PARENTAL PERMISSION FOR CHILD TO PARTICIPATE IN A RESEARCH STUDY AT CHILDREN'S MERCY HOSPITALS
Tirosint®-SOL T21 Study
Use of Liquid Stable Levothyroxine in Trisomy 21 Pediatric Patients

SUMMARY (Details of this information are in the sections below)

We are asking your child to be in this research study. Being in a research study is completely voluntary, and your choice to participate or not participate will not affect your child's regular medical care. This research study is being done to see if your child reacts differently to a liquid form of levothyroxine, called Tirosint®-SOL, compared to the levothyroxine pill used to treat hypothyroidism in children with Trisomy 21 and hypothyroidism. We will use a visual faces scale called the CareCAT tool to evaluate if your child prefers one form of medication more than the other and if your child is more likely to take the liquid versus the tablet.

The following things are parts of this study: your child will take either liquid Tirosint®-SOL or a levothyroxine pill for 8 weeks. After 8 weeks of taking one of these medicines, your child will switch to taking the other for 8 weeks. The treatment forms your child starts on will be selected randomly like flipping a coin. You will answer survey questions, use a faces scale to tell us how well your child took the medicine, video your child taking the medication twice during the study, and keep track of the days your child took medicine. Your child's medical chart will be reviewed, and we will measure your child's height, weight, and head circumference. We will also collect 2 blood samples from your child during the study. Being in this study will include three visits to the Children's Mercy Hospital Endocrine Clinic. Your child's first visit can happen at the same time as your child's regular clinic visit. Your child will be in this study for about 4 months.

The biggest risk from being in this study is that your child could absorb more of the liquid drug than they do the pill which could require your child's doctor to change the dose of thyroid medication they are taking.

There may be no direct benefit of being in this study. Although, your child may benefit from being able to take their medication better based on the CareCAT survey tool. Your child may also have improved thyroid labs from more consistent dosing of medication. Being in this study, your child may help other children with Down Syndrome and hypothyroidism in the future.

There will be no cost to you or your child for being in this study. Instead of being in this study, your child can continue to get regular medical care.

WHO IS DOING THIS STUDY?

A study team led by Dr. Max Feldt is doing this study. Other health care professionals may help them.

IBSA Pharma is working with Children's Mercy Hospital to do this research study. Funding for this study comes from the IBSA Pharma. The study team will not receive any personal payment because of your decision.

We are asking your child to be a part of this research study. Please read the information below and ask questions about anything that you do not understand before you make a choice.

WHY IS THIS STUDY BEING DONE?

Hypothyroidism is a common disorder in children with Trisomy 21 (T21), also known as Down Syndrome. The purpose of this research study to see if the body reacts differently to a liquid form of levothyroxine called Tirosint®-SOL than it does the levothyroxine pill. We also want to know if you and your child like one more than the other and if your child is more likely to take the liquid drug versus the pill.

Tirosint-SOL® and Levothyroxine are both used as a replacement hormone that is normally produced by the thyroid. Both drugs are approved by the United States Food and Drug Administration (FDA) for the treatment of hypothyroidism in adults and children. There have been no studies testing the response of children with Down

Syndrome (T21) to Tirosint-SOL®. The study sponsor would like to learn if the liquid drug is more tolerable for children with Down Syndrome (T21).

WHO CAN BE IN THIS STUDY?

We are asking your child to be a part of this research study because he or she has been diagnosed with Trisomy 21 (T21) and hypothyroidism.

Up to 22 children, ages 2 months to less than 10 years will be in this study.

WHAT WILL HAPPEN TO MY CHILD IN THIS STUDY?

Before we do any study procedures, we will ask you to sign this permission form. A copy of the signed form will be given to you.

Being in this study involves three in-person visits (the first visit may happen virtually) and two phone calls, with some things you will do at home.

The study details are below:

Enrollment Visit (Endocrine Clinic or Virtual):

Medical History: Your child's medical history and use of medications and supplements will be reviewed and documented. You will also be asked about the use of non-prescription and herbal remedies. We will also review your child's medical record.

Nutrition: If your child is 1 year or less, we will ask questions about whether your child is breast fed or formula fed. If your child is formula fed, we will ask if the formula includes soy or cow's milk.

Demographic Data: Demographic data including your child's age, race, and ethnicity will be obtained, as well as your home mailing address and email address.

Measurements: Your child's height, weight, and head circumference will be collected from his/her most recent clinic visit.

Lab tests: We will review and record lab results from your child's most recent clinic visit.

Study Medicine: You will be given either Tirosint®-SOL liquid or levothyroxine pills to give to your child daily for the next 8 weeks. The dose that your child receives will be the same dose that your child's doctor prescribes. Your child will need to take this medicine once a day for 8 weeks. We will know which medicine (liquid or tablet) your child will be on first after the first visit. Whether your child receives liquid or tablet first will be decided randomly like flipping a coin. There is an equal chance of your child being assigned to either group. You or your child's doctor cannot decide which group your child will be assigned to. The study medicine will be mailed to your home after the doctor looks at your child's lab results to make sure we give your child the correct dose of medicine.

Medication Diary: You will be given a diary to record the day each dose of medicine is given to your child for the next 8 weeks.

PQL Survey: You will complete a Pediatric Quality of Life (PQL) survey, which tells us how taking medication affects you and your child. A link to the survey will be emailed to you for you to complete at home.

CareCAT Survey Tool: You will be trained how to complete an electronic survey which will be emailed to you each day for the 1st week your child starts taking the medication. The CareCAT Survey Tool is a simple faces scale that lets you answer how your child tolerates taking the medication. See example below.

CareCAT Example:

Week 1/Days 1-7 (At Home):

Study Medicine: You will give your child one dose, one time each day.

Video: When your child takes their first dose, you will video them taking that dose. You will email that video to the research team at **tirostudy@cmh.edu,** or you may be asked to upload this through an internet link that the study team emails you.

Medication Diary: You will record each day your child takes his/her medicine on a piece of paper provided by the study team.

CareCAT Survey: You will receive an email once a day for the first week your child is on the study medicine. This email will include a link to a survey that will include a faces scale called the CareCAT tool. You will indicate whether your child swallows the medicine well, refuses the medicine, spits up the medicine, vomits, or does not take the medicine using the provided tool. You may also complete this information by using a paper form provided by the study team if unable to do so online.

Phone Call: A member of the study team will contact you about 3 days after your child starts the medication to answer any questions you may have, to ensure you are able to send or upload the video and complete the survey.

Week 2-8/Days 8-56 (At Home):

Study Medicine: You will give your child one dose, one time a day.

Medication Diary: You will record each day your child takes his/her medicine on a piece of paper provided by the study team.

Week 8/Day 56 +/- 4 days (Endocrine Clinic):

Medical History: Your child's medical history and use of medications and supplements will be reviewed and documented. You will also be asked about the use of non-prescription and herbal remedies.

Nutrition: If your child is 1 year or less, we will ask questions about whether your child is breast fed or formula fed. If your child is formula fed, we will ask if the formula includes soy or cow's milk.

Measurements: Your child's height, weight, and head circumference will be measured. Head circumference will only be measured if your child is less than 2 years old.

Study Medicine: We will collect any unused medication you have from the previous 8 weeks. You may return the medication at this visit, or we will provide means for you to ship the medication to us. You will be given the other form of medicine at this time. The dose that your child receives will be the same dose that your child's doctor prescribes. Your child will need to take this medicine once a day for 8 weeks. The study medicine will be mailed to your home after the doctor looks at your child's lab results to make sure we give your child the correct dose of medicine.

Blood collection for lab tests: A blood sample of ½ a teaspoon will be collected from your child for thyroid lab tests (TSH & FT4) twice. A total of 1 teaspoon (5mL) will be collected during the study. Blood will be taken by needle stick from a vein in your child. Numbing cream will be used to help ease the pain of needle sticks. You will be given your child's results of their thyroid labs (TSH & FT4) done for this research study.

Medication Diary: We will collect your first medication diary, and you will be given a new diary to record the day each dose of medicine is given to your child for the next 8 weeks.

PQL Survey: You will complete a Pediatric Quality of Life (PQL) survey, which tells us how taking medication affects you and your child. A link to the survey will be emailed to you for you to complete at home. You will also receive a paper form of this survey if you are unable to do so online.

CareCAT Survey: We will confirm your email and send a link for the CareCAT survey for you to start when your child starts the medication.

Week 9/Days 57-63 (At Home):

Study Medicine: You will give your child one dose, one time each day.

Video: When your child takes their first dose, you will video them taking that dose. You will email that video to the research team at **tirostudy@cmh.edu,** or you may be asked to upload this through an internet link that the study team emails you.

Medication Diary: You will record each day your child takes his/her medicine on a piece of paper provided by the

study team.

CareCAT Survey: You will receive an email once a day for the first week your child is on the study medicine. This email will include a link to a survey that will include a faces scale called the CareCAT tool. You will indicate whether your child swallows the medicine well, refuses the medicine, spits up the medicine, vomits, or does not take the medicine using the provided tool. You may also complete this information by using a paper form provided by the study team if unable to do so online.

Phone Call: A member of the study team will contact you about 3 days after your child starts the medication to answer any questions you may have, to ensure you are able to send or upload the video and complete the survey.

Weeks 10-16/Days 64-112 (At Home):

Study Medicine: You will give your child one dose, one time a day.

Medication Diary: You will record each day your child takes his/her medicine on a piece of paper provided by the study team.

Week 16/Day 112 +/- 4 days (Endocrine Clinic):

Medical History: Your child's medical history and use of medications and supplements will be reviewed and documented. You will also be asked about the use of non-prescription and herbal remedies.

Nutrition: If your child is 1 year or less, we will ask questions about whether your child is breast fed or formula fed. If your child is formula fed, we will ask if the formula includes soy or cow's milk.

Measurements: Your child's height, weight, and head circumference will be measured. Head circumference will only be measured if your child is less than 2 years old.

Medication Diary: We will collect the completed medication diary from you.

Study Medicine: We will collect any unused medication you have from the previous 8 weeks. You may return the medication at this visit, or we will provide means for you to ship the medication to us. We will make sure your child has a new prescription for continuing his/her medicine at home. The study will no longer provide your child's medication after this visit.

Blood collection for lab tests: A blood sample of ½ a teaspoon will be collected from your child for thyroid lab tests (TSH & FT4) twice. A total of 1 teaspoon (5mL) will be collected during the study. Blood will be taken by needle stick from a vein in your child. Numbing cream will be used to help ease the pain of needle sticks. You will be given your child's results of their thyroid labs (TSH & FT4) done for this research study.

Table of Study Events:

Procedures	Enrollment/Baseline Visit 1	Dosing Week 1[b] Days 1-7	Study Visit 2[c] Day 3 +/-1 day	Dosing Weeks 2-8 Days 8-56	Study Visit 3, Week 8 Day 56 +/- 4 days	Dosing Week 9[b] Days 63-70	Study Visit 4[c] Day 65 +/-1 1 day	Dosing Weeks 10-16 Dyas 71-112	Study Visit 5 Day 112 +/- 4 days
Obtain permission/assent or consent	X								
Demographics	X								
Medical history	X								
Randomization	X								
Dispense study intervention	X				X				
Concomitant medication review	X		X		X		X		X
Head Circumference	X				X				X
Height	X				X				X
Weight	X				X				X
Labs (TSH & FT4)	X				X				X
Adverse event review			X		X		X		X
CareCAT Survey[d]		X				X			
Dosing Video[e]		X				X			
PQL Survey	X				X				
Medication Administration Log		X		X		X		X	

a: Head circumference, height, and weight and labs from enrollment/baseline visit will be collected from Standard of Care visit within the previous 6 weeks
b: Day 1 and Day 9 will be the first day of study drug administration in each arm
c: Study Visit 2 and Study Visit 4 will be phone calls
d: CareCAT survey will be done once daily during Week 1 and Week 9
e: Dosing videos to be done within first 5 days of dosing in each arm

Optional Future Research Contact:

You will be asked whether we may contact you in the future about your child taking part in future research studies related to your child's disease or condition. You will also be asked if data collected in this study can be used for future research. Your decision will not affect your child's ability to be in this research study and will not affect your child's routine care. You will be able to mark your choice at the end of this form.

WHAT ARE THE RISKS OF THE STUDY?

There are certain risks in this study. The biggest risk from being in this study is that your child could absorb more of the liquid medicine than they do the pill, which could require your child's doctor to change the dose of thyroid medication they are taking.

The risks for levothyroxine and Tirosint®-SOL are the same and may include shortness of breath, irregular heart rate, heart attack, muscle spasms, headache, nervousness, irritability, insomnia, tremors, muscle weakness, increased appetite, weight loss, diarrhea, heat intolerance, and skins rash. Since your child will be on levothyroxine whether they are in this study or not, there is no increased risk from the medication due to study participation.

It is possible to have an allergic reaction to the other additional components included in either study drug. Allergic reactions usually happen right away after taking the medicine by mouth and symptoms include having a rash, swelling of the face or tongue, or vomiting. These reactions are very rare. If your child experiences a reaction, you should go to your nearest emergency room or call 911.

Risks of drawing blood from your child's arm include discomfort and bruising. Your child will be given the option of numbing cream to help ease the pain of needle sticks. There is a very low risk of infection, bleeding, clotting, or fainting.

If your child has any of these problems or changes in the way he or she feels, you should tell the investigator or other study personnel as soon as possible.

There is a slight risk of loss of confidentiality. Your child's confidentiality will be protected to the greatest extent possible. There also is a risk to confidentiality when using the internet. By providing your email or phone number, the study team may communicate with you regarding setting up appointments, sending copies of permission forms and any other non-clinical, study related communication using phone and email.

Please be aware of the following:

- Corresponding through electronic communication methods is not a secure method of sending information and others may be able to access the information sent.
- The information may not be secure if storing or viewing the permission document on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena.
- Information that is sent electronically may be kept on the Hospital's or your service provider's (Google, Yahoo, MSN, etc.) network servers. Unlike paper copies, e-copies delivered directly to your PED may not be

able to be permanently removed.
- Children's Mercy Hospital is not liable for any security breaches of any information sent electronically.

There may be risks we don't know about right now. We will tell you about any new information that might change your decision to keep your child in the study.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

There may be direct benefit to your child being in this study, but your child may benefit from improved tolerability of absorption of their medication. Patients may also have an improved biochemical response to their medication seen with TSH & LT4 lab results. Being in this study, your child may help other children with Trisomy 21 and hypothyroidism in the future.

WHAT ABOUT EXTRA COSTS?

Both drugs will be provided to your child at no charge. You or your child's insurer will be responsible for all other costs related to participation in this study. You will be responsible for any costs your child's insurer does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact your child's insurer.

Some of the services or items in this study such as a clinic visit are also part of the regular treatment for your child's condition. These services or items would be provided even if your child was not in this study. The costs for these services or items will be billed to your child's insurer. You will be responsible for any such costs your child's insurer does not cover. If your child is uninsured, you will be responsible for these costs. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact a member of the study team. Neither you nor your child's insurer will be billed for the costs of any services or items that are required by the study but are not considered part of your child's regular treatment.

WHAT ABOUT CONFIDENTIALITY?

Your child has rights regarding the privacy and confidentiality of his or her health information. When health information includes identifiers (like names, addresses, phone numbers and social security or individual taxpayer identification (ITIN) numbers) that link it directly to an individual, it is called protected health information (PHI). Federal laws require that PHI be kept secure and private. In certain situations, federal law also requires that you approve how your child's PHI is used or disclosed. A research study is one of those situations.

By signing this permission form, you are permitting the following people to have access to your child's medical record and use your child's PHI for the research purposes described in this form. You are also permitting your child's PHI to be shared with everyone listed below:
- The research team, which includes persons involved in this study at Children's Mercy Hospitals;
- The IBSA Pharma and the people or groups hired to help perform this study;
- The Institutional Review Board at Children's Mercy Hospitals;
- Other researchers, hospitals, and institutions that are part of this study and their Institutional Review Boards;
- People from organizations that provide independent accreditation and oversight of hospitals and research;
- Government/regulatory agencies (both US and international), such as the Office for Human

Research Protections whose job it is to protect human subjects and oversee the conduct of research.

The research record is separate from your child's medical record. Information about your child that is obtained during this study will be recorded in a research record and may also be recorded in your child's medical record. A research record will be created and kept in the Endocrine Research Office. The research record may include documents that have your child's name, assigned study ID number, home street address, telephone number, medical record number, hospital account number, date of birth, dates of service, and email address. All research records will be maintained in a confidential manner.

Additionally, information to include your name, address, and date of birth will be collected from you for the purpose of compensating you for study participation. This information will remain on the Greenphire secure server 7 years after study closure and then will be destroyed. This information is needed for tax purposes related to compensation only.

There will be a separate database, in which all study information is collected. This database will be used to analyze the study information and find out the study results. Information in this database will include your child's study ID number, name, initials, date of birth, and dates of service.

By signing this permission/assent form, you are allowing your child's health information to be recorded in the research record. You are also permitting your child's research record and medical record to be shared with everyone listed above.

Some people or groups who get your child's identifiable health information might not have to follow the same privacy rules that we follow. We will share your child's health information only when we must, will only share the information that is needed, and will ask anyone who receives it from us to protect your child's privacy. However, once your child's information is shared outside of CMH we cannot promise that it will remain private.

You may choose not to sign this permission/assent form and not have your child be in the study. You may cancel your permission to use and share your child's PHI at any time by contacting the study personnel listed on this form. You may also contact Children's Mercy Hospitals Health Information Management (HIM) in writing. If you cancel your permission, your child may no longer participate in this study. Your child's PHI that has already been collected for the study may still be used; however, no new information will be collected except information related to adverse events or other safety issues.

If you do not cancel your permission, your child's PHI may continue to be recorded until the entire study is finished. This may take years. Any study information recorded in your child's medical record will be kept forever. Unless stated elsewhere in this form, you may not have access to your child's research record or research test results.

Results of this study may be made public. If made public, your child will not be identified in any publications or presentations.

In addition to the use of data described above, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE ALTERNATIVES TO BEING IN THIS STUDY?

Instead of being in this study, you may choose for your child not to be in the study.

WHAT WILL MY CHILD RECEIVE FOR BEING IN THIS STUDY?

You will receive up to $150 for completion of this study: $50 for Enrollment Visit, $50 for Week 8, $50 for Week 16.

If your child does not complete the study, you will be compensated only for the visits that were completed. You will not be compensated for any unscheduled study visits.

If the total value of payments to you from Children's Mercy Hospitals totals more than $600 in any calendar year, the hospital must report this to the IRS on a Form 1099 with the recipient's social security number (SSN) or individual tax identification number (ITIN). You will receive a copy of this tax form. Accepting payment for taking part in the study may affect eligibility for Medicaid or other programs.

Children's Mercy Hospitals can only make payment if we have your name, address, and date of birth. If you do not provide this information, your child can still participate in the research study; however, you will not receive payment.

WHAT ARE MY CHILD'S RIGHTS AS A STUDY PARTICIPANT?

Being in a research study is voluntary. Your child does not have to be in this study to receive medical care. If you choose for your child not to be in this study or withdraw you child from this study, there will be no penalty or loss of benefits to which your child is otherwise entitled.

We will inform you of any new information that we find out during this study. This information may affect your decision to keep your child in the study. If you choose to withdraw your child from (quit) the study or if you are asked by your child's personal doctor to withdraw your child from the study, you must tell the study team as soon as possible.

If you withdraw your child from the study early for any reason, the information that already has been collected will be kept in the research study and included in the data analysis. If you withdraw, your child should continue their normal care with his or her Endocrinologist.

Dr. Feldt, IBSA Pharma the Institutional Review Board or the FDA may stop the study at any time. The investigator(s), your child's doctor, or the IBSA Pharma may remove your child from the study at any time without your permission.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

Dr. Max Feldt oversees the conduct of this research study. If you have questions or concerns at any time during the study, you may call Dr. Feldt at **(816) 960-8892**. You may also contact the study coordinator, Darlene Brenson-Hughes, by calling the Endocrine Research Central Phone at **(816) 460-1097**.

You may page Dr. Feldt at **816-458-3697** if you believe that your child is sick or has suffered injury of any kind because of being in this research study.

You may also call Children's Mercy Hospitals' Pediatric Institutional Review Board (IRB) at **(816) 731-7474** with questions or complaints about this study. The IRB is a committee of physicians, statisticians, researchers, community advocates, and others that ensures that a research study is ethical and that the rights of study participants are protected.

SPONSOR AND INSTITUTIONAL RESPONSIBILITIES

If your child has an illness or injury resulting from their participation in this study, notify the study doctor as soon as possible. If Children's Mercy Hospitals provide treatment for this type of injury or illness, they will determine if they may bill insurance or other third-party payers for this care. You will be responsible for any treatment costs not covered by a third-party payer, but you may seek financial assistance from Children's Mercy Hospitals.

PERMISSION OF PARENT OR LEGALLY AUTHORIZED REPRESENTATIVE

The purposes, procedures, and risks of this research study have been explained to me. I have had a chance to read this form and ask questions about the study. Any questions I had have been answered to my satisfaction. I give permission for_____to participate in this research study. A copy of this signed form will be given to me.

Optional Future Research Contact:

Please read each sentence below and think carefully about your choice. After reading each sentence, circle "Yes" or "No" and initial each item.

Someone from this Children's Mercy Hospitals' research team may contact me in the future to ask about my child participating in future research studies.

Yes No _____Initials of Parent/LAR

Making Your Choice for Optional Future Research:

Please read the sentence below and think carefully about your choice. After reading the sentence, circle "Yes" or "No" and initial.

I agree that my child's clinical information can be used by other researchers for future pediatric research studies.

Yes No _____Initials of Parent/LAR

_____ _____ _____

Signature of Parent/Legally Authorized Representative Date Relationship to Participant

ASSENT OF MINOR

I have been told that if I am in this study, I will continue to take the thyroid medicine I normally take every day, or I will take a new liquid type of the medicine. I will have to come to Children's Mercy for a blood draw and to check my height and weight two times during the 16-week study. My parent(s)/legal guardian(s) will answer questions about how well I like/take the medications and take a video of me taking my medication two times during the study. I have been told that I don't have to be in this study. I may quit the study at any time, and no one will be mad at me. I have had a chance to discuss the study and ask questions. My questions have been answered. I agree to be in the study and do what I am asked to do, if I continue in the study.

I have read this form and/or had it read to me, and the research study has been explained to me. I have been given the chance to ask questions, and my questions have been answered.
I voluntarily agree to be in the research study described above. I will receive a copy of this consent form after I sign it.
I authorize the collection, use, and sharing of my personal health information and biological samples as described in this form.
I am not giving up any of my legal rights by signing this form.

_____
Minor's Name (Printed)

_____ _____
Signature of Minor Date

STUDY PERSONNEL

I have explained the purposes, procedures, and risks involved in this study in detail to:

_____
Print name(s) of Parents/ Legally Authorized Representative, and

_____, who in my opinion____IS /____IS NOT capable of assenting to participate in this study.
Print child's name.

If child IS NOT capable of assenting, please state reason why:

___Age of child:_____(insert age)

___Limitation in understanding based on child's condition

___Other, please explain _____

_____ _____ _____
Signature of Person Obtaining Permission/Assent Date Time

Print Name of Person Obtaining Permission/Assent: _____