Appendix 1: Informed consent forms and age-tailored informative booklets

- GABA-1 study Information Sheet (for parents/legal authorized representative of minors)
- GABA-1 study Informed Consent (for parents/legal authorized representative of minors)
- GABA-1 study Exploratory Assessments Information Sheet (for parents/legal authorized representative of minors)
- GABA-1 study Exploratory Assessments Informed Consent (for parents/legal authorized representative of minors)
- GABA-1 study Informed Consent for patients who have turned 18 while participating in the study
- GABA-1 study Assent for children from 7 to 11 years
- GABA-1 study Assent for children from 12 to 17 years
- GABA-1 study Informative booklet for children from 0 to 6 years
- GABA-1 study Informative booklet for children from 7 to 11 years
- GABA-1 study Informative booklet for children from 12 to 17 years

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

GABA-1 study Information Sheet

(for parents/legal authorized representative of minors)

This Information sheet is for parents/legal authorized representative of patients referring to <*NAME OF THE CENTRE*>who are asked to participate in the GABA-1 clinical trial:

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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

EudraCT number:	**2014-004851-30**
Principal Investigator:	***<Name>***
	<Name of Organization>
Sponsor:	**PHARM SRL**
Version:	**1.0**
Date:	**11.02.2016**

INTRODUCTION

Your child is invited to take part in this research study. Before deciding whether participation is the right choice for him/her, we would like to explain why this research is being done and what will be the possible risks and benefits. The study doctor will also give information to your child and ask to express his/her willingness to participate, according to the level of maturity.

You are free to accept or refuse his/her participation in this study and do not hesitate to ask for any further clarifications you may need.

WHY YOUR CHILD IS INVITED TO TAKE PART IN THIS STUDY?

Your child experiences persisting pain and the therapy options used up to now did not result in sufficient pain relief.

Gabapentin is a safe medication approved for the treatment of neuropathic pain in adults. In children gabapentin is approved for the treatment of seizures above 6 years of age, but not for neuropathic pain. However, gabapentin is used nowadays to treat paediatric neuropathic pain but without having established with certainty its efficacy and the appropriate doses to be used in children.
In order to see if gabapentin does work in children, we need the collaboration and help of patients like your child.

WHAT IS THE OBJECTIVE OF THIS CLINICAL STUDY?

The purpose of this clinical trial is to study the safety and efficacy of gabapentin for neuropathic pain in children. We will do this by comparing gabapentin to tramadol (another analgesic medicine used to treat pain) in 94 children living in Albania, Estonia, France, Germany, Greece, Italy and the Netherlands.

MORE DETAILS ABOUT THE STUDY DRUGS

A new liquid formulation (syrup) of gabapentin was developed by DOMPÈ with a flavour and a concentration suitable for children of all ages. The daily dosage (amount of syrup) depends on your child's weight and response to its analgesic properties. It will be administered by a graduated syringe (provided with the treatment kit) and cannot be diluted. Gabapentin is taken orally (by mouth) 3 times a day (morning, early afternoon and before bedtime).

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

Tramadol is already on the market as Tramadol EG and comes as drops which may be diluted with water. It is also taken by mouth, 3 times a day as well (morning, early afternoon and before bedtime).
An interval of at least 4 hours should be observed between the doses.

WHAT WILL HAPPEN DURING THIS CLINICAL STUDY?
The entire study may last from 18 to 22 weeks (depending on the dose of medicine your child needs to control his/her pain). This involves in total, 8 visits at the hospital and 4 phone calls.

The study develops in steps:

1. Screening assessments to check that your child can be included in the study
2. Stop of any ongoing medication (washout)
3. Progressive increase of the study drug to find the optimal dose for your child (up to 3 weeks)
4. Treatment with the drug optimal dose for 12 weeks
5. Progressive decrease of the study drug to exit the study

During the study your child will be carefully and regularly monitored to make sure he/she is doing well.

All possible measures will be adopted to reduce pain, distress, fear and discomfort.

More detailed description of the study steps is given in the following sections:

STEP 1

If you give your consent to your child's participation by signing the Informed Consent form, the study doctor will perform a "screening visit". They will assess your child's medical history, physical condition, and perform some blood tests. At the end of the assessment the doctor will let you know if your child can participate in the study.

STEP 2

If your child is already taking drugs to treat the pain, it will be required to stop them for some days (called washout period). This is needed to properly assess the effect of the study drug. During this period, your child is allowed to take ibuprofen or paracetamol, as prescribed by the study doctor in case of pain.

During the last 3 days of the washout period, the pain intensity will be measured twice daily (morning and evening).

If your child does not take drugs that need to be discontinued, his/her pain intensity will be measured for 3 days as above indicated before taking any study drug (gabapentin or tramadol).

STEP 3

After these assessments, your child will return to the study centre for a second visit where he/she will be randomly assigned to receive either gabapentin or tramadol. Gabapentin is the medicine we want to study, tramadol is the medicine that we are using for comparison.

GABA-1 is a "double blind trial", which means that neither the doctor, nor you, nor your child will know which treatment is administered (gabapentin or tramadol). In order to do so, your child will take two different solutions: one will contain the assigned treatment (gabapentin or tramadol), and the other one will contain a placebo of the other treatment (i.e., tramadol if assigned to gabapentin or gabapentin if assigned to tramadol) that smells, tastes, and looks like the active treatment but does not contain any medicine at all.

One solution will be administered by a graduated syringe (provided with the treatment kit) and cannot be diluted. The other comes as drops which may be diluted with water. Both will be taken 3 times a day (morning, early afternoon and before bedtime). An interval of at least 4 hours should be observed between the doses.

During the first 3 weeks of treatment both solutions dosages will be gradually increased until the best dose for your child is found. During this period you and your child will visit the hospital twice and 2 phone calls will be scheduled. The visits are aimed at assessing how much drug is present in your child's blood, their general wellbeing, and the level of pain they may still experience.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

STEP 4

Once the best dose is determined, your child will continue taking that dose for the following 12 weeks. You will be asked to return to the clinic every month to check upon your child wellbeing, the presence of any side effect or discomfort, and the level of pain, if any, your child is still experiencing.

If the medication proves not to be effective, the study doctor will withdraw your child from the study at any time during the 12 weeks.

STEP 5

At the end of the treatment, your child will gradually discontinue the assigned drug over a period ranging from 1 to 4 weeks, depending on the doses taken during the study. Gradual dose decrease is needed because it is not safe to immediately stop gabapentin or tramadol. After then, your child will return to the centre for the final evaluations.
If at the end of the study your child is still experiencing pain, the doctor will advise on the most appropriate treatment (see paragraph: WHAT WILL HAPPEN WHEN THE STUDY FINISHES?)

HOW TO ASSESS YOUR CHILD LEVEL OF PAIN?

The level of pain your child is experiencing can be assessed by completing an age appropriate pain score questionnaire included in a diary.
Besides the level of pain, you will be asked to record in the diary any side effect your child is experiencing, any time the treatment is forgotten and any other medicine you give your child. At your discretion and under your supervision your child may fill the diary by themselves.

RECOMMENDATIONS

If at any time during the study your child has any abnormal symptom or discomfort, you should call the study doctor or go to the hospital.
It is very important that you and your child will attend the hospital visits as scheduled to check that the drug is working and to monitor if and how much pain your child is still experiencing, if any.

As the effect of both study drugs on unborn baby's development is not known, your child should not become pregnant. For the same reason, pregnant and breast-feeding girls cannot take part in this study. Girls who are able to become pregnant must have a negative pregnancy test from the time of inclusion up to one month after the end of the study. Participating girls must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception throughout the study period and for 30 days after taking the last dose of study drug.

Acceptable methods of contraception are:

- Intrauterine devices (diaphragm with spermicidal gel or foam) and condoms.
- Hormonal contraceptives (i.e., oral, depot, patch, injectable, IUD or vaginal ring) and condoms.

If your daughter becomes pregnant during this study, you must call the study doctor immediately, and she will be withdrawn from the study. With permission, your daughter's health will be monitored until birth. If your daughter gives birth, the baby will be examined and monitored for any medical problems. At birth, the sponsor will ask information about your daughter's health and that of the baby.

WHAT WILL HAPPEN WHEN THE STUDY FINISHES?

Your child's participation in this study is completed when all visits have been performed and the study drug has been gradually stopped.

It is not possible to continue with the study drug after the study has ended, even when your child experienced a good pain relief. This is because the study is blind, which means that the study doctor does not know which one of the two drugs (gabapentin or tramadol) has been assigned to your child. The doctor will be able to find out which drug is being administered only if this is needed to treat a symptom potentially caused by the study drug. Blinding is necessary because knowing the treatment given can sometimes improve a patient's condition or the doctor perception of the patient's condition simply because they have the expectation that the drug will be helpful. This is

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

why, even at the end of the study, you will not know which of the two treatments (gabapentin or placebo) your child has taken.

Participation to the study may end if the doctor believes it's in the best interest of your child, such as because of side effects or insufficient pain relief.

Furthermore, you also may choose to discontinue at any time without giving a reason. In this case it is important to inform the study doctor about your decision so that you can be advised how you can safely stop the study drug. The doctor will always respect your decision.
After discontinuation of the study drug your doctor will discuss the best treatment options. Study discontinuation will not affect the standard of care your child is entitled to receive.

WHICH SIDE EFFECTS CAN BE EXPECTED DURING THIS STUDY?

The document "Detailed Side effects", here attached as Annex 1, includes a list of potential side effects of gabapentin and tramadol. Not all children receiving gabapentin or tramadol will experience these effects, but there is some chance your child may experience one or more of them during the trial. Some may have a serious impact on daily life, like dizziness, excessive sleepiness or behavioural changes. Nevertheless, most of them can be prevented by starting with a low dose and then slowly increasing it.

Contact the study doctor immediately if your child experiences any of these symptoms.

WHAT BURDEN'S CAN BE EXPECTED DURING THIS STUDY?

During STEP 2 your child may experience more pain due to the discontinuation of the drug currently taking. Although rescue medication (paracetamol/ibuprofen) is allowed, your child may still experience some degree of pain.

By participating in the study your child will attend the clinic 8 times. Three blood tests are scheduled and less than 16 ml of blood will be taken during the entire study. Additionally, 2 ml of blood will be required from females of child bearing age for pregnancy testing.

Keeping diaries and completing questionnaires are an additional burden for study participants.

Your child must not participate in any other research study while participating at this one.

Furthermore, you child would need to take two drugs (gabapentin + placebo OR tramadol + placebo) instead of one.

WHAT ARE THE BENEFITS IN TAKING PART IN THIS STUDY?

If your child takes part is this study, he may experience a better pain relief by using the study drug. This may improve quality of life, ability to perform physical activities, attendance at school and general wellbeing. It may be comforting to you knowing that your child's pain and general wellbeing are monitored more frequently than usually done. The information collected in this study will be of help for the treatment of other children suffering for neuropathic or mixed pain like your child.

WHAT ARE THE TREATMENT OPTIONS IF YOU DON'T WANT TO PARTICIPATE IN THIS STUDY?

If you do not consent your doctor will discuss with you the best available treatment option for your child.

IS THERE ANY INSURANCE PROVIDED?

A specific insurance for this study (Company XXXXX Insurance Policy n. _____) covers all medical expenses that may be necessary as a result of problems related to the study drugs and any possible damage, with the exception for bodily injuries to pregnant women and/or genetic malformations to a foetus, which arises when the required contraceptive measures recommended by the doctor have not been adopted. The insurance policy does not cover any amount exceeding its limit of liability and operates only in case of claims for damages submitted within the terms referred in the policy.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

WHAT ARE THE COSTS FOR TAKING PART IN THIS STUDY?

The costs of medicines, visits and examinations are covered by the promoter of this study (Sponsor).

You will not receive any incentive to take part in this research.

WILL YOUR CHILD'S MEDICAL DATA BE KEPT PRIVATE?

People involved in any of the study activities will adopt all measures to guarantee that data concerning your child will be kept confidential (according to the provisions of the European legislation on clinical trials, the Directive 95/46/CE on protection of individuals in the processing of personal data and your national legislation). Data provided to the Authorities will remain anonymous. Moreover, all clinicians and researchers involved are bound by professional secrecy.

This means that all the data collected will be stored and handled with a code and the identity of your child will remain hidden. This means that in every document there will be a letter-number code instead of the name of your child. Only research staff members at the hospital, authorized representatives of the study Sponsor, regulatory authorities and ethical committees' members that approved the study will have access to the individual data.
All the biological samples (blood samples) obtained during this study will be used only for this research and will be destroyed at the end of the study.

WHICH INFORMATION WILL BE MADE PUBLIC?

At the end of the research, you will be informed about the results obtained through this study from your doctor. When results will be disclosed to the public, any confidential information (including the name of your child) will be not revealed.

DOES YOUR CHILD HAVE TO TAKE PART IN THIS STUDY?

The decision to allow your child's participation in this clinical trial is entirely voluntary.

You may interrupt your child's participation in the study at any time without any prejudice on your child and without providing any justification. In this case, no further data will be collected. However, the information already acquired and analysed will be treated according to your national ruling legislation.
If you do not wish your child to take part in this study, your child will be provided with the established standard treatment available at the centre/hospital.

WHAT DO YOU HAVE TO DO TO ALLOW YOUR CHILD TO TAKE PART IN THIS STUDY?

You will be asked to sign the Informed Consent form in order to confirm that you have read all the information and understood the aims, the potential risks and the benefits of this clinical study.

The signed Informed Consent form will be stored in the archives of the hospital. You will be provided a copy of the signed form.

WHO CAN ANSWER YOUR QUESTIONS ABOUT THIS STUDY?

This information has been provided by doctor <*insert details*>_____.

If you wish to ask questions later, you may contact any of the following:

1. <*insert PI details*>_____
2. <*insert independent physician details*>_____

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

Annex 1

DETAILED SIDE EFFECTS

Like all medicines, the medicines studied in the GABA-1 trial, gabapentin and tramadol, may cause side effects. This document details the potential side effects of both. Information provided in this document are sourced by official Patient information leaflets and aims to alert you if any of these symptoms appear.
If this happens, or if you notice any side effects not listed in this leaflet, please tell your study doctor.

Gabapentin

Very common side effects (which may affect more than 1 person out of 10 persons):

- *VIRAL INFECTION (like a cold)*
- *FEELING DROWSY, DIZZINESS, LACK OF COORDINATION*
- *FEELING TIRED, FEVER.*

Common side effects (which may affect more than 1 person out of 100 persons):

- *PNEUMONIA (chest infection), RESPIRATORY INFECTIONS, URINARY TRACT INFECTIONS, INFLAMMATION OF THE EAR OR OTHER INFECTIONS*
- *LOW WHITE BLOOD CELL COUNTS*
- *ANOREXIA, INCREASED APPETITE*
- *ANGER TOWARDS OTHERS, CONFUSION, MOOD CHANGES, DEPRESSION, ANXIETY, NERVOUSNESS, DIFFICULTY WITH THINKING*
- *CONVULSIONS, JERKY MOVEMENTS, DIFFICULTY WITH SPEAKING, LOSS OF MEMORY, TREMOR, DIFFICULTY SLEEPING, HEADACHE, SENSITIVE SKIN, DECREASED SENSATION (NUMBNESS), DIFFICULTY WITH COORDINATION, UNUSUAL EYE MOVEMENT, INCREASED, DECREASED OR ABSENT REFLEXES*
- *BLURRED VISION, DOUBLE VISION*
- *VERTIGO*
- *HIGH BLOOD PRESSURE, FLUSHING OR DILATION OF BLOOD VESSELS*
- *DIFFICULTY BREATHING, BRONCHITIS, SORE THROAT, COUGH, DRY NOSE*
- *VOMITING (BEING SICK), NAUSEA (FEELING SICK), PROBLEMS WITH TEETH, INFLAMED GUMS, DIARRHOEA, STOMACH PAIN, INDIGESTION, CONSTIPATION, DRY MOUTH OR THROAT, FLATULENCE.*
  Feeling sick and being sick might be serious as these may be symptoms of acute pancreatitis (an inflamed pancreas). Contact your doctor immediately if your child has persistent stomach pain
- *FACIAL SWELLING, BRUISES, RASH, ITCH, ACNE*
- *JOINT PAIN, MUSCLE PAIN, BACK PAIN, TWITCHING*
- *DIFFICULTIES WITH ERECTION (IMPOTENCE)*
- *SWELLING IN THE LEGS AND ARMS, DIFFICULTY WITH WALKING, WEAKNESS, PAIN, FEELING UNWELL, FLU-LIKE SYMPTOMS*

- *INCREASE IN WEIGHT*
- *ACCIDENTAL INJURY, FRACTURE, ABRASION*
- *AGGRESSIVE BEHAVIOUR AND JERKY MOVEMENTS reported in clinical studies in children.*

Uncommon side effects (which may affect more than 1 person out of 1000 persons):

- *ALLERGIC REACTIONS: Allergic reactions might be very serious. Contact your doctor immediately your child has any of the following symptoms:*
    - *skin rash*
    - *hives*
    - *fever*
    - *swollen glands that do not go away*
    - *swelling of your child's lip and tongue*
    - *yellowing of your child's skin or of the whites of the eyes*
    - *unusual bruising or bleeding*
    - *severe fatigue or weakness*
    - *unexpected muscle pain*
    - *frequent infections*
- *DECREASED MOVEMENT*
- *RACING HEARTBEAT*
- *SWELLING that may involve the face, trunk and limbs*
- *PROBLEMS WITH THE LIVER*

Other side effects:

- *DECREASED PLATELETS (BLOOD CLOTTING CELLS)*
- *HALLUCINATIONS*
- *PROBLEMS WITH ABNORMAL MOVEMENTS such as writhing, jerking movements and stiffness*
- *RINGING IN THE EARS*
- *ACUTE KIDNEY FAILURE, INCONTINENCE*
- *INCREASED BREAST TISSUE, BREAST ENLARGEMENT*
- *ADVERSE EVENTS FOLLOWING THE ABRUPT DISCONTINUATION OF GABAPENTIN (anxiety, difficulty sleeping, feeling sick, pain, sweating, chest pain)*
- *BLOOD GLUCOSE FLUCTUATIONS in patients with diabetes.*

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

Tramadol

Very common side effects (which may affect more than 1 person out of 10 persons):

- *DIZZINESS*
- *NAUSEA*

Common side-effects (which may affect more than 1 person out of 100 persons):

- *HEADACHES, DROWSINESS*
- *SWEATING*
- *CONSTIPATION, DRY MOUTH, VOMITING, INDIGESTION (DYSPEPSIA), ABDOMINAL PAIN*
- *FATIGUE, WEAKNESS, LOW ENERGY*

Uncommon side effects (which may affect more than 1 person out of 1000 persons):

- *SEVERE RASH involving reddening, peeling and swelling of the skin that resembles severe burns (toxic epidermal necrolysis), severe form of skin rash with flushing, fever, blisters or ulcers (Stevens Johnson syndrome)*
- *POUNDING OF THE HEART, FAST HEART BEAT, FEELING FAINT OR COLLAPSE. These adverse effects may particularly occur in patients in an upright position or under physical strain*
- *ANOREXIA, URGE TO VOMIT (RETCHING), STOMACH TROUBLE (E.G. FEELING OF PRESSURE IN THE STOMACH, BLOATING), DIARRHOEA*
- *SKIN REACTIONS (e.g. itching, rash).*

Rare side effects (which may affect more than 1 person out of 10000 persons):

- *CHANGES IN APPETITE, ABNORMAL SENSATIONS (e.g. itching, tingling, numbness), trembling, slow breathing, epileptic fits, muscle twitches, uncoordinated movement, transient loss of consciousness (syncope), INCREASED MUSCLE STIFFNESS, TASTE DISTURBANCE*
- *HALLUCINATIONS, CONFUSION, SLEEP DISORDERS, ANXIETY AND NIGHTMARES. Psychological complaints may appear after treatment with tramadol. Their intensity and nature may vary (according to the patient's personality and length of therapy). These may appear as a CHANGE IN MOOD (mostly high spirits, occasionally irritated mood), CHANGES IN ACTIVITY (usually suppression, occasionally increase) and DECREASED COGNITIVE AND SENSORY PERCEPTION (changes in senses and recognition, which may lead to errors in judgement).*
- *THOUGHTS OF SUICIDE, DRUG ABUSE AND ADDICTION*
- *SLOW HEART BEAT, INCREASE IN BLOOD PRESSURE*
- *BLURRED VISION*
- *SHORTNESS OF BREATH (dyspnoea). Worsening of asthma has been reported, however it has not been established whether it was caused by tramadol*
- *WEAK MUSCLES*
- *URINARY DISORDERS: passing urine with difficulty or pain, passing less urine than normal*

- *MENSTRUAL DISORDERS*
- *WEIGHT LOSS, ALLERGIC REACTIONS (e.g. difficulty in breathing, wheezing, swelling of skin) and shock (sudden circulation failure).*

Very rare side effects: (which may affect less than 1 person in a 10000):

- *INCREASE IN LIVER ENZYME VALUES.*

Side effects with unknown frequency (which cannot be estimated from the available data):

- *DECREASE IN BLOOD SUGAR LEVEL*
- *SPEECH DISORDERS*
- *EXCESSIVE DILATION OF THE PUPILS (mydriasis).*

If tramadol is taken over a long period of time, dependence may occur, although the risk is very low. When treatment is stopped abruptly signs of withdrawal may appear.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

GABA-1 study Informed Consent

(for parents/legal authorized representative of minors)

I have been invited to let my child participate in the **GABA-1** clinical trial:

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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

EudraCT number:	**2014-004851-30**
Principal Investigator:	***<Name>***
	<Name of Organization>
Sponsor:	**PHARM SRL**
Version:	**1.0**
Date:	**11.02.2016**

- ☐ I hereby declare to have read and understood the foregoing information materials /I confirm they have been read to me.
- ☐ I have had the opportunity to ask questions about the trial and they have been answered to my satisfaction.
- ☐ I confirm that due time was given to me to take the decision.
- ☐ I am aware that participation in this study is fully voluntary. I know I can decide at any time to stop my child's participation without having to explain why and without prejudice in terms of medical care.
- ☐ I consent that my child will undergo eight hospital visits, four phone calls and a maximum of three blood withdrawals.
- ☐ I consent to inform my child's primary care paediatrician/general practitioner about my child participation.
- ☐ I am aware that some people will need to review the personal data of my child as described in the information document. I allow the access to my child's medical documents and data by authorities and other personnel bound to medical secret, as described in the information document.
- ☐ I consent the use of the personal data of my child for the purposes that are described in the consent information document.
- ☐ I consent that the research data are stored accordingly to national legislation.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

By signing this form I confirm that I voluntarily authorise my child to participate in this clinical trial.

Father's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Mother's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

In case of legal authorized representative:

Legal authorized representative's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Investigator's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Statement by the investigator/person taking consent

I hereby confirm that I have accurately informed the patient and his/her parents about the GABA-1 trial. I have given the opportunity to ask questions and answered questions to satisfaction.

If new information arises during the trial that could influence the consent to participate in this study, I will timely inform the patient and his/her the parents.
I hereby confirm that the parents/legal authorized representative have/has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Information Consent Form has been provided to the participant's parents/legal authorized representative.

Signature of Investigator/person taking the consent: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

When completed 1 copy (original) is for Investigator Site File, 1 copy is for parent/legal authorized representative, 1 copy is to be kept in medical notes.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

GABA-1 study Exploratory Assessments Information Sheet

(for parents/legal authorized representative of minors)

This Information Document is for parents/legal authorized representative of children and youngsters referring to <*NAME OF THE CENTRE*> who are asked to participate in the exploratory assessments in (GABA-1) study.

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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

EudraCT number:	**2014-004851-30**
Principal Investigator:	**<Name>**
	<Name of Organization>
Sponsor:	**PHARM SRL**
Version:	**1.0**
Date:	**11.02.2016**

INTRODUCTION

You have consented to the participation of your child in the GABA-1 study on the effects of gabapentin on neuropathic pain. With this document you are asked to consider the participation of your child also in two exploratory assessments that are additional to the original study. As participation in these exploratory assessments is completely voluntary, a separate permission is needed from you to conduct these additional evaluations.

Before you decide to participate or not in these exploratory assessments, it is important you are fully informed about the aim and procedures involved. Therefore take your time to read this information leaflet carefully. If you have any questions after reading this leaflet, please ask your study doctor. He/she will answer all your questions.

If you give permission to the main research study (GABA-1) but not to the exploratory assessments, your child will be included in the main research study only and none of these additional evaluations will be performed. On the contrary, you can participate to the exploratory assessments only if you participate to the main study.

In any case, the treatment received in the main research study in no way will be influenced by your decision of whether to take part or not in these exploratory assessments.

For these reasons, you are asked to sign for permission to the exploratory assessments in a separate consent form for the main research study.

WHAT IS THE PURPOSE OF THESE EXPLORATORY ASSESSMENTS?

The exploratory assessments have two research purposes.

You may choose to participate only in the DNA exploratory study, only in the metabolomics exploratory study or in both exploratory assessments.

1) **Genetic variation: DNA exploratory study**

Not every child responds in the same way to a drug. Some children may have more pain relief than others. This can happen for many reasons, such as how old they are or what kind of pain they have. Another reason may be their DNA, or genetic make-up. DNA is material that is passed from parent to child that determines the makeup of the body and its function. Our DNA is made of many genes, or areas that are found to be related to a specific trait, such as eye or hair colour. It is already known that genes determine how sensitive we are to pain.

This study aims to explore if and to what extend genetic factors influence the effect of the pain treatment in general and of gabapentin or of tramadol treatment in particular. This is expected to provide a better understanding of why some children benefit from some pain treatments and why other children stay painful despite receiving treatment, and a better insight in the development of adverse effects.

2) **Understanding the molecular effect of gabapentin: 'metabolomics' exploratory study**

Each type of cell and tissue has a unique metabolic 'fingerprint' that can explain how it works. By studying the fingerprint of neuropathic pain, it is possible to find out what mechanisms and pathways in the human body define neuropathic pain and how the fingerprint may be influenced by gabapentin.

HOW WILL THE RESEARCH BE PERFORMED?

After you have confirmed your participation by signing the informed consent form, some extra amount of blood (small, approximately 0.5 milliliter) will be taken at the beginning of the GABA-1 study for DNA, and about 1 milliliter at the beginning and at the end of study for metabolomics. This will be done at the same time when blood for the other tests of the GABA-1 study is taken so there won't be an extra puncture for your child, just the collection of some additional blood to extract DNA and specific molecules which will be analysed and studied to understand how they function.

Furthermore the data collected as part of the GABA-1 study on pain relief and the occurrence of side effects will be used to study if genes can explain the response to the drugs and if the mechanisms which determine pain and the response to pain can be better explained.

WHAT ARE THE POTENTIAL BENEFITS WHEN MY CHILD PARTICIPATES?

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

There are no direct benefits for your child, but these assessments may be of benefit to other children who require analgesic treatment in the future. This research will provide useful information on neuropathic pain, on the effects of drug treatment and on how the body's responses to them varies according to a person's specific genes. This may help to decide which drugs are of benefit to children like yours who suffer from pain.

WHAT ARE THE POTENTIAL RISKS AND BURDEN WHEN MY CHILD PARTICIPATES?

There are no risks. As explained above, an extra amount of blood will be drawn but no extra puncture will be done.

WHAT WILL HAPPEN WHEN I DON'T CONSENT TO PARTICIPATION OF MY CHILD?

Your decision to allow your child's participation in this clinical trial is entirely voluntary. You can participate in the GABA-1 study without participation in these exploratory assessments. Furthermore you may choose to participate only in the DNA exploratory study, only in the metabolomics exploratory study or in both exploratory assessments.

You may interrupt your child's participation in these exploratory assessments at any time without any prejudice on your child and without providing any justification. In this case, any biological sample collected from your child will be destroyed and no further data related to your son/daughter will be collected. However, the information already collected and analysed, will be used for the purposes of these exploratory assessments.

WHAT WILL HAPPEN WITH MY CHILD'S PERSONAL DATA?

The personal research data of your child are anonymised and may only be reviewed by authorized personnel bound to medical secrecy: members of the research team, competent authorities, and members of the Institutional Review Boards. Personal data of your child will not be used in any report or publication about these exploratory assessments. Any personal data – like your child's name or date of birth, will be a replaced by a code. Only the study doctor at the clinic where your child participates in the GABA-1 study will know which code belongs to which child.

Any personal data of your child will be kept confidential according to your national ruling legislation.

WHAT WILL HAPPEN TO THE BLOOD SAMPLE?

The blood sample will be coded, just like the personal data. Any direct reference to your child will be replaced by this code. The DNA sample will be sent to the Pharmacogenomics Core Laboratory Rotterdam (the Netherlands), without any clinical patient information. The metabolomics sample will be sent to Netherlands Metabolomics Center, Demonstration and Competence Lab (DCL) (the Netherlands). The samples will be stored according to your national ruling legislation.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

WHAT WILL HAPPEN WHEN THE EXPLORATORY ASSESSMENTS HAVE ENDED?

After the blood draws, the exploratory assessments end for your child. The individual results of the inherited genetic factors and metabolomics in your child's blood will not be disclosed to you, because we don't know yet if the results will be clinically relevant. Results of the genetic and metabolomic assessments will be reported in scientific publications. The overall data on the full group of patients who participated in anonymity.

ARE THERE ANY COSTS OR REIMBURSEMENTS?

No costs will be charged to you when your child participates in these exploratory assessments. There is no reimbursement of costs either.

IS AN INSURANCE COVERAGE PROVIDED?

Please refer to the principal GABA-1 study.

WHO DID REVIEW AND APPROVE OF THE CONDUCT OF THESE EXPLORATORY ASSESSMENTS?

These exploratory assessments were reviewed and approved of by <*Ethics Committee name* >.

WHO CAN I CONTACT WHEN I HAVE QUESTIONS?

If you have any questions regarding these exploratory assessments, you can contact your study doctor <*insert details*>_____

or any of the following:

1. <*insert PI details*>_____
2. <*insert independent physician details*>_____.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

GABA-1 study Exploratory Assessments Informed Consent

(for parents/legal authorized representative of minors)

I have been invited to give my consent to my child participation in two exploratory assessments to GABA-1 clinical trial:

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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

EudraCT number:	**2014-004851-30**
Principal Investigator:	***<Name>***
	<Name of Organization>
Sponsor:	**PHARM SRL**
Version:	**1.0**
Date:	**11.02.2016**

- ☐ I hereby declare to have read and understood the foregoing information materials /I confirm they have been read to me.
- ☐ I have had the opportunity to ask questions about the assessments additional to GABA-1 and they have been answered to my satisfaction.
- ☐ I confirm that due time was given to me to take the decision.
- ☐ I am aware that participation any of these two assessments is fully voluntary. I know I can decide at any time to stop my child's participation without having to explain why and without prejudice in terms of medical care.
- ☐ I understand that my child will undergo one blood withdrawal (approximately 0.5 millilitres) for the DNA sub-study and/or two blood withdrawals (1.0 milliliter each) for the metabolomics sub-study.
- ☐ I consent to inform my child's primary care paediatrician/general practitioner about my child participation.
- ☐ I am aware that some people will need to review the personal data of my child as described in the information document. I allow the access to my child's medical documents and data by authorities and other personnel bound to medical secret, as described in the information document.
- ☐ I consent the use of the personal data of my child for the purposes that are described in the consent information document.
- ☐ I consent that the research data are stored accordingly to national legislation.

By signing this form I confirm that I voluntarily authorise my child to participate in these exploratory assessments additional to GABA-1:

[ ] DNA

[ ] Metabolomics

Father's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Mother's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

In case of legal authorized representative:

Legal authorized representative's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Investigator's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Statement by the investigator/person taking consent

I hereby confirm that I have accurately informed the patient and his/her parents about the GABA-1 trial additional exploratory assessments. I have given the opportunity to ask questions and answered questions to satisfaction.

If new information arises during the trial that could influence the consent to participate in this study, I will timely inform the patient and his/her the parents.
I hereby confirm that the parents/legal authorized representative have/has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Information Consent Form has been provided to the participant's parents/legal authorized representative.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

Signature of Investigator/person taking the consent: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

When completed 1 copy (original) is for Investigator Site File, 1 copy is for parent/legal authorized representative, 1 copy is to be kept in medical notes.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

GABA-1 study Informed Consent
for patients who have turned 18 while participating in the study

As I have reached adult age, I have been asked to confirm my participation in the GABA-1 clinical trial:

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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

EudraCT number:	**2014-004851-30**
Principal Investigator:	***<Name>***
	<Name of Organization>
Sponsor:	**PHARM SRL**
Version:	**1.0**
Date:	**11.02.2016**

- ☐ I hereby declare to have been properly informed about this trial.
- ☐ I have had the opportunity to ask questions about the trial and they have been answered to my satisfaction.
- ☐ I confirm that due time was given to me to take the decision.
- ☐ I am aware that participation in this study is fully voluntary. I know I can decide at any time to stop my participation without having to explain why and without prejudice in terms of medical care.
- ☐ I consent to continue with the study procedures explained to me at the beginning of my participation.
- ☐ I am aware that some people will need to review my personal data. I allow the access to my medical documents and data by authorities and other personnel bound to medical secret.
- ☐ I consent the use of my personal data for the purposes that are described in the consent information document.
- ☐ I consent that the research data are stored accordingly to national legislation.

By signing this form I confirm that I voluntarily consent to continue my participation in this clinical trial.

Patient's signature: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

Investigator's signature: _____

NAME (block capitals): _____

Date:_____ Time (24 hr clock): _____

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

Statement by the Investigator/person taking consent

I hereby confirm that I have accurately informed the patient about the GABA 1 trial. I have given the opportunity to ask questions and answered questions to satisfaction.

If new information arises during the trial that could influence the consent to participate in this study, I will timely inform the patient and his/her the parents.
I hereby confirm that the patient has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Consent Form has been provided to the participant.

I hereby declare I do not have any present or potential conflict of interest deriving from my witness's role in this clinical trial.

Signature of Investigator/person taking the consent: _____

NAME (block capitals): _____

Date: _____ Time (24 hr clock): _____

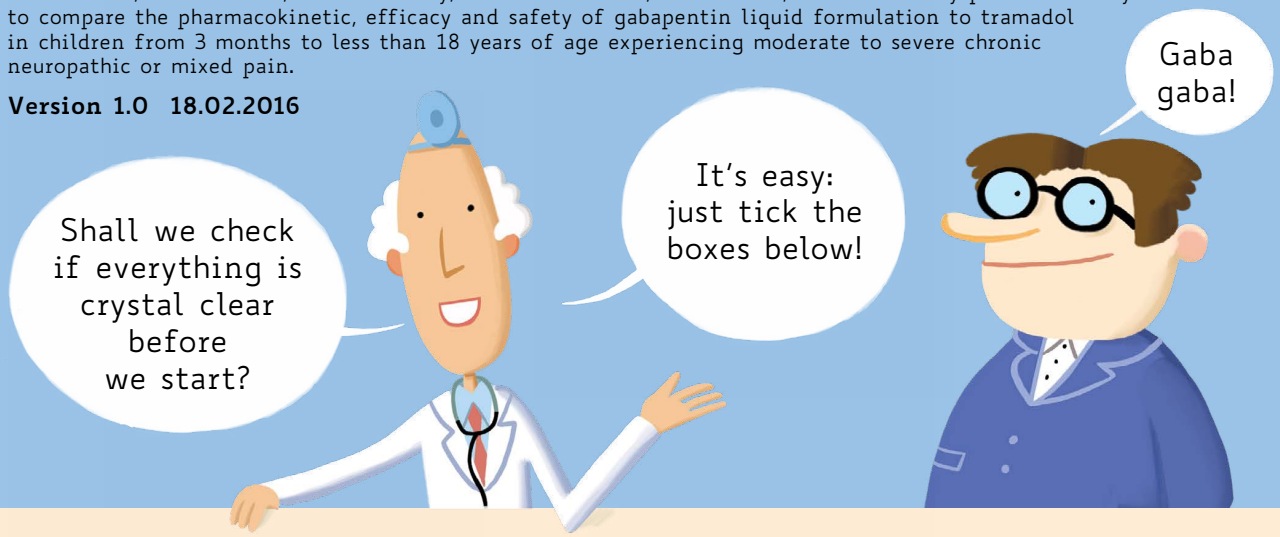
When completed 1 copy (original) is for Investigator Site File, 1 copy is for parent/legal authorized representative, 1 copy is to be kept in medical notes.

GAPP – GAbapentin in Paediatric Pain

GABA-1 Clinical Trial
EudraCT Number: 2014-004851-30

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, 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.

Version 1.0 18.02.2016



ASSENT FORM

☐ I do understand what this trial is for.

☐ I do know that I'll be taking two medications and this might reduce my pain.

☐ I do know that I'll come to hospital for a blood sample and a check-up on the days my doctor says.

☐ If I ever have any questions or worries, I do know that I can ask the doctor as many questions as I like.

☐ If I take the two medications, I do know that I might feel a bit sick.

☐ If I do feel a bit sick, I do know that I have to tell my parents and my doctor.

☐ I do know that if I do not want to carry on, I can change my mind whenever I want and the doctor will simply give me another medicine.

☐ I do understand how the trial works and I do agree to take part of it.

Child's Signature: _____

Full name (BLOCK CAPITALS): _____

DECLARATION BY THE DOCTOR

The child has read this assent form, had the opportunity to ask questions and understood the information provided. The child assent is fully voluntary and without any constraints whatsoever. I will timely inform the child if during the trial new information become available that may influence his/her willingness to participate.

A copy of this assent form has been given to the child's parents.

Doctor's signature: _____

Full name (BLOCK CAPITALS): _____

Date: _____

FOR CHILDREN WHO ARE UNABLE TO READ OR SIGN

If you want to take part in this trial, put a cross inside this box.

Full name (BLOCK CAPITALS):

_____

DECLARATION BY THE WITNESS

I witnessed the careful reading of this assent form to the child who understood the information provided. The child had the opportunity to ask questions about the trial and any concern he/she had have been resolved.
I declare that the child has freely agreed to take part in the trial.
Lastly, I declare that I have no current or potential conflict of interest deriving from my role as a witness in this trial.

Witness's signature: _____

Full name (BLOCK CAPITALS): _____

Date: _____

DECLARATION BY THE DOCTOR

I have read this assent form to the child who had the opportunity to ask questions and understood the information provided. The child assent is fully voluntary and without any constraints whatsoever. I will timely inform the child if during the trial new information become available that may influence his/her willingness to participate.

A copy of this assent form has been given to the child's parents.

Doctor's signature: _____

Print full name (BLOCK CAPITALS): _____

Date: _____

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602962

GAPP - GAbapentin in Paediatric Pain

GABA-1 Clinical Trial
EudraCT Number: 2014-004851-30

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase III study to compare the pharmacokinetic, 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.

Version 1.0 18.02.2016

ASSENT FORM

I have been invited to participate in the GABA-1 clinical trial.

I have read the attached information booklet. If I had any doubts, I had the opportunity to ask questions and the answers were clear and comprehensive.
I have been given enough time to consider my participation.

By participating in this clinical study, I will be discontinuing my previous treatment, and I will begin to take the drug gabapentin (syrup) or the drug tramadol (drops) and a placebo according to the trial plan.
I am aware that the treatment will last 15 weeks, that the trial itself will last up to 22 weeks, during which time I will be available for the monitoring visits and examinations required, which I have read about in the information booklet.

I know that participation is fully voluntary. I know that I can decide at any given time to withdraw without providing any reason and, that if I do, I will still receive full attention from the doctors and all the necessary treatments.

I consent that my general practitioner and other doctors involved in my medical treatment are informed about my participation in this trial.

I know that other authorised people involved in the trial may review my medical files.

I consent to the use of my data for the purposes explained in the information booklet.

I consent to take part in this trial. YES NO

Participant's Signature: _____

Full name (BLOCK CAPITALS): _____

DECLARATION BY THE INVESTIGATOR/ PERSON RECEIVING ASSENT

I have fully informed the patient about the trial.
The patient read this assent form and had the opportunity to ask questions.
All the questions asked were addressed to the patient's satisfaction.
The assent of the patient is fully voluntary and without any constraints whatsoever.
I will timely inform the patient if during the trial new information become available that may influence his/her willingness to participate.

A copy of this assent form has been given to the patient's parents.

Signature of investigator/person receiving assent: _____

Full name (BLOCK CAPITALS): _____

Date: _____

IF THE MINOR IS UNABLE TO READ OR PROVIDE A SIGNATURE

Put a cross inside this box: ☐

Full name (BLOCK CAPITALS):

_____

DECLARATION BY THE WITNESS

I witnessed the careful reading of this assent form to the minor who understood the information provided.
The minor had the opportunity to ask questions about the trial and any concern he/she had have been resolved. I declare that the minor has freely given his/her assent to take part in the trial.
I also declare that I have no current or potential conflict of interest deriving from my role as a witness in this trial.

Witness's Signature: _____

Full name (BLOCK CAPITALS): _____

Date: _____

DECLARATION BY THE INVESTIGATOR/PERSON RECEIVING ASSENT

I have fully informed the patient about the trial.
This assent form was read to the patient who had the opportunity to ask questions.
All the questions asked were addressed to the patient's satisfaction.
The assent of the patient is fully voluntary and without any constraints whatsoever.
I will timely inform the patient if during the trial new information become available that may influence his/her willingness to participate.

A copy of this assent form has been given to the patient's parents.

Signature of investigator/person receiving assent:

_____

Full name (BLOCK CAPITALS): _____

Date: _____

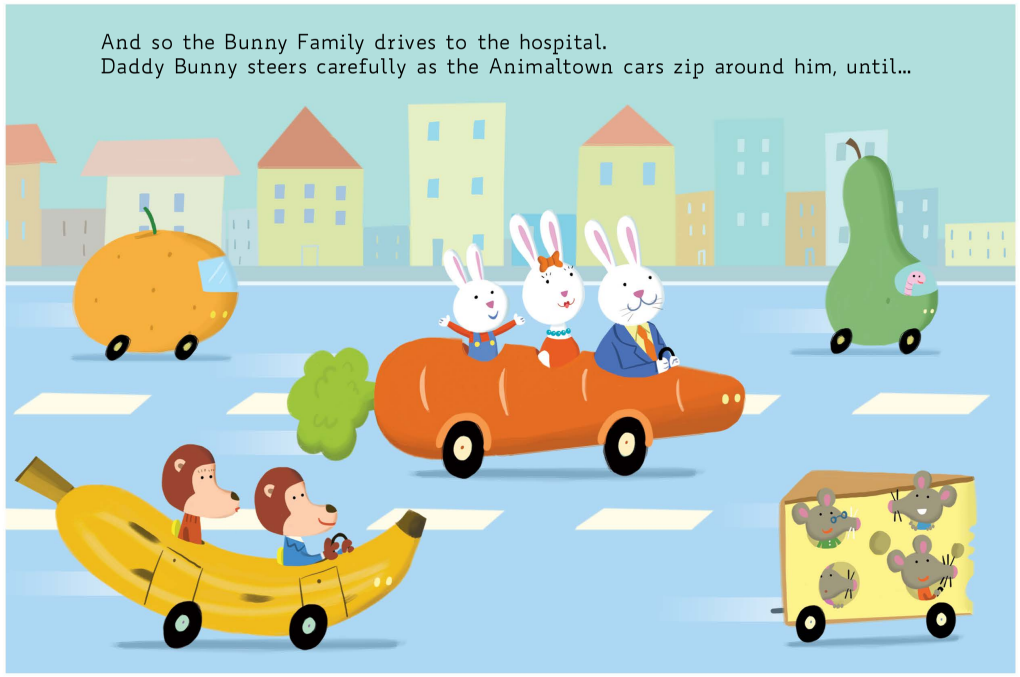
This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602962.

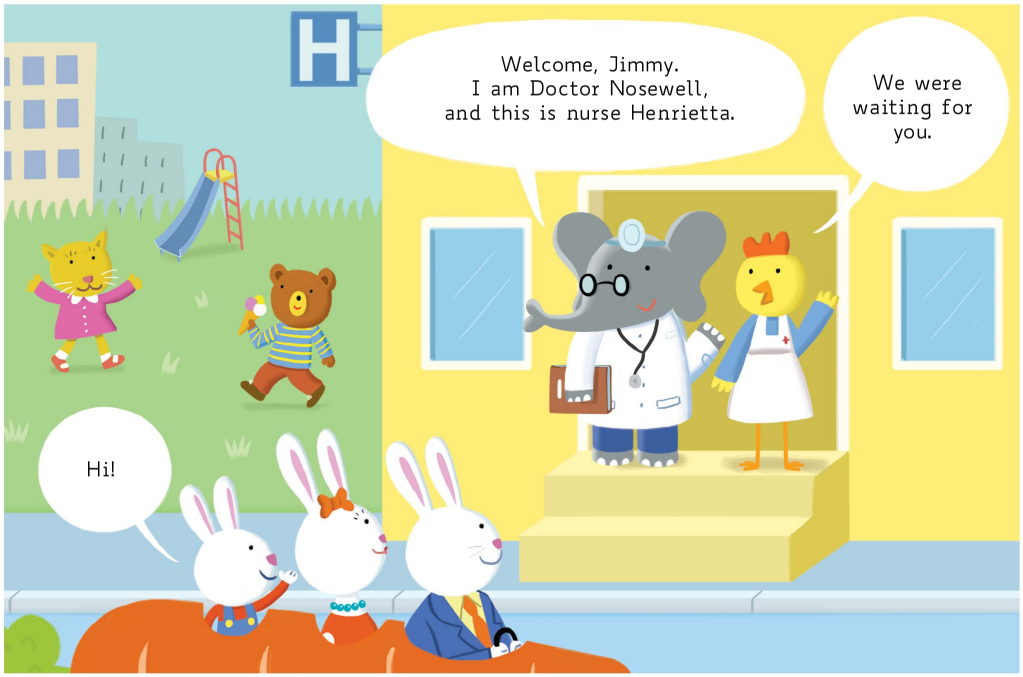

A special visit for Jimmy Bunny
H
GAPP - GAbapentin in Paediatric Pain
GABA-1 0-6 years


In the Bunny home, the brothers and sisters are playing.
But not little Jimmy. For, you see, he is in a lot of pain.


We must do something to help you.
We will take you to the **hospital**.
But I don't want
to go there again...


They have a **medicine**
that might help your pain.
Really?

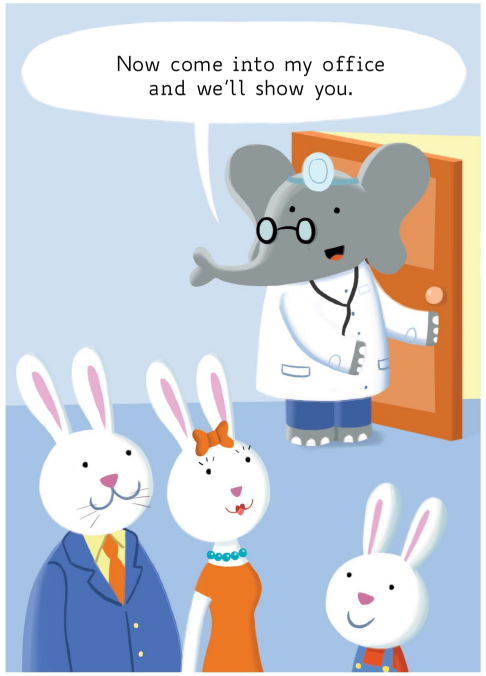

And so the Bunny Family drives to the hospital.
Daddy Bunny steers carefully as the Animaltown cars zip around him, until...


Welcome, Jimmy.
I am Doctor Nosewell,
and this is nurse Henrietta.
We were waiting for you.
Hi!


We have some **medicine** we would like you to try.

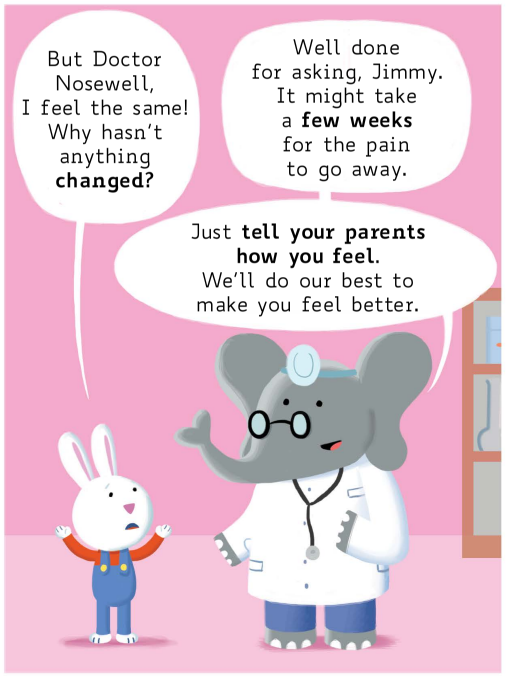

We want to find out **how well** the medicine works to makes the pain better in **children**.


Why are there so many children here?
They feel pain just like you. Some of them decided to try this medicine as well.


Now come into my office and we'll show you.


The first part of the medicine is in **this syrup**.


The second part of the medicine is just a **few little drops**.
Your parents will give you more at home each day.
drip
drip
drip


But Doctor Nosewell, I feel the same! Why hasn't anything **changed?**
Well done for asking, Jimmy. It might take a **few weeks** for the pain to go away.
Just **tell your parents how you feel.** We'll do our best to make you feel better.

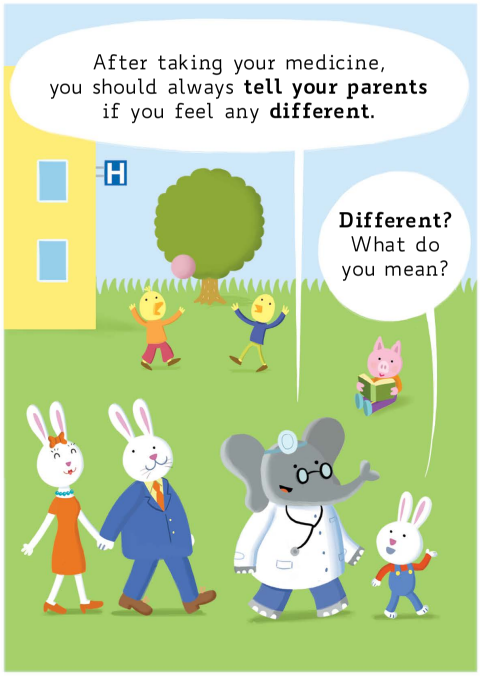

Now I can show you the tests you will need to do after taking the medicine.


This line going up and down shows your heart beating.
Cool!


Oh, no! Why does she have that needle?
She just needs to take a little bit of your blood.
It's really **quite normal** to be frightened, but I'll make you sure you will **hardly feel it**.


Hey, it's not as bad as I expected!


My little hero! You deserve a prize.
Now you will meet other children who are taking this medicine like you.


After taking your medicine, you should always **tell your parents** if you feel any **different.**
Different? What do you mean?


Well, you see, Greta is feeling very **thirsty.**
Paulie finds it hard to **go to the loo.**


Emma is feeling **dizzy.**
And him?


Make way!
pant pant
He is very **agitated.**


And how are you feeling?
It doesn't hurt so much anymore.
Do you want to play with me?


You made a new friend today, Jimmy.


We will see you again in 4 weeks!
Bye-bye! See you soon!

GAPP – GAbapentin in Paediatric Pain

COORDINATOR
Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)

GABA-1 Clinical Trial
EudraCT Number: 2014-004851-30

SPONSOR
PHArmaceutical Research Management SRL (PHARM)

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase III study to compare the pharmacokinetic, 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.

The **Patient Advisory Board**, established in the framework of GAPP Project and coordinated by Rebecca Lundin (PENTA Foundation), has contributed to the **scientific contents**.

COMMUNICATION TEAM
Booklet production coordinator: Maria Cavallo (CVBF)
Content Editor: Leonardo Rizzi
Illustrations and graphics: Piero Corva

Version 1.0 18.02.2016

www.pediatricpain.eu
info@pediatricpain.eu

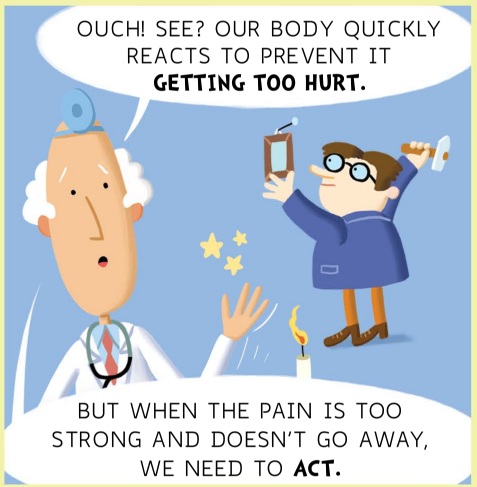
This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602962.

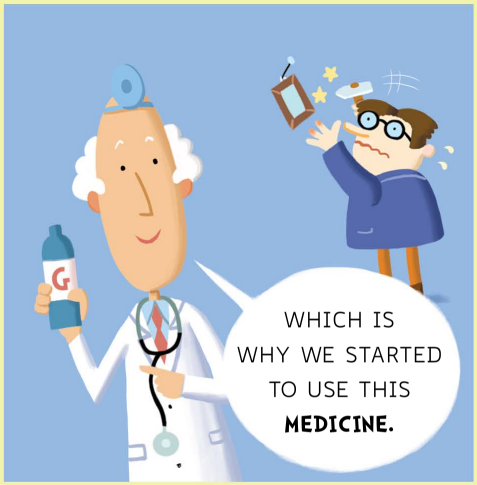
GAPP – GAbapentin in Paediatric Pain

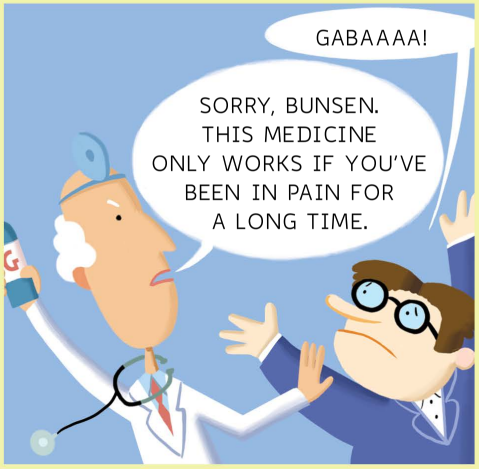
PAINAWAY TO THE RESCUE!

GABA-1 7-11 years

IN DOCTOR PAINAWAY'S STUDY...





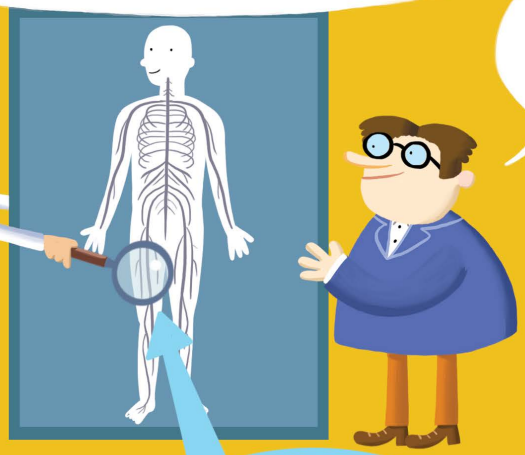


THIS IS WHAT HAPPENS WHEN THE MEDICINE IS TAKING THE PAIN AWAY

THE MEDICINE HAS BEEN USED A LOT, BUT WE DON'T YET KNOW IF IT WILL WORK FOR **CHILDREN LIKE YOU.**

WHICH IS WHY WE'RE ASKING YOU TO TAKE PART TO THE GABA STUDY.

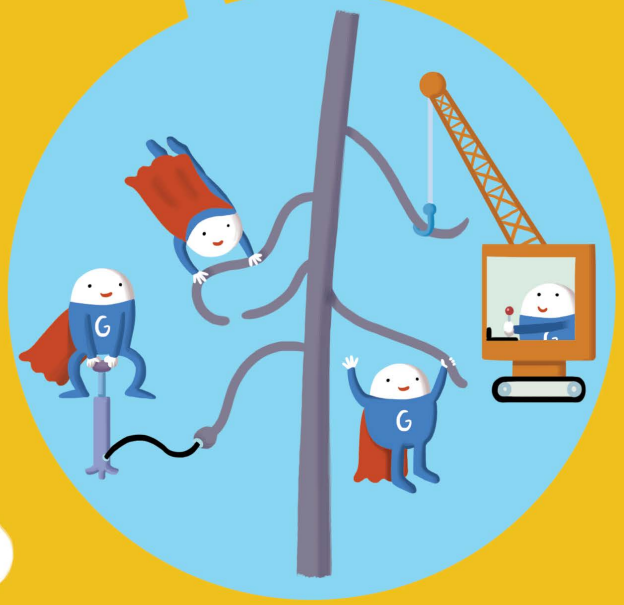
GABA GABA?



YOU DON'T? OH, DEAR...

THE **GABA** STUDY IS JUST A WAY TO UNDERSTAND HOW WELL THE MEDICINE WORKS WITH CHILDREN.

HERE, LET ME SHOW YOU.



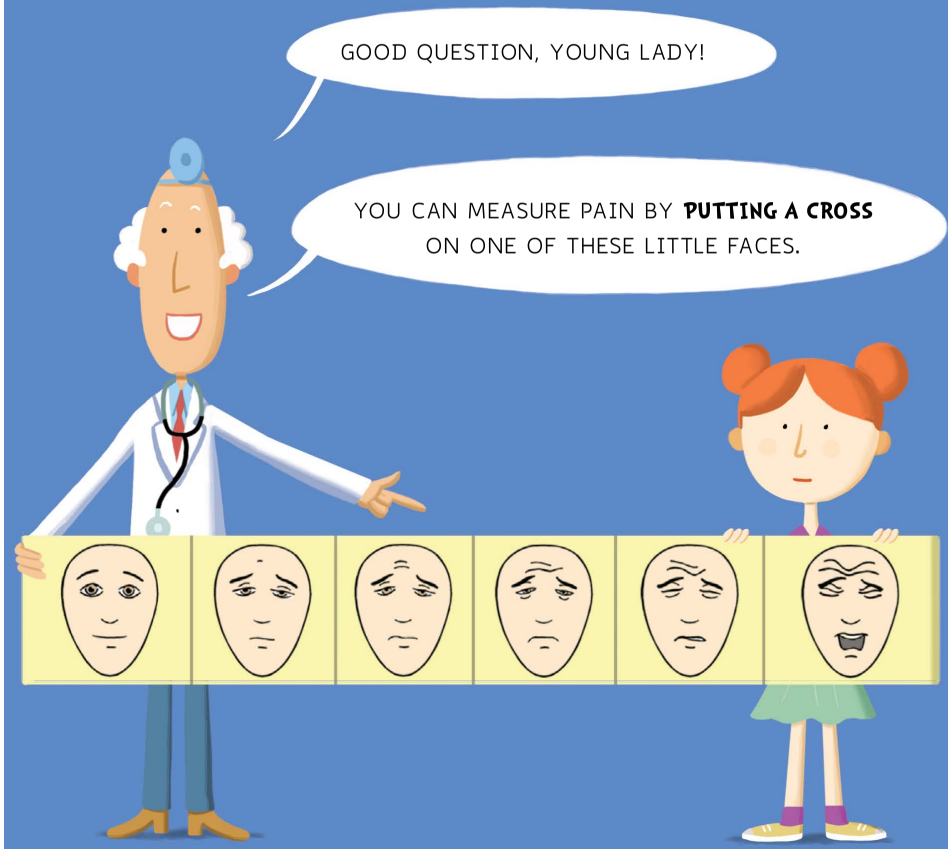
A GROUP OF CHILDREN WILL TAKE SOME **SYRUP** AND A FEW **DROPS** **THREE TIMES A DAY.**

EVERY DAY, THEY WILL TELL THEIR PARENTS **HOW STRONG** THEIR PAIN IS. THIS WILL LET THE DOCTORS KNOW IF THE MEDICINE IS WORKING OR IF THEY NEED MORE.

WE REALLY HOPE THE PAIN WILL GET BETTER, BUT YOUR BODY **TAKES TIME** TO REACT TO THE MEDICINE SO IT CAN TAKE A **COUPLE OF WEEKS.**

SO IT'S IMPORTANT TO ALWAYS **TELL THE TRUTH** ABOUT THE PAIN YOU'RE FEELING.

BUT HOW DO YOU MEASURE PAIN?



IF YOU ARE A BIT OLDER, YOU CAN ALSO MEASURE PAIN BY SAYING HOW MUCH IT HURTS **FROM 0 TO 10.**

0 MEANS YOU'RE FEELING **GREAT**, AND **10** MEANS IT HURTS AN **AWFUL LOT.**

WHAT ELSE WILL HAPPEN IN THE STUDY?

THE STUDY WILL LAST BETWEEN **18 TO 22 WEEKS.**
YOU WILL VISIT THE DOCTOR **12 TIMES,**
EITHER AT THE HOSPITAL OR OVER THE PHONE.

1

THE **FIRST PART** OF THE STUDY WILL BE **1 TO 2 WEEKS** LONG, WITH **2 VISITS.**

ON YOUR FIRST VISIT, THE DOCTOR WILL GIVE YOU A CHECK UP, TAKE SOME OF YOUR BLOOD AND USE A LITTLE MACHINE TO FIND OUT HOW WELL YOUR HEART IS WORKING.

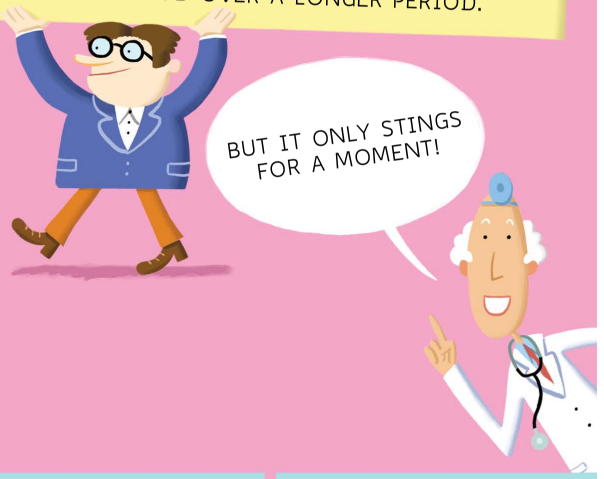
FOR 3 DAYS AFTER THAT YOU WON'T TAKE ANY MEDICINE, EXCEPT FOR FAST PAIN RELIEF MEDICINES IF YOU REALLY NEED THEM.

2

THEN THE **SECOND PART** OF THE STUDY WILL BE **15 WEEKS LONG,** WITH **8 VISITS.**

THE DOCTOR WILL GIVE YOU THE **DROPS** AND **SYRUP** TO TAKE THREE TIMES A DAY.

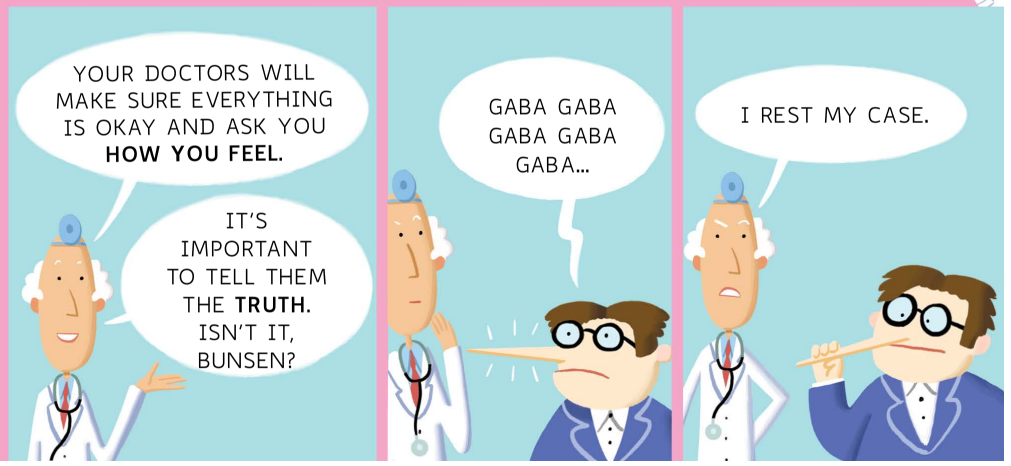
THE DOCTOR WILL ALSO TAKE SOME OF YOUR BLOOD ONCE OR TWICE. ON ONE VISIT, YOU WILL SPEND 4-5 HOURS IN THE HOSPITAL, SO HE WILL TAKE BLOOD OVER A LONGER PERIOD.



3

THE THIRD AND LAST PART OF THE STUDY WILL BE FROM **1 TO 5 WEEKS LONG,** WITH **2 MORE VISITS.**

YOU WILL TAKE LESS AND LESS OF THE MEDICINE AS YOU APPROACH THE END OF THE STUDY.



THESE ARE YOUR 12 VISITS OVER THE 18-22 WEEKS OF THE STUDY.

ARE YOU READY?

SET?

GO!

THE RULES OF OUR STUDY:

- 94 CHILDREN, UNDER 18 YEARS OF AGE
- 18-22 WEEKS IN LENGTH
- 3 DAYS WITH ONLY MEDICINES FOR FAST PAIN RELIEF
- 15-19 WEEKS TAKING THE STUDY MEDICINE
- 2 OR 3 BLOOD SAMPLES

1 2 3 4 5 6 7 8 9 10 11 12

WELL DONE!

CHECK-UP AT HOSPITAL	VISIT OVER THE PHONE
ECG (ELECTROCARDIOGRAM)	BLOOD SAMPLE

GABA!

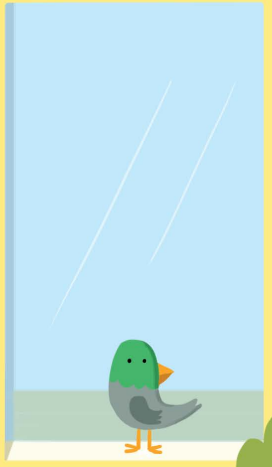
BUNSEN SAYS YOUR DOCTOR MIGHT VISIT YOU A FEW EXTRA TIMES.

AND THAT THIS IS PERFECTLY **NORMAL.**

WHAT TESTS WILL YOU HAVE TO DO?

YOUR DOCTOR WILL EXAMINE YOU TO CHECK YOU'RE OKAY.

YOUR DOCTOR WILL TAKE SOME OF YOUR BLOOD 2 OR 3 TIMES.



YOU MAY FEEL **LESS PAIN** THAN BEFORE.

WHICH MEANS YOU CAN HAVE MORE FUN. MORE GAMES, MORE SCHOOL, MORE EVERYTHING.

WHY SHOULD I TAKE PART?

YOU MAY HAVE **FEWER PROBLEMS** THAN WITH YOUR CURRENT MEDICINES.

YOU MAY **HELP OTHER CHILDREN** WHO ALSO NEED TO TAKE MEDICINE FOR PAIN.

YOUR DOCTOR WILL ALWAYS KEEP AN EYE ON YOU AND MAKE SURE THAT THE STUDY IS NOT DANGEROUS. ALWAYS TELL YOUR PARENTS OR YOUR DOCTOR **HOW YOU ARE FEELING**, SO THAT WE CAN **HELP.**

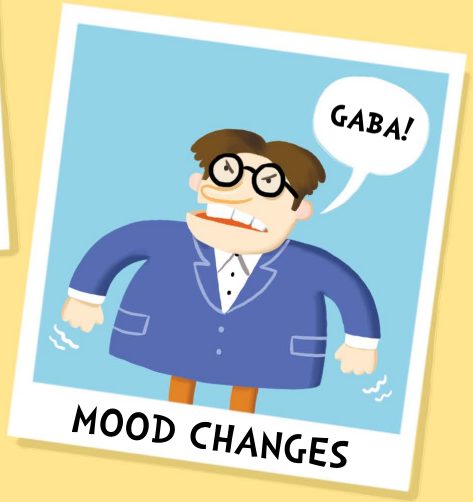
YOU WILL NEED TO **GO TO THE HOSPITAL** 8 TIMES, HAVE A **FEW TESTS** AND TAKE YOUR **MEDICINES**.

AND WHAT ARE THE DOWNSIDES?

IF YOU FEEL TOO MUCH PAIN, YOUR DOCTORS MAY GIVE YOU MORE MEDICINE. BUT IF YOU TAKE A LOT OF THE MEDICINE, YOU MAY GET WHAT WE CALL **SIDE EFFECTS.**

WHAT ARE THESE SIDE EFFECTS?

DRY MOUTH



MOOD CHANGES

SLEEPINESS

DIZZINESS

NAUSEA

TROUBLE GOING TO THE LOO

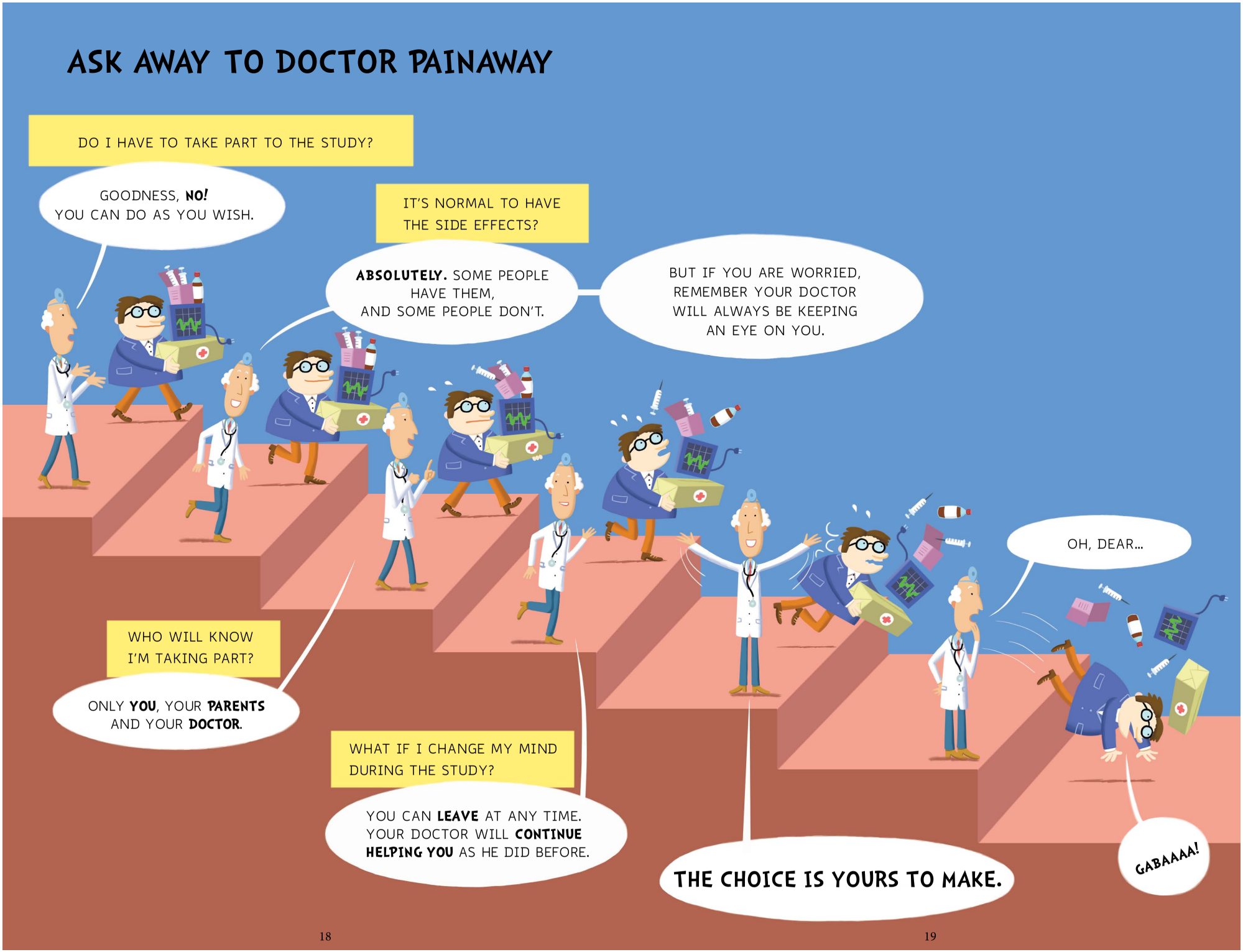
RESTLESSNESS

THAT'S WHY IT'S **IMPORTANT** TO ALWAYS TRUTHFULLY TELL US HOW YOU FEEL.

IF YOU FEEL **ANYTHING STRANGE** HAPPENING, **TELL YOUR PARENTS** OR LET **YOUR DOCTOR** KNOW STRAIGHT AWAY.

YOUR DOCTOR WILL TELL YOU **WHAT TO DO.**

ASK AWAY TO DOCTOR PAINAWAY



GAPP – GAbapentin in Paediatric Pain

COORDINATOR
Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)

GABA-1 Clinical Trial
EudraCT Number: 2014-004851-30

SPONSOR
PHArmaceutical Research Management SRL (PHARM)

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase III study to compare the pharmacokinetic, 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.

The **Patient Advisory Board,** established in the framework of GAPP Project and coordinated by Rebecca Lundin (PENTA Foundation), has contributed to the **scientific contents**.

COMMUNICATION TEAM
Booklet production coordinator: Maria Cavallo (CVBF)
Content Editor: Leonardo Rizzi
Illustrations and graphics: Piero Corva

Version 1.0 18.02.2016

www.pediatricpain.eu
info@pediatricpain.eu

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602962.

FREE TO FLY

LIVING WITHOUT PAIN

GAPP - GAbapentin in Paediatric Pain

GABA-1 12-17 years

GAPP - GAbapentin in Paediatric Pain

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602962.

FREE TO FLY – LIVING WITHOUT PAIN

Chronic pain, which is pain that lasts more than three months, severely limits people's lives. Help can come in the form of drugs to ease the pain, called **analgesics.**

However, the effectiveness of analgesics can decrease over time, leaving some patients without pain relief.

Using several analgesics can help manage chronic pain better. A drug given to adults called **Gabapentin** is safe and can ease certain types of pain, but is **not yet approved** for people **under 18 years of age.**

A group of doctors and researchers have planned a new Gabapentin study for young patients, the **GABA-1 study**. During the study all measures will be taken to ensure **patient's safety.** If the results are positive, Gabapentin will be approved for all children and teenagers who need chronic pain relief.

The information in this booklet will help you decide if you want to take part in the study. Your doctor will answer any questions and help you make your choice, along with your parents.

This choice is yours to make.

If you don't feel like taking part, or you wish to leave the study at any point, **you are free to do so**. Your doctors will **continue to help you** as best they can.

THE GABA-1 STUDY

To verify that Gabapentin is effective and safe in young patients, researchers will **compare it** to another analgesic already used in children called **Tramadol.**

To do so, 94 patients under 18 years of age from Albania, Estonia, France, Germany, Greece, Italy and Netherlands will be randomly **split in two groups.**

Also, you probably noticed that your pain can **increase** or **decrease.** For instance, your mood can affect how you feel, and it's possible that knowing which medicine you're taking could change the way you experience your pain.

How can we avoid this influence?

Easy. **You won't know** which of the two medicines you are taking.

This is how the study works

Over the course of 18-22 weeks, you will take **two different preparations** 3 times a day (morning, afternoon and evening).

One preparation will contain an **analgesic** (Gabapentin or Tramadol). The other will contain a **placebo**, a substance that looks, smells and tastes like a medicine, but is not a medicine at all.

Group 1 will take
a syrup with Gabapentin (analgesic)
and drops with a placebo

Group 2 will take
a syrup with a placebo
and drops with Tramadol (analgesic)

Neither you nor your doctor will know which group you are in. So the way you are feeling won't be influenced by knowing which medicine you are taking.

And yet you will **always be taking a drug** to reduce your pain.

Each day you will measure your pain on a **scale from 0 to 10**. You and your parents will write this number in a diary and eventually give it to your doctor.

You should remember that your pain **may not decrease right away**. It may take a **couple of weeks**.

Gabapentin is very effective in adults, but there is **no absolute certainty** that it works as well in teenagers. Your body might react **differently**.

Being **honest** is crucial. Tell your doctor and your parents exactly how you feel, without diminishing or exaggerating it.

1 Study, 3 Phases

Phase 1

1-2 weeks

2 visits

screening, assessment and interruption of the medicines you are currently taking

Your doctor will **examine you**, give you a few **tests** and **stop the medicines** you are currently taking (except for paracetamol and ibuprofen).

On visit 1, you will be given a **general check-up**, your **heart** will be tested with an ECG, and a sample of your **blood** will be collected. Female patients will have a pregnancy test and will be monitored for pregnancy for the rest of the study.

On visit 2, all participants will be given a **general check-up**, and female patients will also do a **pregnancy test**.

Phase 2

15 weeks

8 visits

treatment

You will start taking the **study medicine.**
Over the course of 3 weeks, the dosage will be raised or adjusted in order to be **more effective.**

The **correct dosage** will then be kept over the course of the following 12 weeks.

You will talk to the doctor 3 times over the **phone.**

The remaining 5 visits will be **in person** at the hospital. During 1 or 2 of these visits, samples of your **blood** will be collected.

Phase 3

1-5 weeks

2 visits

discontinuation of study treatment and final check-up

The doctor will slowly **decrease** your medicine.
This may take up to 4 weeks.

You will have one visit at the **hospital.**

A week after you take your last dose of medicine, you will have one final visit over the **phone.**

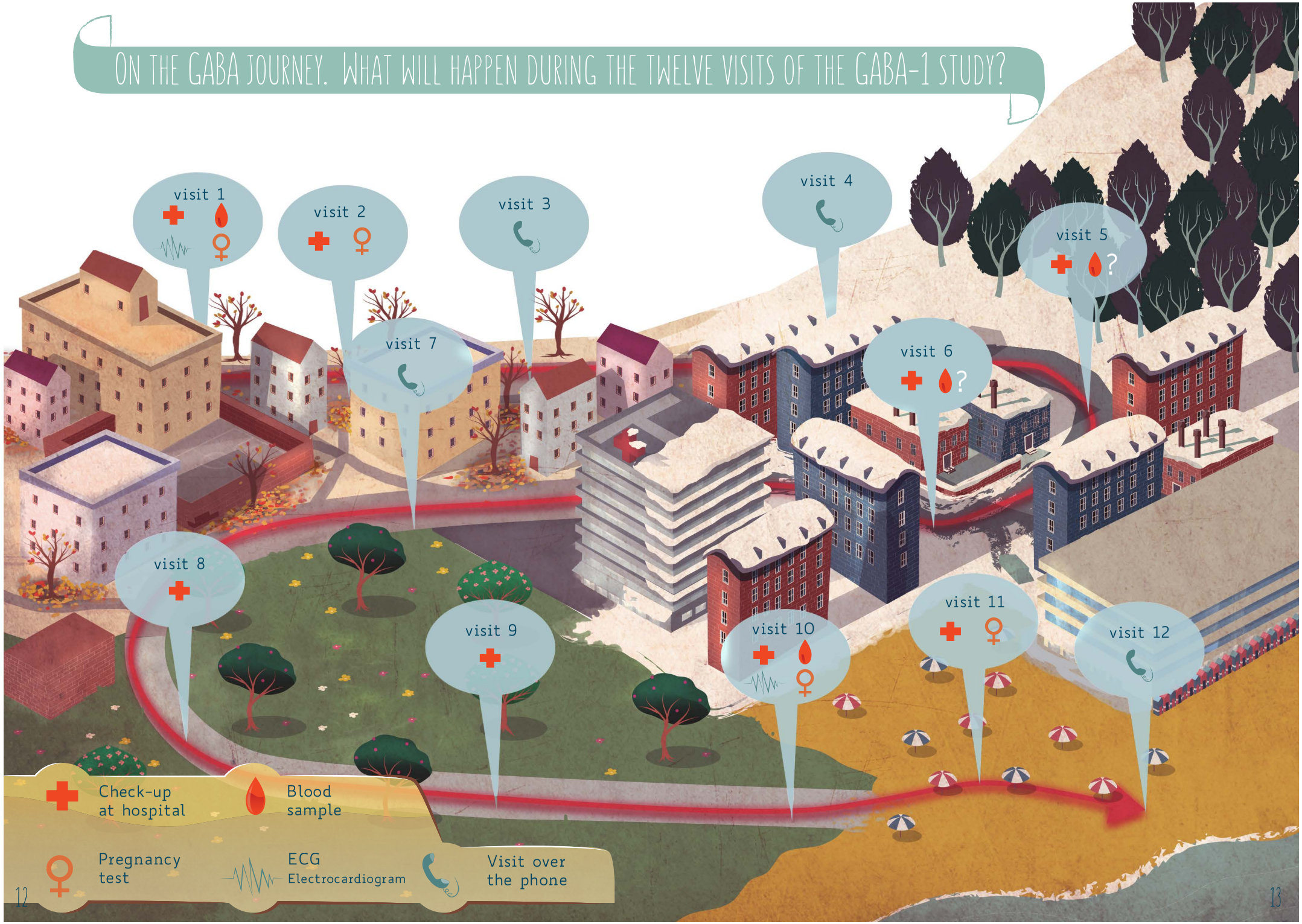
The GABA-1 study will last **between 18 and 22 weeks.**

There are 12 planned visits in total, but your doctor may choose to see you for a few extra visits.

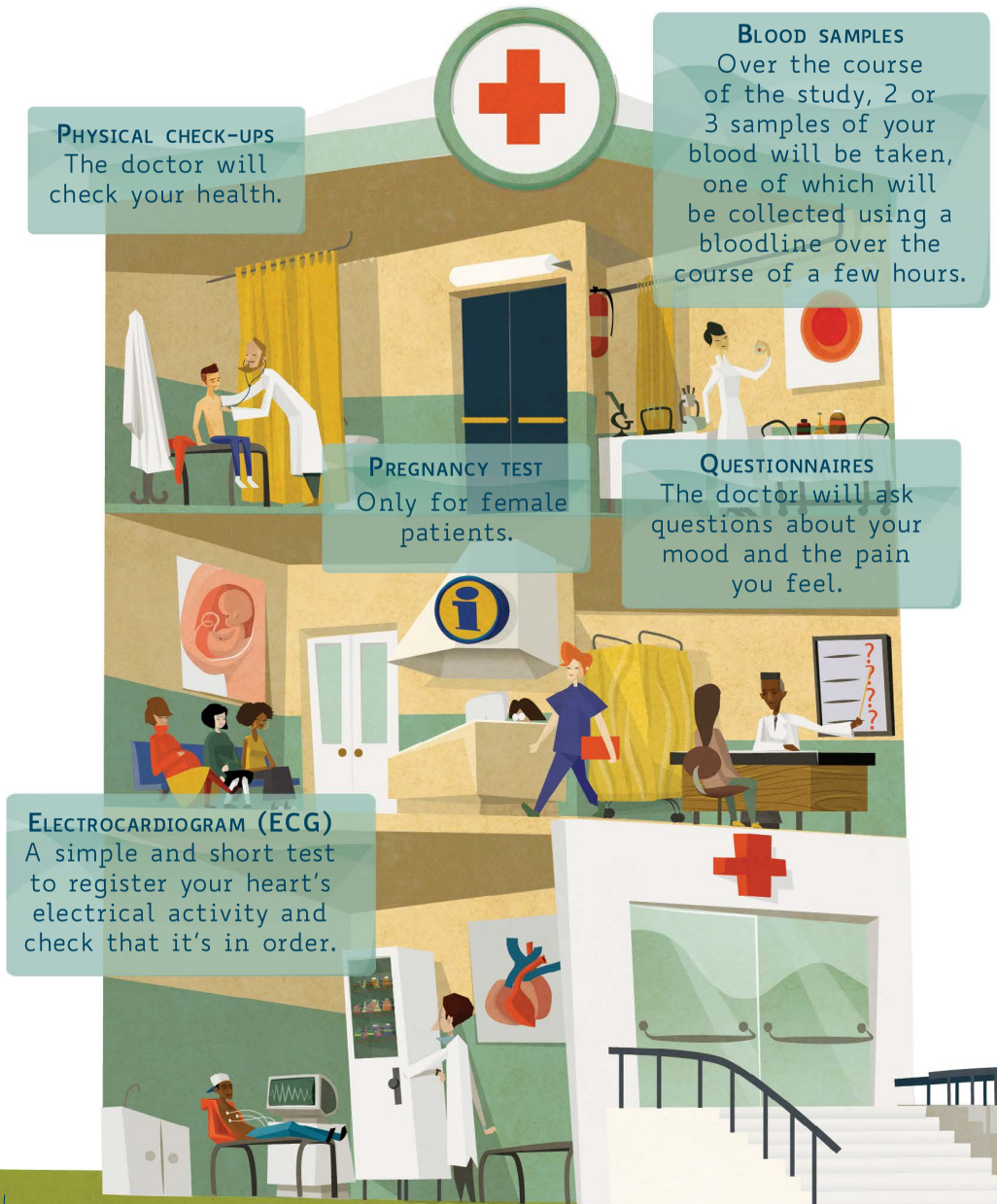
At one of the blood tests, 2 or 3 samples of your blood will be taken, spread over a few hours using a bloodline.

If you feel no reduction in pain while taking the new drugs, **alert your doctor.**
He/she will help you by changing your treatment.

On the GABA journey. What will happen during the twelve visits of the GABA-1 study?



What are the tests in the GABA-1 study?



Benefits

You may feel **less pain** than before or **no pain at all.**

You may have a **better quality of life**, and resume your old activities.

You may have **fewer side effects** with the medicine you're taking.

You will help test Gabapentin and possibly make it available to treat **other young patients like you**.

Risks

The GABA-1 study is not dangerous or harmful. You will be closely monitored by your doctor. Most of your duties will involve taking your medication, attending 12 visits, and taking a few tests.

Among the disadvantages, you may find:

- For the first 3 days of the study, you won't be able to take any of your current **analgesics**. However, you will be able to take **paracetamol or ibuprofen** as recommended by your doctor.

- It may take **a couple of weeks** before the new analgesic becomes effective.

- We do not know if these drugs can be **dangerous** for a foetus, so **pregnancy must be avoided**. Your doctor can tell you more about this.

- The drugs may not work properly or have **undesirable side effects**. Generally, higher dosages can cause worse side effects. **Honesty is crucial** when reporting your pain to your doctor and letting him/her know when it is bearable and when it is not.

Side effects

Every human body is **slightly different**. This is why the medicines studied in GABA-1 may have undesirable side effects on you.

These side effects are **known and reversible**. Some people have them, some don't.

They include:

Dizziness

Constipation

Dry mouth

Nausea

Sleepiness

Restlessness

Mood altered

Anger

Depression

Self-harming

Most of these are not dangerous. However, if you ever experience any of these, **alert your doctor immediately** and he/she will be able to help you.

If you ever experience sad thoughts, or are considering harming yourself, remember that **it might be an effect of the drug.** Reaching out to your **parents and your doctor is very important** and can provide a huge relief. Also, your doctor will be able to help you by lowering your dosage.

Pregnancy

We do not yet know whether the drugs in this study are **dangerous for a foetus** and might cause abnormalities and birth defects. So it is **extremely important to avoid pregnancy**. You can discuss this with your doctor who will be able to advise you about using **contraceptives.**

If you do become **pregnant, or suspect that you are,** alert your **doctor** immediately.

Frequently Asked Questions

- Is the GABA-1 study compulsory?

No. You have **total freedom** to decide whether or not to take part.

- Is the GABA-1 study safe?

Yes. Each patient will be in close contact with his/her doctor, and his/her health will **be monitored constantly.**

- Can I leave the GABA-1 study once I've started it?

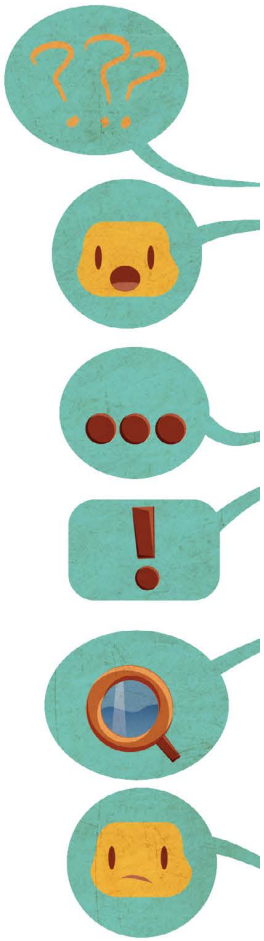
You can leave the study whenever you like. If you don't feel like taking part any longer, tell your doctor. He/she will slowly decrease your medicine and then you will be able to **leave** the GABA-1 study. After this, he/she will continue to treat you with other medications.

- What happens if I miss a dose of syrup or drops or both?

Make sure you take all the doses on schedule. However, if you do miss one, **follow the instructions provided in the diary.**

- What will happen if I get any undesirable side effects?

Alert your doctor immediately. Undesirable side effects are generally not dangerous and go away over time. Your doctor will decide if it's best for you to continue taking part in the study, or to return to your old treatment.



- What happens if I have a lot of pain?

Alert your doctor. He/she will adjust your treatment to help you feel better.

- Beyond my family and my doctor, who will know if I take part in the study?

Nobody. All your details are confidential and won't be given to anybody. You can decide whether to tell your friends or not.

Protection of privacy and personal data

The personal data of study participants will be treated with the strictest confidentiality and will not be disclosed to anyone outside of the doctor and close family members.

By law (European Directive 1995/46/EC on data confidentiality and local applicable laws), all personnel involved in the study have an obligation to use all the means at their disposal to ensure that any information about you and your condition is kept confidential and that nobody can trace you through the information that is collected about you, except your doctor and the people entrusted to take care of you.

The data will be used anonymously to inform the Ethics Committees of each country involved and the national and European health authorities.

You are entitled to know the results of the study, both general ones and those that directly concern you.

Once the study is completed, the results will be made available to the public, published in a medical journal or presented at a scientific conference.

In any case, any information will be disclosed anonymously and no participants in the study will be identifiable.

GAPP - GAbapentin in Paediatric Pain

COORDINATOR
Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)

GABA-1 Clinical Trial
EudraCT Number: 2014-004851-30

SPONSOR
PHArmaceutical Research Management SRL (PHARM)

Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase III study to compare the pharmacokinetic, 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.

The **Patient Advisory Board,** established in the framework of GAPP Project and coordinated by Rebecca Lundin (PENTA Foundation), has contributed to the **scientific contents.**

COMMUNICATION TEAM
Booklet production coordinator: Maria Cavallo (CVBF)
Content Editor: Leonardo Rizzi
Illustrations and graphics: Gianfranco Bonadies

www.pediatricpain.eu
info@pediatricpain.eu

Version 1.0 18.02.2016