GAPP Study

Multi-center, single-arm, adaptive, prospective cohort study to evaluate the pharmacokinetics, efficacy and safety of gabapentin liquid formulation in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic, nociplastic or mixed pain.

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Study Objectives

PRIMARY OBJECTIVE

To assess the efficacy of gabapentin for the treatment of moderate to severe chronic neuropathic, nociplastic or mixed pain in children from 3 months to less than 18 years of age assessed by the difference in average pain scores among baseline and the end of the maintenance period.

PRIMARY ENDPOINT

Defined as the change in the average daily pain score (average of 2 measures each day for 3 days before end of study visit) at the end of the maintenance treatment period compared with the average of the daily pain scores at baseline (average of 2 measures each day for 3 days), assessed by age-appropriate pain scales (FLACC, FPS-R, NRS-11).

Study Objectives

SECONDARY OBJECTIVES

→ Assess the efficacy of gabapentin by evaluating the patients who achieved a reduction of at least 30% from baseline or below 4/10 of pain intensity assessed by appropriate scale.
→ Assess the efficacy of gabapentin by evaluating the pain-free days (<4/10 without rescue medication). Assess the efficacy of gabapentin by evaluating the dropouts due to lack of efficacy
→ Assess safety of gabapentin for the treatment of chronic neuropathic, nociplastic and mixed pain in children 3 months to less than 18 years of age.
→ Describe daily pain intensity during dose optimization period
→ Describe the frequency of rescue medication use and time of first dose of rescue medication
→ Pharmacokinetics profile of the paediatric dose
→ Assess the effect of gabapentin on quality of life and global satisfaction with treatment
→ Assess treatment acceptability

SECONDARY ENDPOINTS (part I)

- Percentage of responders to treatment defined as subjects with a reduction of at least 30% from baseline or below 4/10 of pain intensity assessed by appropriate scale (on FLACC scale for patients less than 3 years of age, FPS-R for patients from 3 years to less than 8 years or on NRS for patients equal/above years of age) assessed at baseline and at End of study (EOS).
- Number of pain-free days (< 4/10 average pain score without the use of rescue medications) days during treatment period assessed at EOS.
- Number of participant dropouts due to lack of efficacy assessed at EOS.
- Incidence of Adverse Events at all visits.

SECONDARY ENDPOINTS (part II)

- Monitoring of suicidality, hyperkinesia and behavioural changes, at the screening/baseline and at the end of Optimisation period and EOS.
- Percentage of subjects discontinuing the trial due to treatment-emergent adverse events at EOS.
- Daily pain scores assessed by age-appropriate pain scales (FLACC, FPS-R, NRS-11) assessed at EOS.
- Number and proportion of patients using a rescue medication during maintenance treatment period assessed at EOS...
- Pharmacokinetic parameters including Cmax, AUC, t1/2, C steadystate, assessed at V4
- Quality of life (physical, emotional, social and school functioning and quality of sleep) will be assess using the PedsQL Generic Core Scales, including both patient-reported outcomes (PROs) and parent proxy-reported measures (caregivers) at screening and at EOS.
- Global satisfaction with treatment (NRS-11, including both patient-reported outcomes (PROs) and parent proxy-reported measures caregivers at End of study (EOS) .
- Clinical Global Impression of Change (CGI-S, CGI-I; by Investigator) assessed at screening (CGI-S), GI-I scale at end of optimisation and EOS /Early termination (ET) visits.
- Patient/parent Global Impression of Change (PGIC; including both patient-reported outcomes (PROs) and parent proxy-reported measures (caregivers) at the end of optimization phase and at EOS.
- Acceptability of treatment (Five-Point Facial Hedonic scale) at EOS

Study population

Inclusion criteria

1. Male or female aged 3 months to less than 18 years at screening.
2. Informed consent by parent(s) and/or legal guardian according to each country's legal requirement.
3. Assent by the patient, where applicable, according to each country's legal requirement.
4. Subjects that meet the diagnostic criteria for neuropathic, nociplastic or mixed pain.
5. Subjects that present with chronic pain defined as the recurrent or continuous pain persisting more than 3 months. Duration of pain will be determined from the date of the first pain experienced.
6. Subjects that present with at least moderate pain as defined by average pain intensity of ≥ 4/10 as assessed during a 3-day screening period (i.e., baseline assessment period, where pain intensity is assessed 2 times daily for 3 days; at least 5 out of the 6 pain intensity assessments must be available).

Who is not eligible?

Exclusion criteria (part I)

- **Pain duration of more than 3 years.**
- **History of failure to respond to treatment by gabapentin for neuropathic pain.**
- **History of epileptic condition except febrile seizure disorder.**
- **Subjects with sleeping apnoea syndrome of any origin or subjects with severe respiratory impairment.**
- **Subjects with diagnosis of sickle cell disease.**
- **Subjects that present significant cognitive impairment.**
- **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.**
- **Subjects with a history of suicidal ideation or behavior.**
- **Subjects in need for corticosteroid infiltrations to treat pain caused by infiltration or compression of neural structures, e.g. peripheral nerves or spinal cord.**
- **Subjects born prematurely at ≤ 36 weeks of gestational age if recruited in the first year of age.**

Who is not eligible?

Exclusion criteria (part II)

- **Subjects with a body mass index (BMI) for age and gender of < 5th percentile or > 95th percentile.**
- **Subjects with glomerular filtration rate < 90 mL/min/1.73 m2 (Schwarz equation).**
- **Subjects with significant hepatic impairment or with Aspartate Transaminase (AST) or Alanine Transaminase (ALT) enzymes 3 times the upper limit of the age-specific reference range.**
- **Subjects with a known allergy, hypersensitivity, or clinically significant intolerance to gabapentin or any component found in the study drug.**
- **Subjects with fructose intolerance, diabetes, glucose-galactose malabsorption or lactase-isomaltase deficiency.**
- **Subjects participating in another clinical interventional trial.**
- **Subjects scheduled for surgery or in recovery from surgery occurring within 1 month of baseline assessment.**
- **Female subjects who are pregnant or currently lactating.**
- **Subjects that failed screening or were previously enrolled in this study.**

Trial Design Overview

GAPP GAbapentin in Paediatric Pain

Arms:
Single arm trial

Blinding:
Not applicable
(No blinding)

Number of Participants:
At least 42,
6 (3m-<3y);
12 (3-<8y);
18 (8-<18y)



- Total trial participation: 24 weeks
- Trial intervention: 18 weeks (Dose optimisation + Fixed dose)

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Trial Design Innovative Approaches

Applying a **single-arm**, **Bayesian**, and **adaptive** design to this trial design is an **innovative approach** that presents unique regulatory and methodological challenges.

In a single-arm trial, **Bayesian methods** are essential because they compensate for the lack of a control group. This approach significantly reduces the number of new patients to be enrolled (sample size), as the statistical model "borrows" strength from what is already known about gabapentin.

An **adaptive design** allows the trial to be modified based on interim data analysis, without compromising the scientific integrity of the study. If the interim Bayesian analysis shows overwhelming **success** or clear **futility**, the trial can be **stopped early**.

Optimisation phase

- **6-week dose optimisation with weekly dose escalation**
- Start at **Dose Level 1** based on body weight → up to **Dose Level 5**
- Dose escalation stops once a **sustained clinical response ≥1 point** in average weekly pain score is achieved
- Once response is achieved:
  - Maintain the effective gabapentin dose
  - Initiate gradual background analgesic tapering
- If no response → continue escalation up to Dose Level 5
- If pain worsens during tapering → previous effective background dose may be reinstated
- Background therapy must never exceed baseline dose

Background therapy Tapering

- Stepwise reduction according to individual treatment characteristics:100% → 75–50% → 50–25% → 25–0% of baseline dose
- Typically initiated after Dose Level 3 or 4, but may start at any dose level once response is achieved
- Percentages represent a therapeutic framework, not mandatory reductions
- Tapering adapted by the Investigator based on:

✓ formulation and available strengths

✓ dose divisibility

✓ clinical judgement

✓ patient safety

IMP: Gabapentin 50mg/ml, oral solution

GAPP GAbapentin in Paediatric Pain

IMP Information

- IMP in liquid form
- **Gabapentin is the active substance**
- Concentration 50 mg/mL
- Clear, colorless, slightly viscous oral solution with an added pediatric-friendly flavoring agent

Storage and Shipment

- IMP storage in fridge (Transient shift to temperatures < 25°C are permitted.), in a temperature-controlled room.

Route and Mode of Administration

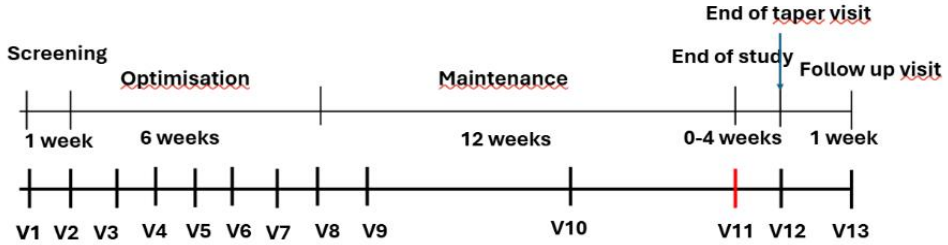
- The route of administration is strictly oral (PO)
- IMP will be administered three times daily using a calibrated, CE-marked pediatric oral syringe (e.g., 10 mL syringes with 0.5 mL graduations)

Dosing

Weight group	D1 (V2)	D2 (V3)	D3 (V4)	D4 (V5)	D5 (V6)
≤ 15 kg	7 mg/kg/day	14 mg/kg/day	21 mg/kg/day	42 mg/kg/day	63 mg/kg/day
>15 kg	5 mg/kg/day	10 mg/kg/day	15 mg/kg/day	30 mg/kg/day	45 mg/kg/day

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Trial Assessments and Procedures Considerations



Trial Assessments and Procedures

Pain scales, charts

Pain charts
Pain Scales: FLACC scale; The Faces Pain Scale – Revised (FPS-R); The numerical rating scale (NRS-11).
Time Of Pain Assessment
Patient diary assessment
Global satisfaction with treatment (NRS-11, subject, parent)
Clinical Global Impressions (CGI-EI) Scale (Investigator)
PedsQL Generic Core Scale v4
Five-Point Facial Hedonic Scale (subject, parent)

Safety assessments and procedures:

Physical Examination at V1, V5, V7, V8, V9, V10
Vital Signs
Weight/height/BMI at V1, V9
Electrocardiograms at V1, V9 Renal ultrasound scan (only for < 3 years of age) V1, V11
Clinical Laboratory Assessments: - Biochemistry V1, V9 - Haematology V1, V9
Pregnancy Testing: - beta hCG pregnancy test at V1 - urine pregnancy testing V1, V9, V10, upon PI discretion
Suicidal Ideation and Behaviour Risk Monitoring at V1, V6, V10, V11.

Pharmacokinetics

- PK-sampling at V3,V5, V7

T0-Pre dose	T1	T2	T3
5-15 min before IMP administration	0-2 hr after IMP administration	2-4 hr after IMP administration	4-6 hr after IMP administration

Adverse events

Adverse events:

- any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator;
- exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition;
- new conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study;
- signs, symptoms, or the clinical sequelae of a suspected drug interaction involving the IMP;
- deterioration of a pre-existing illness;
- an accident.

Event Type	Situational Scope	Reportable Period Start	Reportable Period End	Timing for Reporting to Sponsor or Designee	Method for Reporting	Back-up Method for Reporting
AE and Medical event	•Observation of the patient •Information volunteered by the parents •Patient questioning	Signature of the informed consent	Last follow-up visit	Timely manner, and no later than 5 working days after the investigator or study staff becomes aware of the event.	Recording in the Adverse Event Form included in the electronic case report form (eCRF)	NA
SAE	•Observation of the patient •Information volunteered by the parents •Patient questioning	Signature of the informed consent	Last follow-up visit	**Within 24 hours learning of the event**	E-mail/Fax	Phone call
Pregnancy	•Observation of the patient •Information volunteered by the parents •Patient questioning	Signature of the informed consent	End of pregnancy outcome follow-up	Within 24 hours learning of the pregnancy	E-mail/Fax	Phone call

Adverse events

All **Adverse Events of Special Interest (AESI)** will be handled according to the same reporting, documentation, and follow-up procedures applicable to SAEs.

As propylene glycol is an excipient of the gabapentin, adverse events consistent with propylene glycol toxicity will be considered AESIs., which include:

- hyperosmolarity or increased osmolar gap;
- metabolic acidosis, including lactic acidosis;
- renal dysfunction, including increased serum creatinine and acute kidney injury;
- hypotension;
- clinically significant neurological manifestations suggestive of propylene glycol toxicity (e.g., unexplained altered mental status, excessive sedation, coma, or other neurological abnormalities not attributable to the underlying disease or concomitant medications).

Thank You!

For your attention

