

**INFORMATION SHEET AND INFORMED CONSENT FORM**  
**For the purposes of participation of children (between 7 and 13 years of age) in a pediatric study**

**Study Title: "Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chloroprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships ".**



Clinical trials aim at providing new knowledge that may help other people in the future.

**Why are we conducting this Study?**

The purpose of this Study is to evaluate the efficacy of a local anaesthetic. You have been asked to participate in this Study because you parents and doctor think it is useful for you and other children with flat foot or inguinal hernia to evaluate if the local anaesthetic administered you for surgery may avoid the administering of further anaesthetic.



## What happens during the Study?

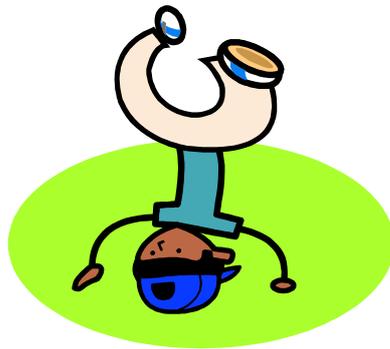


1. During surgery you will be given a local anaesthetic; the Study envisages patients to be allocated to two treatment groups and will be allocated to one of the two groups at random. One group will be administered a higher dose of anaesthetic, the other a lower dose.
2. You will be examined twice over a 3-week period. During Visit 1 the doctor will assess whether you can participate in the Study. During Visit 2 you will undergo surgery. The following day and the in the week after surgery you and your parents will receive a telephone call to know how do you feel.
3. During the visit, the doctor will ask you about your health from the time you have been last visited and measure an electrocardiogram and perform some specific tests for your condition.

We think that you can participate in this Study which will last approximately one month.

### What good things can happen?

Good things can happen to persons who participate in research studies and that may help to feel better. These are the “benefits”. The benefits you may obtain by participating in this Study are that you can go home in short time feeling very little pain after surgery. Furthermore, you may avoid some adverse effects connected with the use of other anaesthetics.



### What discomfort may you feel?



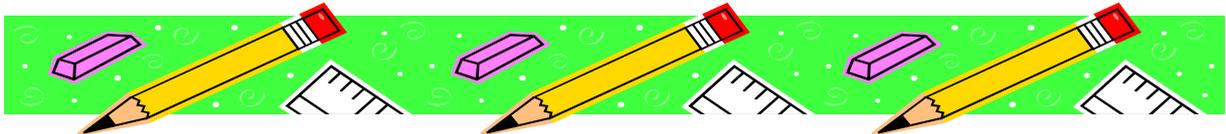
We ask you to tell your doctor if you do not feel well, if you feel pain or nuisance in the zone subjected to surgery or if you hear sounds and voices in a different manner, if you feel an unusual taste in your mouth, if you have a tingling sensation in your hands or feet, if you cannot breath well, if your heartbeat is unusual, if your blood pressure is high or low and if you suffer from convulsions. However, do not worry, if you do not feel well we will help you feel better.

**Any questions?**



If you want, you may ask your doctor at the Hospital to explain you if you do not understand any of these.

**You may decide to participate in the Study with your parents.**



\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Write your name in capital letters if you want to participate in the Study

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Signature of the Investigator who provided the information to the patient

**INFORMATION SHEET AND INFORMED CONSENT FORM**  
**For the purposes of participation of adolescents (between 14 and 17 years of age) in a pediatric study**

**Study Title: “Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chlorprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships”.**

.....(Name of the boy/girl),

As you are aware, your need to undergo surgery because you suffer from flat foot or inguinal hernia.

A medical-scientific research entitled **“Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chlorprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships”** is programmed in this Hospital.

This is a Multi-Center Study, i.e. several Hospitals are involved in Italy and abroad. This Study is financed by “Azienda farmaceutica Sintetica SA”, with headquarters in Mendrisio, Via Penate 5, 6850, (Switzerland) (the “Sponsor”).

**What is the Study about?**

The general purpose of this research study is to evaluate the effectiveness of a drug called Chlorprocaine, a local anaesthetic used for your surgery.

In particular, the research study presented here, aims to obtain data concerning the effectiveness of the above anaesthetic with two different concentrations (1% and 2%) in a pediatric population undergoing surgery for inguinal hernia or flat foot under local anaesthesia through peripheral nerve block, in subjects requiring no additional anaesthesia during surgery.

This anaesthetic with 1% concentration is marketed in Italy in a different kind of regional anaesthesia (spinal anaesthesia), while with the 2% concentration is currently marketed in the United States, Canada and Switzerland as local anaesthetic blocking the peripheral nerve. In Europe, instead, said anaesthetic is not currently marketed for this indication, in pediatric or adult patients.

The block of the peripheral nerve allows administering local anaesthesia at the time of surgery and reduces post-operative pain in infants and children, thereby decreasing the

use of systemic opioids and thus avoiding related adverse effects. Moreover, the use of new technologies, as the advent of ultrasound-guided local anaesthesia which is a well-known and routinely used technique that confirmed the greater efficiency and safety of local anaesthesia, combined with the use of Chloroprocaine, is the most efficient and safe option in local anaesthesia in the pediatric population.

Surgery for inguinal hernia or flat foot have been proposed as model surgical interventions to evaluate the effectiveness and safety of Chloroprocaine in pediatric patients because require short surgical procedures and postoperative pain is mild.

### **What does your participation in the research study entail?**

If you decide to participate in the Study, you will continue to undergo all necessary medical tests, to ensure you the best possible treatment of your condition, regardless of your participation in the study.

This is a prospective, randomized, multi-center, double-blind Study to evaluate the tolerability and safety of a local anaesthetic (Chloroprocaine 1% or 2% according to the different treatment arm) in 174 pediatric patients diagnosed with inguinal hernia or flat foot for whom surgery is envisaged.

A randomized, double-blind, prospective, multi-center clinical study involving two parallel groups of patients means that:

1. A group of patients receives the investigational treatment with Chloroprocaine 1% and the other Chloroprocaine 2%;
2. "Randomized", means that a patient is allocated to one of the treatment groups above according to a random statistical criterion that cannot be influenced by the doctor or the patient conditions; for this study randomization is 1:1, i.e. the number of the patients treated with the two treatments will be the same. Your allocation to the former or latter group of patients is decided via a computerised system that divides the patients taking part in this study among these two groups at random (similarly to the tossing of a coin);
3. "Double blind", means that nor you or your doctor will know which treatment you will receive, until when the clinical study is complete; however, where needed, you can be immediately informed about the treatment received;
4. "Multi-center", means that patients from different Italian and foreign Hospitals are taking part in this study;
5. "Prospective", means that patients will be observed from the date of their enrollment for over a 28-day period, approximately.

These methods are needed in order to avoid wrong assessments and obtain valid results, without entailing an increased risk.

This research study is due to last approximately 28 days and in this hospital, about 25 patients will be selected among all those with your same condition.

If you decide to take part to this study, you will undergo a first physical examination in order to check whether your conditions meet the study criteria. During this visit, the Investigator will collect demographic information (sex, weight, height, BMI) and personal data; the study doctor will measure your blood pressure and heart rate (vital parameters). The Investigator will collect data on your medical history and record the medications taken now and in the past. An electrocardiogram will be performed at the discretion of the Investigator. If you are a girl of child-bearing age potential, a urine pregnancy test will be performed.

If tests confirm that you meet inclusion/exclusion criteria, you will undergo a further medical examination (V2) on the day of surgery during which vital parameters (blood pressure and heart rate) shall be checked again, an electrocardiogram will be performed at the discretion of the Investigator; if you are a girl of child-bearing age potential, a urine pregnancy test will be performed and the medications taken now and in the past shall be recorded and you will be randomized in one of the two treatments arms (Chloroprocaine 1% or Chloroprocaine 2%).

At the time of surgery, parameters will be evaluated and procedures performed, as follows:

- Administration of Midazolam 45 minutes before surgery (according to clinical practice);
- Inhalatory administration of Sevoflurane in order to induce general anaesthesia, according to clinical practice; you will breath autonomously and should not be intubated as part of this pre-operative procedure, if not necessary as an emergency measure;
- Administration of Chloroprocaine 1% or Chloroprocaine 2%;
- Before surgery, a testing of the degree of the sensitivity to pinprick will be carried out (i.e. absence of sensitivity to temperature and sensory perception);
- The degree of motor block will be assessed (assessed in terms of complete block/ reduced muscle motor functionality) according to the Bromage scale (only in the event of flat foot surgery);
- Systemic administration of Fentanil in the event of incomplete sensory block assessed through the above mentioned tests;

- Immediately after the end of surgery, intravenously administration of Paracetamol (15 mg/kg).

After surgery, post-surgical pain intensity will be assessed according to the Wong-Baker scale at varying intervals of time.

Furthermore, possible adverse events will be recorded.

Afterwards, the possibility of discharging you will be examined using the Ped-PASS scale. In the event you can be discharged, the Investigator will prescribe Paracetamol (oral or suppositories) to be administered in case of pain and you will be given a patient diary to be filled in in the days after the surgery.

The day after the surgery and approximately a week after the surgery the Investigator (or a member of the Investigator's staff) will contact you by phone to check the state of your health. During said telephone calls, the drugs you take will be recorded again and questions will be asked about the intensity of the patient's pain according to the Wong-Baker scale. The Investigator will check the information recorded in your diary, the drugs taken after your discharge from hospital because of possible post-operative pain or adverse events.

You are asked to cooperate and carefully follow the instructions provided by the Investigator.

The participation in this Study does not entail extra costs for you.

### **What benefits will you derive from the participation in this Study?**

Chloroprocaine is a short-acting local anaesthetic, characterised by a rapid onset of the anaesthetic effect and providing anaesthesia up to 60 minutes, according to the quantity used and method of administering it. Chloroprocaine is used for short surgery procedures, mainly carried out on an outpatient basis, when a quick recovery and rapid return home are envisaged.

Other clinical trials showed the benefits of anaesthesia through the block of the peripheral nerve in terms of clinical results. In particular, the use of this technique is associated with better post-operative pain control and a reduction in the use of opioids (which in turn minimize the risk of adverse events). Thanks to recent developments of ultrasonic technology, we can obtain an ideal position of the needle with a very low dose of anaesthetic. This makes anaesthesia through the block of the peripheral nerve an ideal option for pediatric patients.

### **What are the risks deriving from the participation in the Study?**

The side effects of local anaesthetics are extremely rare in the pediatric age group. In particular, the block of the peripheral nerve is relatively devoid of complications where local anaesthetics are appropriately administered in terms of dosing and methods of administering them. Potential risks may include local infection, vascular puncture and local bleeding, damages to the peripheral nerve (mild mono-neuropathies), systemic infection and blood coagulation problems. The systemic toxicity of local anaesthetics may vary from mild systemic symptoms (hearing alterations, circulatory numbness, metallic taste and agitation), to events affecting the central nervous system (convulsions, coma, respiratory arrest) and cardiovascular events (hypertension, hypotension, tachycardia, bradycardia, ventricular arrhythmia and cardiac arrest).

Allergic reactions caused by local anaesthetics are uncommon but itching, hives, oedema and tachycardia may occur. Adverse reactions affecting the central nervous system and the cardiovascular are generally dose-related and only occur with high plasma concentrations of local anaesthetics. These reactions are not expected on the basis of this clinical protocol.

An appropriate insurance coverage is provided for any injury caused by taking part in this Study.

In the event new data become available that may change your decision about your participation in the Study (or to continue your participation) you will be promptly informed.

Since the absence of embryo/foetal toxicity effects for this drug is not demonstrated, if you are a girl of childbearing age, you will be required to adjust your behaviour in order to avoid pregnancy during the treatment and at the time of surgery. Likewise, if you are a boy in reproductive age, you will be required to adjust your behaviour in order to avoid procreating during the Study. In the event a pregnancy occurs, you are required to promptly inform the doctor who will set the most appropriate treatment.

Patients of child bearing potential are authorised to take the contraceptive pill.

### **What if you decide not to participate in the Study**

You are free not to participate in the Study. In this case, you will anyway receive all the treatments for your condition without limitation and doctors will continue to treat you paying all due attention.

### **Withdrawal from the Study**

Taking part in this research Study is entirely voluntary and you may decide to withdraw at any time.

Similarly, the research Study may be interrupted if the doctor finds that you did not obtain any benefit or undesirable effects occurred.

In this case, you will be promptly informed about other valid treatments for your condition and the doctor will discuss these treatment options with you.

### **Protection of personal data**

We inform you that the Investigational Site (Hospital) and the Sponsor, that commissioned the above described Study, each as regards its own area of competence and according to the responsibilities required by the standards of Good Clinical Practice (Law Decree 211/2003), Regulation (EU) No. 679/2016 of the European Parliament and of the European Council regarding the protection of natural persons personal data and the free circulation of said data (hereinafter GDPR EU No. 679/2016), by the General Authorisation No. 9/2016 for processing personal data for purposes of scientific research of 15 December 2016, and following the Resolution of the Authority on the “Guidelines concerning the processing of personal data in the conduct of clinical trials on medicinal products” of 24 July 2008 as amended and supplemented, will treat your data, in particular personal health information and other data relating to your lifestyle and origin, only insofar they are indispensable for the purposes and conduction of the Study and for the purposes of pharmacovigilance.

To this end, the above data will be collected by the Investigational Site (Hospital) and transferred to the Sponsor, other persons or external companies acting on their behalf, among which “L.N.Age srl” (Link Neuroscience and Healthcare srl) with headquarters in Rome (Italy), Via Luigi Rizzo 62, 00162.

Furthermore, we inform you that the personal data collected by the Investigator that will take care of you during this Study are indispensable for the conduction of this Study: your refusal to provide the above personal data will preclude your participation in the Study.

The Investigator that will take care of you during this Study will identify you with a code: your data collected during the Study, with the exception of your name, will be forwarded to the Sponsor, recorded, processed and retained together with the above code, date of birth, sex, weight and height. Only the Investigator and authorized parties can connect this code to your name.

The above data, treated mainly using electronic instruments, will be released in a strictly anonymous form, for example, through scientific and statistical publications and scientific conferences. Your participation in the Study also entails that, according to the regulations on clinical trials on medicinal products, the staff of the Sponsor or of the external companies carrying out the monitoring and assessment of the Study, the Ethics Committee and Italian and foreign health authorities can know your data, including also those in the original medical documentation, under conditions ensuring the protection of your identity.

You may exercise the rights pursuant to Article 7 of the Code concerning the protection of Personal Data (for example to gain access to your personal data, to integrate, update and correct them, to oppose to their treatment for legitimate reasons, etc.) by addressing the Trial Center or the Sponsor directly.

You may discontinue your participation in this Study at any time and without giving a reason. If so, the related biological samples will be destroyed. Additional data will not be collected, without prejudice to the use of the data already collected for determining the findings of the research without altering them.

### **Information on the findings of the research study**

At the end of the Study, you may request the general results and, in particular, those concerning you.

### **Contact for further information**

For further information and communications during this Study, please contact the following persons: .....

The Protocol of the Study being proposed was prepared following the EU Guidelines of Good Clinical Practice and the Declaration of Helsinki and it was approved by the Ethics Committee for medicinal products investigation of this Hospital.

You may report the Ethics Committee for medicinal products investigation of this Hospital any facts you deem important concerning the Study in which you are participating.

**INFORMED CONSENT FORM**

**For adolescents (between 14 and 17 years of age)**

I, the undersigned: \_\_\_\_\_

Hereby declare to have obtained by (Doctor's name)\_\_\_\_\_

exhaustive information concerning the request to participate in this research Study, according to the information sheet attached herewith, a copy of which I was given sufficiently in advance in order to make a decision and possible prior consultation with a medical practitioner of my choice.

I also declare that I had the chance to discuss said explanations, ask all the questions I deemed necessary and that I have had these questions answered to my satisfaction. Furthermore, I had the opportunity to obtain detailed information about the Study from a person whom I trust.

Therefore, I hereby voluntarily agree to take part in this Study, having fully understood the meaning of your request and the risks and benefits that may derive from my participation.

I agree to the processing of my personal data for the purposes of this Study and their transfer outside the EU within the limits and at the terms and conditions set forth in the information sheet given to me with this document.

Furthermore, I was informed on my right of free access to the Study documentation (pharma-therapeutic, clinical and scientific documents) and to the opinion given by the Ethics Committee for medicinal products investigation

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Signature of the Doctor/Investigator who provided the information to the patient

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Patient's Signature

**INFORMATION SHEET and PARENT/LEGAL GUARDIAN  
INFORMED CONSENT FORM  
For the purposes of participation in a pediatric study  
(For Parents/Legal Guardian)**

**Study Title: “Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chlorprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships”**

Dear Parents/Legal Guardian of.....,

As you are aware, your child has to undergo surgery because suffers from flat foot/inguinal hernia.

A medical-scientific research entitled **“Randomized, multi-center, double-blind, two-armed, parallel active groups, prospective trial, to evaluate, in pediatric population undergoing 'Calcaneo stop' surgery or Inguinal hernia repair, the efficacy and safety of chlorprocaine 1% and 2% for peripheral nerve block based on concentration–response relationships”** is programmed in this Hospital.

This is a Multi-Center Study, i.e. several Hospitals are involved in Italy and abroad. This Study is financed by “Azienda farmaceutica Sintetica SA”, with headquarters in Mendrisio, Via Penate 5, 6850, (Switzerland) (the “Sponsor”).

**What is the Study about?**

The general purpose of this research study is to evaluate the effectiveness of a drug called Chlorprocaine, a local anaesthetic to be used for your child surgery.

In particular, the research study presented here, aims to obtain data concerning the effectiveness of the above anaesthetic with two different concentrations (1% and 2%) in a pediatric population undergoing surgery for inguinal hernia or flat foot under local anaesthesia through peripheral nerve block, in subjects requiring no additional anaesthesia during surgery.

This anaesthetic with 1% concentration is marketed in Italy for a different kind of regional anaesthesia (spinal anaesthesia), while the 2% concentration is currently marketed in the United States, Canada and Switzerland as local anaesthetic blocking the peripheral nerve. In Europe, instead, said anaesthetic is not currently marketed for this indication, in pediatric or adult patients.

The block of the peripheral nerve allows administering local anaesthesia at the time of surgery and reduces post-operative pain in infants and children, thereby decreasing the use of systemic opioids and thus avoiding related adverse effects. Moreover, the use of new technologies, as the advent of ultrasound-guided local anaesthesia which is a well-known and routinely used technique that confirmed the greater efficiency and safety of local anaesthesia, combined with the use of Chloroprocaine, is the most efficient and safe option in local anaesthesia in the pediatric population.

Surgery for inguinal hernia or flat foot have been proposed as model surgical interventions to evaluate the effectiveness and safety of Chloroprocaine in pediatric patients because require short surgical procedures and postoperative pain is mild.

### **What does the participation of your child to the research study entail?**

If you decide that your child will participate in the Study, your child will continue to undergo all necessary medical tests, to ensure the best possible treatment of your child's condition, regardless of the child participation in the study.

This is a prospective, randomized, multi-center, double-blind Study to evaluate the tolerability and safety of an investigational drug (1% or 2% Chloroprocaine according to the different treatment arm) in 174 pediatric patients diagnosed with inguinal hernia or flat foot.

A randomized, double-blind, prospective, multi-center clinical study involving two parallel groups of patients means that:

1. A group of patients receives the investigational treatment with Chloroprocaine 1% and the other with Chloroprocaine 2%;
2. "Randomized," means that a patient is allocated to one of the treatment groups above according to a random statistical criterion that cannot be influenced by the doctor or the patient conditions; for this study randomization is 1:1, i.e. the number of the patients treated with the two treatments will be the same. Your child allocation to the former or latter group of patients is decided via a computerised system that the patients taking part in this study among these two groups at random (similarly to the tossing of a coin);
3. "Double blind" means that nor you/your child or your doctor will know which treatment you/your child will receive, until when the clinical study is complete; however, where needed, you/your child can be immediately informed about the treatment received;
4. "Multi-center" means that patients from different Italian and foreign Hospitals are taking part in this study;

5. “Prospective” means that patients will be observed from the date of their enrollment for over a 28-day period, approximately.

These methods are needed in order to avoid wrong assessments and obtain valid results, without entailing an increased risk.

This research study is due to last approximately 28 days and in this hospital, about 25 patients will be selected among all those with the same condition suffered by your child.

If you decide your child to take part to this study, your child will undergo a first physical examination in order to check whether your child’s conditions meet the study criteria. During this visit, the Investigator will collect demographic information (sex, weight, height, BMI) and personal data; the study doctor will measure your child’s blood pressure and heart rate (vital parameters). The Investigator will collect data on the child’s medical history and record the medications taken now and in the past. An electrocardiogram will be performed (compulsory for children aged from 0 to 6 months; it will be performed where it is a routine procedure at the investigational site). Furthermore, if your child is of child-bearing potential a urine pregnancy test will be performed).

If tests confirm that your child meets inclusion/exclusion criteria, the child will undergo a further medical examination (V2) on the day of surgery during which vital parameters (blood pressure and heart rate) will be checked again, an electrocardiogram will be performed (compulsory for children aged from 0 to 6 months and during the whole period of the surgery); if your child is of child-bearing potential a urine pregnancy test will be performed; the medications taken now and in the past will be recorded and the child will be randomized in one of the two treatments arms (Chloroprocaine 1% or Chloroprocaine 2%).

At the time of surgery, parameters will be evaluated and procedures performed, as follows:

- Oral administration of Midazolam to patients > 6 months of age 45 minutes before surgery (according to clinical practice);
- Inhalatory administration of Sevoflurane in order to induce general anaesthesia, according to clinical practice; your child will breath autonomously and should not be intubated as part of this pre-operative procedure, if not necessary as an emergency measure;
- Administration of Chloroprocaine 1% or Chloroprocaine 2%;
- Before surgery, a testing of the degree of the sensitivity to pinprick will be carried out (i.e. absence of sensitivity to temperature and sensory perception);

- The degree of motor block will be assessed (assessed in terms of complete block/ /reduced muscle motor functionality) according to the Bromage scale (only in the event of flat foot surgery);
- Systemic administration of Fentanil in the event of incomplete sensory block assessed through the above mentioned tests;
- Immediately after the end of surgery, intravenously administration of Paracetamol (15 mg/kg).

After surgery, post-surgical pain intensity will be assessed at varying intervals of time using different scales and taking into account the age of the patient:

- i. COMFORT scale for patients under 2 months;
- ii. FLACC scale for patients aged between 2 months and 6 years;
- iii. Wong-Baker scale for patients over the age of 6.

Furthermore, possible adverse events will be recorded.

Afterwards, the possibility of discharging your child will be examined using the Ped-PASS scale. In the event your child can be discharged, the Investigator will prescribe Paracetamol (oral or suppositories) to be administered in case of pain and you will be given a patient diary to be filled in in the days after the surgery.

The day after the surgery and approximately a week after the surgery the Investigator (or a member of the Investigator's staff) will contact you by phone to check the state of your child's health. During said telephone calls, the drugs your child is taking will be recorded again and questions will be asked about the intensity of the patient's pain through the FLACC, Wong-Baker or COMFORT scales. The Investigator will check the information recorded in the diary, the drugs taken after the discharge from hospital because of possible post-operative pain or adverse events.

You are asked to cooperate and carefully follow the instructions provided by the Investigator.

The participation in this Study does not entail extra costs for you.

### **What benefits will your child derive from the participation in this Study?**

Chloroprocaine is a short-acting local anaesthetic, characterised by a rapid onset of the anaesthetic effect and providing anaesthesia up to 60 minutes, according to the quantity used and method of administering it. Chloroprocaine is used for short surgery procedures, mainly carried out on an outpatient basis, when a quick recovery and rapid return home are envisaged.

Other clinical trials showed the benefits of anaesthesia through the block of the peripheral nerve in terms of clinical results. In particular, the use of this technique is associated with better post-operative pain control and a reduction in the use of opioids (which in turn minimize the risk of adverse events). Thanks to recent developments of ultrasonic technology, we can obtain an ideal position of the needle with a very low dose of anaesthetic. This makes anaesthesia through the block of the peripheral nerve an ideal option for children.

### **What are the risks deriving from the participation of my child in the Study?**

The side effects of local anaesthetics are extremely rare in the pediatric age group. In particular, the block of the peripheral nerve is relatively devoid of complications where local anaesthetics are appropriately administered in terms of dosing and methods of administering them. Potential risks may include local infection, vascular puncture and local bleeding, damages to the peripheral nerve (mild mono-neuropathies), systemic infection and blood coagulation problems. The systemic toxicity of local anaesthetics may vary from mild systemic symptoms (hearing alterations, circulatory numbness, metallic taste and agitation), to events affecting the central nervous system (convulsions, coma, respiratory arrest) and cardiovascular events (hypertension, hypotension, tachycardia, bradycardia, ventricular arrhythmia and cardiac arrest).

Allergic reactions caused by local anaesthetics are uncommon but itching, hives, oedema and tachycardia may occur. Adverse reactions affecting the central nervous system and the cardiovascular are generally dose-related and only occur with high plasma concentrations of local anaesthetics. These reactions are not expected on the basis of this clinical protocol.

An appropriate insurance coverage is provided for any injury caused by taking part in this Study.

In the event new data become available that may change your decision about the participation of your child in the Study (or continue to participate) you will be promptly informed.

Since the absence of embryo/foetal toxicity effects for this drug is not demonstrated, if your daughter is of childbearing age, she will be required to adjust her behaviour in order to avoid pregnancy during the treatment and at the time of surgery. Likewise, if your son is in reproductive age, he will be required to adjust his behaviour in order to avoid procreating during the Study. In the event a pregnancy occurs, your daughter is required to promptly inform the doctor who will set the most appropriate treatment.

Patients of child bearing potential are authorised to take the contraceptive pill.

### **What if you decide not to make your child participate in the Study**

You are free not to make your child participate in the Study. In this case, your child will anyway receive all the treatments for his/her condition without limitation and doctors will continue to treat your child paying all due attention.

### **Withdrawal from the Study**

Taking part in this research Study is entirely voluntary and you may decide to withdraw your child at any time.

Similarly, the research Study may be interrupted if the doctor finds that your child did not obtain any benefit or undesirable effects occurred.

In this case, you will be promptly informed about other valid treatments for your child's condition and the doctor will discuss these treatment options with you.

### **Protection of personal data**

We inform you that the Investigational Site (Hospital) and the Sponsor, that commissioned the above described Study, each as regards its own area of competence and according to the responsibilities required by the standards of Good Clinical Practice (Law Decree 211/2003), Regulation (EU) No. 679/2016 of the European Parliament and of the European Council regarding the protection of natural persons personal data and the free circulation of said data (hereinafter GDPR EU No. 679/2016), by the General Authorisation No. 9/2016 for processing personal data for purposes of scientific research of 15 December 2016, and following the Resolution of the Authority on the "Guidelines concerning the processing of personal data in the conduct of clinical trials on medicinal products" of 24 July 2008 as amended and supplemented, will treat your child's data, in particular personal health information and other data relating to your child's lifestyle and origin only insofar they are indispensable for the purposes and realization of the Study and for the purposes of pharmacovigilance.

To this end, the above data will be collected by the Investigational Site (Hospital) and transferred to the Sponsor, other persons or external companies acting on their behalf, among which "L.N.Age srl" (Link Neuroscience and Healthcare srl) with headquarters in Rome (Italy), Via Luigi Rizzo 62, 00162.

Furthermore, we inform you that the personal data collected by the Investigator that will take care of your child during this Study are indispensable for the conduction of

this Study: your refusal to provide the above personal data will preclude the participation of your child in the Study.

The Investigator that will take care of your child during this Study will identify him/her with a code: your child's data collected during the Study, with the exception of his/her name, will be forwarded to the Sponsor, recorded, processed and retained together with the above code, date of birth, sex, weight and height. Only the Investigator and authorized parties can connect this code to your child's name.

The above data, treated mainly using electronic instruments, will be released in a strictly anonymous form, for example, through scientific and statistical publications and scientific conferences. The participation of your child in the Study also entails that, according to the regulations on clinical trials on medicinal products, the staff of the Sponsor or of the external companies carrying out the monitoring and assessment of the Study, the Ethics Committee and Italian and foreign health authorities can know the data concerning your child, including also those in the original medical documentation, under conditions ensuring the protection of his/her identity.

You may exercise the rights pursuant to Article 7 of the Code concerning the protection of Personal Data (for example to gain access to your child's personal data, to integrate, update and correct them, to oppose to their treatment for legitimate reasons, etc.) by addressing the Trial Center or the Sponsor directly.

You may discontinue the participation of your child in this Study at any time and without giving a reason. Additional data concerning your child will not be collected, without prejudice to the use of the data already collected for determining the findings of the research without altering them.

### **Information on the findings of the research study**

At the end of the Study, you may request the general results and, in particular, those concerning your child.

### **Contact for further information**

For further information and communications during this Study, please, contact the following persons: .....

The Study Protocol being proposed was prepared following the EU Guidelines of Good Clinical Practice and the Declaration of Helsinki and it was approved by the Ethics Committee for medicinal products investigation of this Hospital.

You may report the Ethics Committee for medicinal products investigation of this Hospital any facts you deem important concerning the Study in which your child is participating.

**INFORMED CONSENT FORM**

**For Parent/Legal Guardian**

I, the undersigned: \_\_\_\_\_

Parent/Legal Guardian of \_\_\_\_\_

Hereby declare to have obtained by (Doctor's name) \_\_\_\_\_

exhaustive information concerning the request to participate in this research Study, according to the information sheet attached herewith, a copy of which I was given sufficiently in advance in order to make a decision and a possible prior consultation with a medical practitioner of my choice.

I also declare that I had the chance to discuss said explanations, ask all the questions I deemed necessary and that I have had these questions answered to my satisfaction. Furthermore, I had the opportunity to obtain detailed information about the Study from a person whom I trust.

Therefore, I hereby voluntarily agree to have my child take part in this Study, having fully understood the meaning of your request and the risks and benefits that may derive from this participation.

I agree to the processing of my child's personal data for the purposes of this Study within the limits and at the terms and conditions set forth in the information sheet given to me with this document.

Furthermore, I was informed on my right of free access to the Study documentation (insurance, clinical and scientific, pharma-therapeutic documents) and to the opinion given by the Ethics Committee for medicinal products investigation

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Signature of the Doctor/Investigator who provided the information to the Parent or Guardian

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Parent or Guardian's Signature

\_\_\_\_\_  
Date/time

\_\_\_\_\_  
Parent or Guardian's Signature

*[In the event the Parent/Guardian cannot sign]*<sup>1</sup>

I the undersigned: \_\_\_\_\_

Hereby confirm to have witnessed the information brief  
between \_\_\_\_\_ (Doctor/ Investigator) and  
Mr./Ms. \_\_\_\_\_ and I confirm that the latter cannot give his/her consent in  
writing.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Independent Witness' Signature

<sup>1</sup> In the event the Parent/Legal Guardian or legal representative cannot read, a witness independent from the Investigator or Sponsor must be present during the whole discussion on the informed consent. The witness must personally date and sign the Informed Consent Form after this form and any other information have been read and explained to the subject or legal guardian and after they have given their verbal consent on the participation to the Study.