Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetics, efficacy and safety of gabapentin liquid formulation to tramadol in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic or mixed pain.

Published: 02-05-2016
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Primary objectiveThe primary objective of this study is to assess the efficacy of gabapentin relative to tramadol for the treatment of moderate to severe chronic neuropathic or mixed pain in children from 3 months to less than 18 years of age....

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

Summary

ID

NL-OMON45930

Source
ToetsingOnline

Brief title
GABA 1

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

Primary objective
The primary objective of this study is to assess the efficacy of gabapentin relative to tramadol for the treatment of moderate to 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 relative to tramadol on quality of life (physical, emotional,
social and school functioning) and global satisfaction with treatment.
2. To assess safety of gabapentin relative to tramadol for treatment of chronic neuropathic or
mixed pain in children 3 months to less than 18 years of age.
3. To characterise 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, double-dummy active controlled, multicentre non-inferiority phase-III study to compare efficacy and safety of gabapentin liquid formulation to tramadol in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic or mixed pain.

Intervention

IMP test: Gabapentin oral solution (syrup) at 75 mg/ml
IMP comparator: Tramadol oral drops at 100 mg/ml

Study burden and risks

Uncontrolled pain may have a substantial impact on a child*s daily life and lead to absence at

school, decreased quality of life decreased physical exercise, depression and anxiety and social
isolation. Lack of timely treatment may lead to a lifetime of chronic pain.
There is a well-recognised need to improve management of chronic pain in children.
All patients in this trial will receive pharmacological analgesic treatment and therefore may
experience better pain relief with less adverse events, due to pre-defined and controlled titration
of the study drugs as well as close monitoring of pain and adverse events. To limit the occurrence
and severity of the side effects, the dose will be up-titrated slowly and down-titration is allowed
when side effects are unacceptable.

The level of pain may increase during the wash-out period. We believe this is acceptable, because current treatment has proved to be ineffectieve in adequately decreasing pain levels after all. Thus increase in painscore due to the interruption of paintreatment is expected to be limited. Children that experience sufficient comfort under current pain treatment do not qualify for participating in this study.

The risks of venipuncture are minimal.

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. informed consent
2. 3 months - 18 years of age
3. meet the diagnostic criteria for neuropathic or mixed pain
4. chronic pain defined as the recurrent or continuous pain persisting more than 3 months
5. at least moderate pain as defined by average pain intensity of *4 /10
6. Stable underlying disease condition and treatment
7. For oncology patients: clinical remission or no expected changes in therapeutic protocol

Exclusion criteria

1. Pain duration of more than 5 years
2. Current use of gabapentin or tramadol for treatment of neuropathic pain or exposure in the year before screening for the GABA-1 study.
3. History of failure to respond to adequate treatment by gabapentin or tramadol/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 suicidal ideation or behaviour.
9. Subjects under prohibited concomitant medication (refer to specific protocol section 6.6.2 *Prohibited medications*).
10. 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.
11. Subjects aged 3 months to less than 18 years old with a body mass index (BMI) for age and gender of < 5th percentile or > 95th percentile (charts provided as Appendix 5).
12. Subjects with glomerular filtration rate < 90 mL/min/1.73 m2 (Schwarz equation).

13. 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.
14. Subjects with known allergy, hypersensitivity or clinically significant intolerance to gabapentin or tramadol or any component found in the study drugs.
15. Subjects with clinically relevant abnormal ECG at the screening visit in the discretion of the investigator/cardiologist.
16. Subjects participating in another clinical interventional trial.
17. Subjects scheduled for surgery or in recovery from surgery occurring within 3 months of baseline assessment.
18. Female subjects who are pregnant or currently lactating.
19. Subjects that failed screening or was previously enrolled in this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2017
Enrollment:	18
Type:	Actual

Medical products/devices used

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

Product type:	Medicine
Brand name:	Placebo Gabapentine
Generic name:	Placebo Gabapentine
Product type:	Medicine
Brand name:	Placebo tramadol
Generic name:	Placebo tramadol
Product type:	Medicine
Brand name:	Zamadol
Generic name:	Tramadol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	21-12-2017
Application type:	Amendment

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	EUCTR2014-004851-30-NL
CCMO	NL55805.078.16