducted according to the amended protocol. Non substantial amendment should only be notified.

Consent or assent:

Voluntary written ICF must be obtained from each subject prior to performing any study related procedures in compliance with the recommendations of the Declaration of Helsinki.

Subject should not be screened or treated until the subject has signed an approved ICF written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The ICF should be signed and personally dated in two originals by the subject and the person who conducted the informed consent discussion. The

Investigator, or the attending physician, will explain the nature, purpose and risks of the study. The subject will be informed that he has the right to withdraw at any time from the study, without giving reasons. In this case, the subject will not receive any indemnity. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his participation in the study.

The Investigator is responsible for assuring the appropriate content of the ICF and that informed consent is obtained from each subject in accordance with all applicable regulations and guidelines. The ICF will be reviewed and approved by the Sponsor, and then submitted to the IEC.

Each subject should receive one original of the signed and dated written ICF and any other information provided to the subject.

The second original of the signed and dated ICF should be retained in the Investigator's file.

The Investigator should maintain a log of all subjects who sign the ICF.

Confidentiality:

The information in this document and in any future information supplied contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but exclusively by an identification code.

Declaration of interests:

No competing interests.

Access to data:

The promoter is responsible for obtaining the agreement of all parties involved in research in order to guarantee direct access to all places of conduct research, source data, source documents and reports in a goal quality control and audit by the sponsor.

The investigators will make available documents and individual data strictly necessary monitoring, quality control and auditing of biomedical research, available to people with access to these

documents in accordance with legislative and regulatory provisions (Articles R.5121-13 L.1121-3 and the code of public health).

Ancillary and post-trial care:

If the patient is at the waning of the study indicates a marked improvement in his symptoms, unblinding procedure will be permitted to determine the drug to be prescribed after the study. Unblinding procedure and packaging of therapeutic units will maintain intact the double blind until the end of the study. Patients will be referred to their general practitioner or a specialist pain doctor who will be informed of the treatment received by the patient during the study. Note that the requirement in Zarontin® or Stodal® for the treatment of neuropathic pain being out of their marketing authorization framework, the sponsor does not support a continuation of treatment after the study. No patient follow-up is planned after the study.

Dissemination policy:

The data set will be propriety of the sponsor (CHU Clermont-Ferrand). However, the principal investigator (AE) and the project manager (NK) will have a full access to the final data set. The results will be disseminated in a peer-reviewed journal, presented at international congresses and completed online on ClinicalTrials.gov.

APPENDICE 1 – INFORM AND CONSENT FORM (French version)

Evaluation de l'efficacité antalgique de l'éthosuximide dans le traitement de douleur neuropathique d'origine traumatique

Promoteur

C.H.U. de Clermont-Ferrand
58 Rue de Montalembert, 63000 Clermont-Ferrand

Investigateur principal

Pr Alain ESCHALIER
UMR INSERM / UdA 1107 NEURO-DOL
CHU Gabriel-Montpied, 63000 Clermont-Ferrand

Le Docteur …….. vous a proposé de participer à un protocole de recherche clinique, dont le CHU de Clermont-Ferrand est promoteur. Toutes les consultations que vous aurez à effectuer, dans le cadre de cette étude, se feront au sein du centre de traitement de la douleur qui vous suit.

L'objectif de cette étude est d'évaluer l'efficacité de l'éthosuximide (commercialisé en France sous le nom de Zarontin®) sur le type de douleurs que vous présentez.

Comme plusieurs autres médicaments largement utilisés pour traiter les douleurs neuropathiques, l'éthosuximide, est aujourd'hui prescrit dans le traitement de l'épilepsie aussi bien chez l'enfant que chez l'adulte.

L'étude est dite faite en double aveugle, c'est-à-dire que vous recevrez, par tirage au sort, soit l'éthosuximide, soit une formulation ne contenant pas de produit actif. Le médecin et vous ne seront pas autorisés à avoir connaissance du traitement reçu.

Modalité de recrutement

Ce protocole vous est proposé ainsi qu'à 219 patients adultes souffrant de douleurs chroniques sévères. Selon un tirage au sort, vous recevrez, pendant la durée de votre participation à l'étude, soit de l'éthosuximide (sirop) soit un traitement homéopathique (sirop Stodal®) à titre de traitement contrôle. Les traitements que vous recevez habituellement seront poursuivis.

Traitements administrés dans le cadre de cette étude

Le traitement (éthosuximide ou homéopathie) sera administré de la façon suivante (qui comporte une progression des doses par paliers durant les premières semaines):

- **10 ml** (500mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours ;
- **15 ml** (750mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **20 ml** (1000mg)/jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **25 ml** (1250mg) /jour réparti en 2 prises (matin et soir) pendant 4 jours,
- **30 ml** (1500 mg)/jour réparti en 2 prises (matin et soir) pendant 26 jours.

Les doses sont déterminées à l'aide d'une pipette en plastique graduée

Paraphe du Médecin **Paraphe du Sujet**

Evaluations réalisées

Echelle Numérique Simple (ENS)
à l'aide d'une échelle allant de 0 à 10, vous devrez, chaque jour, avant le coucher, relever sur votre carnet de suivi l'intensité douloureuse maximale et moyenne ressentie durant la journée.
Questionnaires sur les caractéristiques votre douleur et son impact sur votre vie courante :
Ils vont seront présentés et expliqués par le médecin investigateur afin que vous puissiez les remplir avec compréhension. Ces questionnaires sont au nombre de 4 : QEDN, Leeds, QCD et PGIC.
Ils devront être remplis pendant vos deux visites (J0 et J+43).

Dosages biologiques et d'éthosuximide
Un prélèvement sanguin (7,5 ml) sera effectué à chacune de vos deux visites dans le centre investigateur (J0 et J+43). Ces prélèvements seront réalisés par une infirmière.

Déroulement de l'étude

Dans le cadre de cette étude vous aurez à participer à 3 visites au centre d'investigation clinique et d'une période d'étude de 50 jours. Il vous est demandé de ne changer aucun de vos traitements habituels tout au long de l'étude. Cependant, si cela s'avérait nécessaire, il est important d'informer le médecin qui vous suit dans le cadre de cet essai, des éventuelles notifications dans les traitements que vous prenez régulièrement ou de l'introduction de nouveaux médicaments pris ou modifiés.

Recrutement
Vous serez préalablement sélectionnés par les médecins du centre d'évaluation et de traitement de la douleur et contactés par téléphone par le médecin investigateur afin de vous présenter brièvement le but de l'étude et de prendre rendez-vous pour la visite d'inclusion.

Récapitulatif de l'étude (tableau)
L'étude à laquelle vous participez se déroulera comme décrit dans le tableau ci-dessous.

Visites	Visite d'information	Inclusion	Période de traitement	Visite de fin d'étude
Jour	J-7	J0	J0 à J+42	J+43
Lieu	Centre	Centre	Domicile	Centre
Signature formulaire de consentement	+			
Examen clinique	+			
Remise du carnet de suivi	+			
Remplissage des questionnaires : - Leeds, SF12, QEDN, QCD (+PGIC)		+		+
Remise de votre traitement		+		
Contact téléphonique à votre domicile tous les 4 jours par l'ARC		+*	+*	
Evaluation journalière de votre douleur, de votre qualité de sommeil / endormissement	+	+	+	+
Ramener traitements et cahier de suivi				+
Prélèvement sanguin	+			+

* Contacts téléphoniques tous les 4 jours (à chaque augmentation de dose) à partir de J0 (inclus)

Paraphe du Médecin **Paraphe du Sujet**

Les bénéfices

Compte tenu de la durée limitée du traitement qui vous est prescrit dans le cadre de cette étude, il n'y a pas à attendre de bénéfice individuel durable résultant de la participation à l'étude. Toutefois, en cas d'amélioration sensible des épisodes douloureux durant la période de participation à l'étude, vous serez orienté vers votre médecin traitant ou éventuellement vers un centre spécialisé d'évaluation de traitement de la douleur avec un compte rendu des résultats observés pour optimiser votre traitement antalgique.

Les Risques attendus

L'éthosuximide est prescrit dans le traitement de l'épilepsie depuis 1965. La posologie retenue pour cet essai thérapeutique est celle habituellement utilisée dans cette indication. Dans cet essai, les paliers d'augmentation de dose ont été fixés à 4 jours. Comme la plupart des traitements médicamenteux, celui-ci peut générer quelques effets indésirables, à savoir principalement vertiges, céphalées et somnolence, rendant la prise de ce médicament incompatible avec la conduite sans avis préalable du médecin. Dans des cas très rares, la survenue de graves réactions cutanées (syndrome de Stevens-Johnson, lupus érythémateux disséminé, DRESS...) est possible. L'intensité de ces effets reste cependant légère à modérée et disparaissent à l'arrêt du traitement.

Afin d'éviter la survenue de ces effets indésirables, il vous est fortement recommandé de respecter l'augmentation progressive des doses par paliers pendant les quatre premières semaines jusqu'à la dose maximale. Des contacts téléphoniques tous les 4 jours (à la fin de chaque palier) seront destinés à vous rappeler les modifications de posologie et recueillir les éventuels effets indésirables que vous pourriez ressentir.
De plus, compte tenu de la mise sur le marché déjà ancienne de ce médicament, son profil de sécurité est aujourd'hui bien connu.

Le traitement contrôle (sirop Stodal) possède une forte concentration en sucre (3,75g pour 5ml) et contient un peu d'alcool (éthanol 0,069g = 1,74%). Pour ces raisons, ce médicament est déconseillé chez les personnes présentant une intolérance au fructose, un syndrome de malabsorption du glucose et du galactose ou un déficit en sucrase/isomaltase ou chez des personnes alcooliques.

Les règles d'asepsie seront rigoureusement appliquées pour les prélèvements sanguins. Le volume de sang prélevé est minime (7,5 ml deux fois, à environ 50 jours d'intervalle).

Indemnisation

Pour compenser les contraintes liées à votre participation au protocole, vous recevrez une indemnisation de 200 € pour la totalité de l'essai. Dans le cas d'un arrêt prématuré de l'essai, un calcul de l'indemnisation sera effectué au prorata des visites effectuées (arrêt en visite 2 = 50€, arrêt durant la période d'essai = 80€).

Paraphe du Médecin **Paraphe du Sujet**

Période d'exclusion pour participer à une autre recherche biomédicale

Vous n'êtes pas autorisé à participer à un autre essai clinique durant toute la durée du protocole.
De plus, la période d'exclusion définie dans le cadre de cette étude est de 30 jours, période pendant laquelle vous ne pourrez participer à un autre protocole de recherche clinique.
Le CHU de Clermont-Ferrand, qui organise cette recherche biomédicale en qualité de promoteur, a contracté une assurance conformément aux dispositions législatives, garantissant sa responsabilité civile et celle de tout intervenant auprès de la Société Hospitalière d'Assurances Mutuelles (SHAM, contrat n°135372).

Dans le cas où votre état de santé serait altéré du fait de votre participation à l'étude, conformément à la loi de Santé Publique n°2004-806 du 9 août 2004, vous seriez en droit de recevoir des dédommagements dans le cadre de ce contrat d'assurance spécifique.

Cette recherche a reçu l'avis favorable du Comité de Protection des Personnes Sud Est VI lors de la séance du 6 décembre 2013 ainsi que l'autorisation préalable de l'autorité compétente de santé datée du 26/03/2014. Il est possible que cette recherche soit interrompue, si les circonstances le nécessitent, par le promoteur ou à la demande de l'autorité de santé.

Confidentialités des données

Dans le cadre de la recherche biomédicale à laquelle le CHU de Clermont-Ferrand vous propose de participer, un traitement informatique de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté.
Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement.

En accord avec la loi Informatique et Liberté, le nom des sujets est automatiquement remplacé par un numéro de code dont la correspondance est connue des seuls médecins investigateurs.
Les données feront l'objet d'un traitement informatisé anonyme et leur consultation sera autorisée aux collaborateurs participant à la recherche, désignés par le promoteur et éventuellement au représentant des autorités de santé.
Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, vous disposez d'un droit d'accès et de rectification auprès du médecin qui vous suit dans le cadre de la recherche.
Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L. 1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.
Vous êtes libre d'accepter ou de refuser de participer à cette recherche. De plus vous pouvez exercer à tout moment votre droit de retrait de cette recherche.

Paraphe du Médecin **Paraphe du Sujet**

Par ailleurs, vous pourrez être tenu informé des résultats globaux de cette recherche à la fin de l'étude.

Si vous le souhaitez, vous pourrez à tout moment demander des informations complémentaires sur l'étude au personnel médical du Centre de Pharmacologie Clinique au 04.73.17.84.24 ou 04-73-17-84-23 du lundi au vendredi de 8h à 17h.
En cas d'urgence, et pendant toute la durée de l'étude, vous pourrez joindre à tout moment l'équipe médicale qui vous suit dans le cadre de votre participation à cette étude au N° suivant ……. Ou à défaut, le médecin d'astreinte du Centre de Pharmacologie Clinique de Clermont-Ferrand au 06-84-44-63-14.

Lorsque vous aurez lu cette note d'information et obtenu les réponses aux questions que vous vous posez en interrogeant le médecin investigateur, il vous sera proposé, si vous en êtes d'accord, de donner votre consentement écrit en signant le document préparé à cet effet.

Date : ……/……/……

Paraphe du Médecin **Signature du Sujet**
Précédée de la mention « Lu et compris »

Evaluation de l'efficacité antalgique de l'éthosuximide dans le traitement de douleur neuropathique d'origine traumatique

Investigateur principal:
Pr Alain ESCHALIER
UMR INSERM / UdA 1107 NEURO-DOL
CHU Gabriel-Montpied, Service de Pharmacologie-Toxicologie 63000 Clermont-Ferrand
alain.eschalier@udamail.fr

Je soussigné(e) M. (*nom, prénom*)……Né(e) le _ _ / _ _ / _ _ _ _
Demeurant…….
Déclare : que le Docteur (*nom, prénom, téléphone*) ……
m'a proposé de participer à l'étude sus nommée, qu'il m'a expliqué en détail le protocole, qu'il m'a notamment fait connaître :

- l'objectif, la méthode et la durée de l'étude

- les contraintes et les risques potentiels encourus

- mon droit de refuser de participer et de retirer mon consentement à tout moment sans avoir à me justifier

- mon obligation d'inscription à un régime de sécurité sociale

- que, si je le souhaite, à son terme, je serais informé(e) par le médecin investigateur de ses résultats globaux

- que je ne serai pas autorisé(e) à participer à d'autres études cliniques pendant une durée de 3 semaines.

- que le Comité de Protection des Personnes Sud Est VI a émis un avis favorable le 06/12/2013. ainsi que l'autorisation préalable de l'autorité compétente de santé datée du 26/03/2014.

- que dans le cadre de cette étude le promoteur, le CHU de Clermont-Ferrand, a souscrit à une assurance couvrant cette recherche.

- que la période d'exclusion définie dans le cadre de cette étude est de 30 jours, période pendant laquelle vous ne pourrez participer à un autre protocole de recherche clinique.

L'étude comporte la création d'une collection d'échantillons sanguins pour le dosage de l'éthosuximide. Les échantillons seront détruits consécutivement à la fin de l'étude. J'accepte et je donne mon avis de non opposition pour le prélèvement, pour l'analyse et pour la création d'une collection d'échantillons biologiques dans le strict cadre de l'étude clinique ci-présente.

Les informations relatives à l'étude recueillies par l'investigateur sont traitées confidentiellement.

J'accepte que ces données puissent faire l'objet d'un traitement informatisé anonyme. J'ai bien noté que le droit d'accès prévu par la loi du 6 août 2004 relative à l'informatique, aux fichiers et aux libertés s'exerce à tout moment auprès du médecin qui me suit dans le cadre de la recherche et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin, qui contactera le promoteur de la recherche.

J'accepte mon inscription dans le Fichier National des personnes qui se prêtent à des recherches biomédicales (Art. L 1121-16 du Code de la Santé Publique).

Après avoir discuté librement et obtenu réponse à toutes mes questions, j'accepte librement et volontairement de participer à cette recherche biomédicale dans les conditions précisées dans le formulaire d'information et de consentement.

Nom et prénom du sujet :……..
Date :……./……./…….
Signature *précédée de la mention « Lu et compris » :*

Nom de l'investigateur : ……
Date :……./……./…….
Signature

APPENDICE 2 – BIOLOGICAL SPECIMEN

Blood Test	**Time**
ALT	D-7 (screening)
AST	D-7 (screening)
ALP	D-7 (screening)
GGT	D-7 (screening)
Creatininemia	D-7 (screening)
Hematocrit	D-7 (screening)
Beta-HCG	D-7 (screening)
Ethosuximide	D0+42 or end of the study (compliance)

APPENDICE 3 – REFRENCES

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