Randomized, double-blind, placebo controlled, multi-centre superiority phase II study to evaluate the safety, pharmacokinetic, efficacy of gabapentin liquid formulation as add-on to morphine in children from 3 months to less than 18 years of age experiencing severe chronic neuropathic or mixed pain.

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The primary objective of this study is to assess the efficacy of gabapentin as add-on to morphine for the treatment of severe chronic neuropathic or mixed pain in children from 3 months to less than 18 years of age. Secondary objectives 1. To assess...

Ethical review	Approved WMO
Status	Pending
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON45684

Source
ToetsingOnline

Brief title
GABA 2

Condition

- Neurological disorders NEC

Synonym
Neuropathic pain

Research involving
Human

Sponsors and support

Primary sponsor: Pharm SRL
Source(s) of monetary or material Support: FP7 EU grant 602962 (GAPP)

Intervention

Keyword: Gabapentin, Neuropathic pain, Paediatrics

Outcome measures

Primary outcome

Average pain score at the end of the treatment period (average of 2 measures each day for 3 days before end of study visit, V10) as assessed by age-appropriate pain scales (FLACC, FPS-R, NRS-11).

Secondary outcome

Secondary endpoints a) Percentage of responders to treatments, defined as subjects with a 30% reduction from baseline in assessment scale (FLACC, FPS-R, NRS-11). b) Average daily pain intensity assessed by age appropriate scale during dose optimisation (FLACC, FPS-R or NRS-11). c) Observational assessment of pain using the NRS-11 completed by parents and Investigator (or caregiver) at each visit. d) Self-assessment of pain for children >8 years of age using the FPS-R pain scale at each visit. e) Number of episodes of breakthrough pain (> 4/10 pain score and use of rescue medications) during treatment period. f) Number of rescue interventions required during treatment period. g) Number of pain-free (< 4/10 average pain score without the use of rescue medications)

days during treatment period. h) Number of participant dropouts due to lack of efficacy. i) The total cumulative weight normalized dose of each rescue drug. j) Quality of life, physical, emotional, social and school functioning and quality of sleep on the PedsQL Generic Core Scales (by parent, patient) assessed at randomisation (V2) and at EOS (V10). k) Acceptability of treatment (Five-Point Facial Hedonic scale) at EOS visit (V10). l) Global satisfaction with treatment (NRS-11, by parent, patient) at EOS visit (V10). m) Clinical Global Impression of Change (CGI-S, CGI-I; by Investigator) at randomisation (V2) for CGI-S and V6 and EOS visit (V10) for CGI-I. n) Patient/parent Global Impression of Change (PGIC; by parent, patient) at V6 and at EOS visit (V10). o) Primary (CL/F, Vd/F, Ka) and secondary (AUC, Cmax, Tmax, Css and Cmin) pharmacokinetic parameters for gabapentin and tramadol. p) Systemic exposure to investigational products during maintenance period, as assessed by predicted steady-state concentrations. q) Incidence of Adverse Events at all visits. r) Percentage of subjects discontinuing the trial due to treatment-emergent adverse events. s) Aggressive behaviour in children aged >6 years using the Retrospective-Modified Overt Aggression Scale (R-MOAS) at V2, V6 and EOS visit (V10). t) Suicidal ideation/behaviour in subjects aged 6 years and older using the Columbia - Suicide Severity Rating Scale (C-SSRS) scores before IMP (screening V1), V6 and at the EOS visit (V10). u) Assessment of blinding: guess of the subject*s treatment group (by Investigator, parents and subject if at adequate maturity level) at V10. Exploratory endpoints v) Metabolomic profile at screening (V1) and at EOS visit (V10), and in responders and non-responders.

w) PK or PD outcomes based on genetic variation.

Study description

Background summary

Gabapentin has been successfully used to treat neuropathic pain in adults and has been used offlabel to treat children with the same condition. However, the paediatric use of gabapentin in children is hampered by two main factors: 1. The lack of a suitable oral formulation 2. The significant variability of gabapentin PK profile demonstrated in children less than 4 years of age leading to a variable drug plasma concentration. These differences should be taken into account to define a safe/efficacious dosing regimen in younger children.

Study objective

The primary objective of this study is to assess the efficacy of gabapentin as add-on to morphine for the treatment of severe chronic neuropathic or mixed pain in children from 3 months to less than 18 years of age. Secondary objectives 1. To assess effect of gabapentin as a add-on to morphine on quality of life (physical, emotional, social and school functioning) and global satisfaction with treatment. 2. To assess safety of gabapentin as a add-on to morphine for treatment of chronic neuropathic or mixed pain in children 3 months to less than 18 years of age. 3. To characterize the population pharmacokinetic-pharmacodynamic (PKPD) relationship of gabapentin liquid formulation and provide confirmation of the recommended paediatric dose. Additional exploratory objectives of the study are: 4. To describe the metabolomic profile following drug treatments. 5. To explore genetic polymorphisms and their impact on pharmacokinetics (PK) and pharmacodynamics (PD). 6. To assess the population pharmacokinetics of tramadol and, if feasible, its PKPD relationship in the paediatric population.

Study design

Randomized, double-blind, placebo controlled, multi-centre superiority phase II study to evaluate the safety, pharmacokinetic, efficacy of gabapentin liquid formulation as add-on to morphine in children from 3 months to less than 18 years of age experiencing severe chronic neuropathic or mixed pain.

Intervention

IMP test: Gabapentin oral solution (syrup). IMP comparator: Gabapentin placebo oral solution

Study burden and risks

Risks and burden of participation in the study are related to possible:
1. During the washout period of the medication, before starting the IMP, the child could experience a period of increase in pain, due to stopping of their usual pain medication. However, the child will be included in the study, because the current treatment of the pain is already ineffective. Therefore it is our opinion that this washout period (and possible short period of increase in pain) can be justified. Also it is our expectation that the increase in pain will be limited in this washout period, as the treatment of the pain was already ineffective. Children who have an effective treatment of their pain (pain score < 4) are not eligible for inclusion in the study.
2. The risk during the study is that the installed study medication is also insufficient and the patient remains in significant pain or that the patient experiences adverse events of the medication, despite slowly up titrating the dose to prevent side effects. The burden during the study consists of a number of hospital visits and telephone calls, as well repeated pain scores, other scores and questionnaires that need to be completed. Also, limited blood sampling may be burdensome
3. The benefits of the study are that patients may receive treatment that reduces their pain and (group benefit) that we know better how to treat this pain for future patients.
Overall, considering the very large burden of untreated severe chronic pain with a substantial impact on a child*s daily life leading to absence at school, decreased quality of life, decreased physical exercise, depression and anxiety and social isolation, we believe that the benefit for both individual patients in the study and future patients (expected reduction in pain) strongly outweighs the risks and burdens of the study with short period of possible increased pain, risk of adverse events (but drug will be decreased when adverse events will be not tolerable), and the visits/questionnaire time/limited blood samples.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. 3 months-< 18 years
2. Informed consent
3. Meet diagnostic criteria for chronic neuropathic or mixed pain
4. Severe pain as defined as an average pain score of >= 7/10
5. Stabel underlying disease condition and treatment
6. Patients with chemotherapy induced neuropathic pain: clinical remission or maintenance phase of treatment protocol

Exclusion criteria

1. Pain duration of more than 5 years
2. Current use of gabapentin or strong opoids
3. History of failure to respond to adequate treatment by gabapentin or opioids for neuropathic pain. 4. History of epileptic condition except febrile seizure disorder.
5. Subjects with diagnosis of sickle cell disease.
6. Subjects that present significant cognitive impairment.
7. Subjects that present current, controlled or uncontrolled, co-morbid psychiatric diagnosis that can impair pain diagnosis and assessment such as severe depressive conditions or psychosis.
8. Subjects with history of or current suicidal ideation or behaviour.
9. Subjects with a history of substance abuse in particular opoids
10. Subjects under prohibited concomitant medication (refer to specific protocol section 5.6.3.1 *Prohibited medications*).

11. Subjects in need for corticosteroid oral treatment or corticosteroid infiltrations to treat pain caused by infiltration or compression of neural structures, e.g. peripheral nerves or spinal cord.
12. Subjects old with a body mass index (BMI) for age and gender of < 5th percentile or > 95th percentile (charts provided as Appendix 5).
13. Subjects with glomerular filtration rate < 90 mL/min/1.73 m2 (Schwarz equation).
14. Subjects with significant hepatic impairment with Aspartate Transaminase (AST) and Alanine Transaminase (ALT) enzymes 3 times the upper limit of the age-specific reference range.
15. Subjects with known allergy, hypersensitivity or clinically significant intolerance to gabapentin or any component found in the study drugs.
16. Subjects with clinically relevant abnormal ECG at the screening visit in the discretion of the investigator/cardiologist.
17. Subjects participating in another clinical interventional trial.
18. Subjects scheduled for surgery or in recovery from surgery occurring within 3 months of baseline assessment.
19. Female subjects who are pregnant or currently lactating.
20. Subjects that failed screening or was previously enrolled in this study.
21. Subjects with fructose intolerance, diabetes, glucose-galactose malabsorption or lactase-isomaltase deficiency.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2017
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Neurontin
Generic name:	Gabapentin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Oramorph
Generic name:	Morphine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Placebo gabapentin
Generic name:	Placebo gabapentin

Ethics review

Approved WMO Date:	07-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004897-40-NL
CCMO	NL61386.078.17