SUBJECT INFORMATION AND INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Royal Hospital for Children

Study Title:	A Multi-center, Double-blind, Randomized, Two-Arm, Parallel group, Placebo Controlled Study to Assess the Efficacy and Safety of ELGN-2112 on Intestinal Malabsorption in Preterm Infants
Study Code:	FIT-PIV
Sponsoring Company:	ELGAN Pharma Ltd. https://elganpharma.com/
Principal Investigator:	Dr Judith Simpson/Dr Helen McDevitt 0141 232 7600

Please read this document about a clinical study

We invite your baby to participate in a clinical study looking to understand the effect of a study medicine, ELGN-2112, on babies who are born prematurely. Participation in the study is entirely voluntary. Before taking the decision whether your baby will participate, it's necessary that you understand the reason why the study is conducted and what it will involve for your baby. Please, be sure to read the following information carefully, taking as long as necessary, and discuss the content with anyone you like, for example, with a friend

or a relative or your baby's doctor. Please, don't hesitate to ask questions if any aspect isn't clear or if you need further information. We are available to answer any question that you'd like to ask at any time during the study.

If you decide you would like your baby to participate in the study, you should sign and date this document. You will receive one copy (or a second original) of the document, signed and dated by a member of the research team.

INTRODUCTION

The digestive tract includes the oesophagus (gullet), stomach and intestines and in many preterm infants it is not fully developed when they are first born. These infants may not tolerate milk or absorb nutrients as well as in full-term infants. Your baby is being invited to take part in a clinical study to test the effect of a medicine called ELGN-2112. We want to see if this improves the development of the gut of preterm infants.

Mother's milk contains various components that are vital for a baby's development, and one of them is insulin. Oral consumption of this natural hormone produced by the mother's breast milk has important roles in the development of the infant's intestine. However, the insulin concentration in breast milk normally drops within three days after birth. The activity of insulin is also

destroyed by pasteurisation (heating up) of donated human milk and insulin is also not present in commercial formula milk.

There is good evidence from clinical studies that oral administration of insulin in infants speeds up the development of the gastrointestinal tract, and therefore improves food absorption. This means infants may manage without intravenous nutrition (parenteral nutrition, “outside of the digestive tract”) more quickly. Insulin added to oral milk feeds cannot be absorbed and there is good evidence to show that this insulin added to the milk does not affect the blood sugar level of the infant. Studies already show it is safe and there were no drug-related side effects.

Up to 360 infants will participate in this study across approximately 30 hospitals in the United States, Israel and Europe.

Before you agree your baby can participate in this study, we would like to provide you with this information and will answer any questions you may have. We will explain the study in more detail, and carefully explain any risks and benefits. After this you can decide for your baby to join the study or not. This is known as giving “informed consent”.

Please read this information carefully. Ask the research team any questions you want. You will have up to the 5th day after your baby’s birth to decide if you want to join. There are 2 parts to this document: the information essential to your decision and your written consent.

WHAT IS THE PURPOSE OF THE STUDY?

We wish to test the effect of adding ELGN-2112, an investigational medicinal product on gut function in preterm infants.

ELGN-2112 contains human insulin which is taken by mouth like daily milk feeds, at a dose of 0.3 Insulin Units per Kg per day. This is roughly the same dose as the amount of insulin found in breast milk in the first few days after birth. This dose has been tested in a study including 303 preterm infants.

The insulin in ELGN-2112 was designed as a dry powder that can be mixed with milk, water, or saline. It can then be given orally (by mouth) or with a feeding (gastric) tube along with your baby's milk. The insulin in ELGN-2112 is not absorbed into the blood circulation and only works inside the gut. ELGN-2112 is not currently available or approved for routine use in the NHS and is therefore called an investigational medical product. This study aims to find out if it is helpful for premature babies, however there is no guarantee that your baby will benefit from taking part.

We will measure the time until your baby tolerates full enteral feeding, meaning how long it will take for your baby to be fed only by oral feeding. This study will also look at the number of days to discharge from the hospital, and the number of days to wean-off parenteral nutrition. Parenteral means "outside of the digestive tract", this type of feeding is given directly into your baby's bloodstream intravenously (through a vein).

WHO HAS REVIEWED THE STUDY?

All NHS research is assessed by an independent group of people called a Research Ethics Committee to protect the interests of the people taking part in it. This study has been reviewed by Wales Research Ethics Committee 5.

DOES MY BABY HAVE TO TAKE PART?

No. The choice of whether you would like your baby to take part or not is completely up to you. A doctor or nurse will discuss the study and answer any questions. Your baby's care will not be affected in any way if you decide not to take part. If you decide you want to take part, you can change your mind at any time. You can withdraw from the study without giving a reason and without affecting your baby's treatment.

WHAT WILL HAPPEN IF MY BABY DOES TAKE PART?

If your baby takes part in this study, there will be a Screening Phase, a Treatment Phase, and a Follow Up Phase. Below these phases are described in detail.

Screening Phase:

The research team at your hospital will assess your baby's notes and clinical condition to decide if your baby can participate in this study, the following information would be reviewed.

- Infant's gender
- Date and time of birth
- Week of pregnancy at birth (Gestational age)
- Maternal medications and information about previous pregnancies including drug, smoking and alcohol use.
- Maternal age
- Complications during the pregnancy and mother's conditions that can have an effect on the subject

- Neonatal medications taken since birth (including probiotics)
- Neonatal medical history since birth
- Infant's condition at enrollment (within 24 hours before first dose of study drug), this will be done by a physical exam and collecting vital signs
- Blood tests (blood tests taken as part of routine standard of care within 48 hours of enrolment may be used for screening):
    - FBC (Full Blood Count) ○ Biochemistry – A blood sample will be analysed for body chemistry (sodium, calcium etc.)
- Birth weight, head circumference, APGAR score (condition at birth)
- Parenteral Nutrition use
- Breathing support and oxygen needs
- Enteral feeding (milk feeds)

These assessments are done within 24 hours prior to the first dose of the study drug. If the study doctor decides that your baby is eligible to participate, your baby must receive the first dose of study drug within five days from birth.

Treatment Phase:

If your baby qualifies to be in the study, he/she will be randomized (by chance, like rolling a dice) to one of two study groups:

- ELGN-2112 at a dose of 0.3IU/ kg/ day
- Placebo

The placebo looks like the study drug but does not have any study drug (insulin) ingredients in it.

The active ingredient in ELGN-2112 is Insulin, a natural health-promoting component present in human breast milk. Mixed with the active form of ELGN-2112 is Maltodextrin. Maltodextrin is commonly used as a component in infant formula or breast milk fortifier and dissolves immediately in liquid. In the placebo, there is no study drug, and this is made up of Maltodextrin only.

The group your baby is in will be decided randomly, which is like rolling a dice. Your baby will have a 50% (1 out of 2) chance of being assigned to the ELGN-2112 group or placebo. Neither you nor the study doctor will know if your baby is getting the study drug or placebo. This is the only way we can be sure that we test the effect of the supplement without bias. If required, the doctors can quickly find out which group your baby is in.

Siblings (twins) will be assigned to the same group, so they receive the same treatment (insulin or placebo).

The medicine we are testing (study drug) will be given 4 times a day. The vials' contents will be mixed with some of your baby's nutrition (formula, breast milk), water or saline and given during your baby's feeding. Daily dose will be based on your baby's weight.

Study duration:

Your baby will receive study drug for 28 days, or until discharge from the hospital, whichever comes first, and it will start within 5 days of birth.

If your baby is not ready for discharge from the neonatal unit after 28 days of treatment, an additional evaluation will be performed on day of discharge.

As part of the follow up of your baby's health, we would like to review your baby at corrected age of 3 months, 6 months, 1 year and 2 years. If the standard care of the site is a Follow-up visit on 6 Months, the visit would be recorded as well. Participation in this study is expected to last for a maximum of 27 months.

Treatment period:

During the treatment period from Day 1 to 28 / discharge date, your baby will be monitored but no additional tests will be required. The following information would be recorded:

- Physical examination and vital signs (blood pressure, pulse rate, respiratory rate, , body temperature) – these are collected routinely
- Blood glucose level (tests done as routine will be recorded twice a day in the first 96 hours, then periodically)
- Weight, length, head circumference
- Respiration status
- The investigational medical product (IMP) will be administered with the some of the milk feeding and total daily oral (enteral) and intravenous (parenteral) nutrition information will be recorded in infant medical and nursing records
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- Record of adverse events (any untoward medical occurrence) and/or other medicines used
- Imaging and other relevant diagnostic examinations results may be collected as well
- Eye examinations (as performed in standard-of-care)

The above-described procedures will be performed also in case of Early Discontinuation of study treatment, this will occur if your baby is taken out of the study early or if you decide you no longer wish your baby to participate.

Information on parenteral and enteral feeding, body weight, length, and head circumference will be collected for days 29 and 30, without any drug administration.

If your baby is hospitalised and not discharged home at 40 weeks post-menstrual age, additional information at that time will be documented.

If your baby is discharged after 28 days of treatment, the following tests and information will also be collected for the discharge day. Please ask your study team if you have any questions about the tests listed below.

- Administration and recording of study medication
- Assessments of safety: Physical examination and vital signs
- Glucose monitoring recorded as captured by Standard of Care, this is tested to measure the amount of sugar in your baby's blood
- Blood tests (as performed routinely by the hospital):
    - Complete Blood Count: leucocytes, haemoglobin, haematocrit, platelets

- General chemistry: Urea, creatinine, K, Na, PO4, ionized Ca, triglycerides, glucose

- Adverse events (any untoward medical occurrence)
- Any other medicines your baby has been given, including probiotics.
- In cases of Necrotising Enterocolitis (a type of gut inflammation in preterm infants), additional information will be documented, including imaging and other diagnostic examinations done while your baby is being monitored
- Measurements of how much your baby has been fed orally (by mouth)
- Measurements of how much your baby has been fed intravenously (through a vein)
- Body weight, body length and head circumference
- Respiration support and oxygen level
- Number of days on central venous line support
- Ability to keep body temperature

If your baby is transferred to a different hospital, for example your local hospital, information will be collected until the day of discharge from the hospital they are transferred to. However, they can only receive the study medication whilst at the hospital who recruited them to the study.

Follow up period:

Once your baby completes the treatment phase of the study, he/she will need to return for follow-up visits at 3 Months, 6 Months, 1 year and 2 years old of the corrected age of the infant. You will be asked to bring your baby in for these visits even if your baby stopped the study drug early. After your baby completes the 2 year follow up, you may be contacted again to take part in an additional follow up study. Taking part in this additional study is also optional. The Sponsor will

review all the available data and if required, will make arrangements for follow up study beyond 2 years of corrected age of enrolled babies.

The following tests and information will be collected in the 3-month follow up visit:

- Physical examination and vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and growth (weight, height, head circumference)
- Blood glucose level (will be recorded when performed)
- Respiration status
- Record of adverse events (any untoward medical occurrence) and any medications your baby is taking
- Blood test results as performed as standard of care for the analysis of blood Chemistry and complete blood count will be performed. This can be obtained from last 30 days before visit. If a parameter is not taken as routine, it will not be retaken for the study.
- Enteral feeding and parenteral feeding information
- Eye examinations performed post discharged (as performed in standard-of-care)

  If you and your infant/legal protected are not able to attend the follow-up visit at 3 months corrected age, the site staff will reach out to you via phone call and ask you to provide any information you might have regarding any unwanted events, medications, food consumption, and weight.

The following tests and information will be collected in the 6, 12 and 24 months follow up visits.

- If a 6-month corrected age follow-up visit is not performed per the site standard of-care, the site staff will reach out to you via phone call and ask you to provide any information you might have regarding the below assessments:
- Growth assessment (weight, head circumference, and height)
- Known diagnosed allergies at 1 year and 2 year follow-up visits.

- Diagnoses and evaluation of hospitalisation history
- Your baby will be invited to a development evaluation at 2 years old

Special Considerations:

You should inform your study doctor if your baby is given any new drugs (either prescribed or over-the counter medicines for example Cal-Pol). It is very important the study doctor is aware of all the drugs your baby is taking. **WHAT IF SOMETHING GOES WRONG?**

If your NHS team need to know what group your baby has been allocated to for treatment reasons, they can find this out from the study team.

If at any stage you have any concerns about this study, or the way it has been carried out, you can contact the lead Investigator at your Neonatal Unit, or other research team member or nurse (their names and contact details are provided in this document). They can then discuss any concerns with the team leading the research. You can also speak to any other neonatal consultant at your hospital.

WHAT HAPPENS IN THE EVENT THAT I HAVE A COMPLAINT ABOUT THIS STUDY?

If you wish to complain about any aspect of the way you or your baby has been treated you can discuss with the research team or you may use the normal National Health Service complaints procedures. The Patient Advice and Liaison Service at your hospital will advise you about this.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The sponsor for this study is ELGAN Pharma, Ltd. The study sponsor has responsibility for the study. They will pay the research teams NHS hospital trust for the work involved.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

You will be told of any new information we learn about the study medication, ELGN-2112, during your baby's participation in this study that may affect the health and welfare of your baby, or your willingness to let your baby continue in the study. We will keep up to date with any similar studies and look closely at their results. We will inform you if any important new information becomes available during the study, including information that might make you think again about your involvement in this study.

ARE THERE ANY RISKS, BENEFITS OR SIDE EFFECTS FOR MY BABY?

The sponsor and the investigator hope this product may offer advantages for preterm infants. There is, however, no guarantee that your baby will benefit from taking part in this study, either because the study medication does not improve their condition, or because they receive the placebo.

Insulin formulation (ELGN-2112) might speed the development of his/her digestive tract and improve his/her intestinal absorption; therefore, your baby might be able to consume more oral nutrition sooner, reducing the prematurity-related risks and may provide better growth and better development.

The participation of infants in the study will help us learn whether a new medication may help preterm infants in the future.

No side effects thought to be related to ELGN-2112 have been reported in infants treated with the medication so far. Four clinical studies have been performed with this study medication without any detected reason for concern, the most recent including 303 preterm infants. In these studies, no baby has experienced a change in their blood sugar levels and no babies have shown any sign that it has affected the way their body processes insulin. In addition, two other clinical studies with a much higher concentration of insulin in the milk feeding didn't result in changes in blood sugar. Unknown risks and discomforts could appear. It is therefore very important that any new health problem is reported to your study research team, regardless of whether or not you think it has to do with the study.

As part of checking your baby's health, blood is taken which may be associated with discomfort. However, where possible we will time these blood tests at the same time as any routine blood tests are needed.

There may be other potential risks or side effects associated with ELGN-2112 that we are not yet aware of.

WHAT ALTERNATIVE TREATMENT IS AVAILABLE FOR MY BABY?

To the best of the Elgan Pharma, Ltd.'s knowledge, there are no alternative medicines to improve gastrointestinal tract maturity in preterm infants. If your baby does not participate in the study, he/she will receive standard nutrition support. The only difference if your baby participates in the study is the addition of the medicine we are testing, ELGN-2112, or placebo to the standard milk feeding.

WHAT ARE THE COSTS INVOLVED IN TAKING PART IN THIS STUDY?

There will not be any cost to you if your baby participates in this study. All tests beyond normal standard of care (e.g. medical history and physical examinations done by the study doctor, blood tests, study specific procedures) and study drug will be provided at no cost.

WILL I BE PAID IF MY BABY TAKES PART IN THIS STUDY?

You will not be given any incentives to have your baby participate in this study. For follow up visits, reasonable travel expenses shall be reimbursed. You may opt in to be reimbursed through a company appointed by the Sponsor to manage this service (Scout Clinical). You will need to sign a separate consent form to use this service.

IS MY DECISION FOR MY BABY TO PARTICIPATE VOLUNTARY?

Whether your baby takes part in this study is completely your decision. They do not have to take part if you do not want them to.

CAN I WITHDRAW MY BABY FROM THE STUDY?

You may choose to stop your baby's participation in this study and withdraw at any time. Please talk to your study doctor first about this decision to help ensure your baby's safe withdrawal from the study. If you decide to withdraw your baby, the information already collected about him/her may still be used in the study, but additional information will not be collected, unless you give us permission, and study medication will no longer be given. Your decision to stop your baby's participation will have no effect on the access or quality of medical care she/he will receive.

Your baby may be withdrawn from the study without your consent, and therefore stop receiving the study medication, by the study doctor or study sponsor (ELGAN Pharma, Ltd.) at any time. Some of the reasons your infant could be withdrawn are:

- The study doctor feels it is not in your baby's best interest to continue
- Your baby experiences a side effect or develops a medical condition during the study that the study doctor thinks necessitate stopping treatment on the study
- The entire study is stopped

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED ABOUT ME AND MY BABY DURING THE STUDY?

If you do provide permission for your baby to take part, we will collect personal information about you and your baby. You can find out how research uses NHS patient data by reading:

Every effort will be made to keep the information we learn about your baby private. Study personnel, the study sponsor (ELGAN Pharma, Ltd.) and its representatives and agents, the Food and Drug Administration (FDA), the MHRA (Medicines Healthcare Regulatory Authority) and other regulatory authorities, the Ethics Committee and any other necessary site organisation(s) may review your baby's study records, to ensure the study has been conducted appropriately. If study results are published, your baby's name will not be used. Study data may be submitted to regulatory agencies in other countries, but your baby will not be identified.

A description of this clinical trial will be available on the following website, http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Please refer to the following website which contains the most up to date information on how your data is used in research, provided by the UK Health Research Authority –

https://www.hra.nhs.uk/planning-and-improving-research/policies-standardslegislation/data-protection-and-information-governance/gdprguidance/templates/template-wording-for-generic-information-document/

The information collected for this study will be kept indefinitely. While this study is ongoing, you may not have access to the research information, but you may request it after the research is complete.

HOW WILL INFORMATION ABOUT ME AND MY BABY BE USED?

We would like to use information about you and your baby during this study. We will need to use information from you and your baby's medical hospital records to do this research project.

This information will include:

- The NHS number of you and your baby;
- The name and date of birth of you and your baby;
- The contact details for you and your baby including your postal address, email address, home telephone number and mobile telephone number;
- NHS data about your baby's birth, and their feeding and health on the Neonatal Unit will be collected
- NHS data about your baby's feeding and health and any health conditions will be collected. Authorised people will also use this information to check your records and make sure that the research is being done properly – this includes authorised staff from the research team, regulatory bodies, and your local hospital.

Your GP will also be told that your baby is taking part in this study should your baby be registered at a GP.

We will only collect and use information that we need for the research study. We will only let people who need to know your name and contact details have this information.

Everyone involved in this study will keep your data safe and secure, and follow all privacy rules, including the General Data Protection Regulation (GDPR) and the Data Protection Act in its current form.

WHAT ARE MY CHOICES ABOUT HOW MY INFORMATION IS USED?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your child's health from central NHS records/ your hospital. If you do not want this to happen, tell us and we will stop.

At the end of the study, the research team will keep identifiable information about you and your baby from this study for 25 years after the study has finished in case we need to check it.

WHERE CAN I FIND OUT MORE ABOUT HOW MY INFORMATION IS USED?

You can find out more about how we use your information

- by asking one of the research team
- by sending an email to the hospital Data Protection Officer ggc.dataprotection.generic@nhs.scot

WHO CAN I CONTACT IF I HAVE A COMPLAINT ABOUT HOW MY DATA HAS BEEN COLLECTED/USED/STORED?

If you are not happy with their response or believe the research team are processing your data in a way that is not right or lawful, you can discuss with the research team, with the Patient Advice and Liaison Service (PALS) team at your local hospital.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

At the end of the study, the results will be published in medical journals and presented at scientific conferences. It is hoped that the results from this study will help babies in the future.

WHAT HAPPENS IN THE EVENT THAT I HAVE A COMPLAINT ABOUT THIS STUDY?

If you wish to complain about any aspect of the way you or your baby has been treated you can discuss with the research team or you may use the normal National Health Service complaints procedures. The Patient Advice and Liaison Service at your hospital will advise you about this.

WHO SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

If you have questions about this study or need to report any problems, side effects, or injuries, please call Dr Judith Simpson/Dr Helen McDevitt at 0141 232 7600 or via email at GGC.obstetric.gcrf@nhs.scot

You may also contact any member of the research team on 0141 232 7600.

You may also contact the Patient Advice and Support Service on Helpline telephone number: 0800 917 2127

For more information about this service and to find your local bureau, including contact details: https://www.cas.org.uk/pass

You may discuss your baby's rights as a research participant with the Wales Research Ethics Committee 5 at 02922 940910. The Ethics Committee is a group of people not involved with this study who have reviewed the study to protect study participant rights.

You will receive a signed copy of this consent document after it has been signed.

Statement of Participation

By signing this form, you declare that:

Please Initial Box

- I have read and understood the information contained in this consent form, and had an opportunity to ask the research team questions about the nature and procedures of the study. ☐

- I have had sufficient time to reflect and the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my infant to participate as a participant in this study. ☐

- I consent to being contacted in the future regarding the additional follow up study ☐

Print Name of Participant: _____

Name of Parent/Legal Guardian 1

_____

Signature

Date: _____ / _____ / _____ **Time:** _____:_____

Day Month Year hour min

Relationship to Patient: _____
Name of Parent/Legal Guardian 2 *(Optional)*

_____

Signature

Date: _____ / _____ / _____ **Time:** _____:_____

Day Month Year hour min

Relationship to Patient: _____

I confirm that the parent/legal guardian was given the opportunity to ask questions about the study, and all the questions asked by the parent/legal guardian have been answered correctly and to the best of my ability. I confirm that consent has been given freely and voluntarily.

A copy of this form has been provided to the participant's parent/legal guardian.

Print Name of Person Conducting Consent_____

Signature of Person Conducting Consent_____

Date _____