PROTOCOL TITLE:

Use of Liquid Stable Levothyroxine in Trisomy 21 Pediatric Patients

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2	19AUG2020	Addition of AE/SAE Language	No
3	23SEP2020	Removing "vitals" from Summary of Events Table, this was an error	Yes
4	12NOV2020	Addition of Endocrine Clinic Intake Room and Outpatient Lab for Study Visits added. Addition of IRB approved recruitment flyers and Scope ad. Added recruitment at the Down Syndrome Clinic and associated Down Syndrome Support Group.	Yes
5	29MAR2021	Updated Sections 2.2, 11.0, and 12.0 to increase maximum age from less than 5 to less than 10 years. Updated Section 15.0 to increase study compensation to $50.00 per visit for a total of $150.00 for completion of all study visits. Corrected formatting in Section 28.00. Changed "Consent" to "Consent/Assent" in Summary of Events Table.	Yes
6	17JUN2021	Updated TOC to reflect correct page numbers, removed repetitive screening language, clarified that SOC visit labs must typically be within 6 weeks of baseline visit, clarified that head circumference should be obtained for	Yes

		participants less than 2 years old, added that drug can be shipped or given to participants at CMH location, Recruitment at DS clinic described more clearly, changed protocol version and date. Updated Schedule of Events to reflect correct study visit days.	
7	29OCT2021	Reformatted protocol to match latest CM Research IRB version, and updated TOC to reflect changes; replaced Summary of Events table with Table of Events; redefined study drug vs control, inclusion/exclusion criteria, & identification/pre-screening/recruitment of participants; more clearly explained and defined study procedures, including blood collection, & study surveys; added clarification to consent/assent process and assessment of participant's ability to assent; updated withdrawal of participants language to allow study staff to withdraw due to study conduct concerns; clarified AE/SAE monitoring and investigator's responsibilities; clarified statistical analysis, data and specimen management, and study setting/location; various changes in grammar and word usage to make language and content consistent throughout the protocol	Yes
8	12NOV2021	Typo in exclusion criteria: ≥ changed to ≤	No
9	13JAN2022	PQL survey moved in Schedule of Events table in protocol and ICF	Yes
10	22MAR2022	Remove PQL survey from visit 3 schedule of events. Reworded primary objective and other parts of protocol to remove the word compliance and changed to ease of use.	yes

Table of Contents

STUDY INFORMATION

1.0 Study Summary

1.1 Synopsis

Study Title	Use of Liquid Stable Levothyroxine in Trisomy 21 Pediatric Patients
Study Design	Single-center, pilot, randomized, open-label crossover study
Primary Objective	Assessment of and tolerability ease of use of levothyroxine therapy based on CareCAT validation tool and medication administration log
Secondary Objective(s)	Compare biochemical effect of liquid stable LT4 versus tablet LT4 on TSH and FT4 in T21 hypothyroid patients
Research Intervention(s)/ Investigational Agent(s)	Tirosint®-SOL liquid stable levothyroxine
IND/IDE#	N/A
Study Population	Pediatric patients with Trisomy 21 and hypothyroidism
Sample Size	22
Study Duration for Individual Participants	Approximately 4 months
Study Specific Abbreviations/ Definitions	CH – congenital hypothyroidism CMH – Children's Mercy Hospital FT4 – Free thyroxine GI – gastrointestinal LT4 – levothyroxine SOC – standard of care TSH – thyroid stimulating hormone T21 – Trisomy 21

2.0 Objectives

2.1 Purpose, specific aims, or objectives: Hypothyroidism is a common medical disorder in children with Trisomy 21 (T21). Treatment with oral tablet levothyroxine (LT4) is primarily used to treat this condition. However, children with T21 have developmental delay and other functional gastrointestinal (GI) issues that may negatively affect LT4 tolerability and absorption. For an age group unable to swallow tablets whole by mouth, tablets must be crushed and suspended in water, breast milk or formula for administration to treat children with hypothyroidism. For this age group, ease of administration may have a significant impact on compliance and ability to remain euthyroid. Until recently, there was no liquid preparation of LT4 in the United States for use in children.

Tirosint®-SOL (liquid stable LT4) is now FDA-approved for use in children. We propose that Tirosint®-SOL will be more favorably received due to ease of administration, improved tolerability, and palatability, therefore leading to improved adherence when compared to LT4 tablets. Our aims for this study are as follows:

- **Aim 1:** *Utilize medication tolerability questionnaire, CareCAT, to understand parental perceptions of liquid stable LT4*
- **Aim 2:** *Evaluate differences in ease of use of liquid stable LT4 compared to LT4 tablets*
- **Aim 3:** *Compare biochemical effect of liquid stable LT4 versus table LT4 on TSH and FT4 in T21 hypothyroid patients*

2.2 Hypothesis: We hypothesize that Tirosint®-SOL will be biochemically comparable to tablet LT4 as well as tolerated well and accepted by children with T21 and hypothyroidism ages 2 months to < 10 years. Caregivers will perceive Tirosint®-SOL as a preferred dosage form.

3.0 Background

3.1 To date, there are no studies evaluating the response of liquid stable LT4 in hypothyroid T21 children.

3.2 Trisomy 21 (T21) is one of the most common chromosomal disorders among live born infants. Its prevalence varies from 1 in 700 to 1 in 1500 live births. T21 is associated with many medical problems as well as developmental delay. Thyroid dysfunction is the most common endocrine abnormality and occurs in 4-8% of T21 children. Hypothyroidism in T21 has a prevalence estimated to be 28-35 times higher than the general population. Not all the mechanisms of hypothyroidism in T21 are known. Autoimmune hypothyroidism is one common etiology as children with T21 have increased prevalence of autoimmunity. Other possible etiologies include: 1. Exaggerated response to TRH stimulation in response to delayed maturation of hypothalamic – pituitary – thyroid axis; 2. Peripheral resistance to thyroid hormones (T4 and T3); 3. Reduced dopamine inhibition of TSH from altered dopaminergic regulation; and 4. Reduced TSH bioactivity. Due to these complex interactions, the use of traditional oral LT4 can lead to persistent elevation of TSH in 20-50% of hypothyroid T21 patients. The use of adjunctive liothyronine (L-T3) has been used to help normalize TSH but at the expense of complicating medication therapy. Recently, a liquid stable formulation of LT4 has been FDA approved for children in the United States. This form has been approved, extensively studied, and utilized in Europe for many years. Tirosint®-SOL is packaged in mono-dose ampules in 12 different dosage strengths. Tirosint®-SOL may be administered either directly into the mouth or a spoon or diluted in a glass of water. This novel form of LT4 has advantages in pharmacokinetic profile compared to traditional tablet LT4 due to direct intestinal absorption without a dissolution phase.

Traditional LT4 exists as a sodium salt that requires optimal acidic environment for dissolution and is susceptible to drug interference with calcium and iron supplements, estrogen, and other medications. On average approximately three quarters of the tablet LT4 is effectively absorbed. In contrast, multiple studies have demonstrated liquid stable LT4 is less affected by concomitant medication and supplement administration, offers improved biochemical levels of TSH, FT4 and FT3, and improved treatment compliance.

4.0 Study Endpoints

4.1 *Primary endpoint: Parent perception responses from CareCAT medication tolerability tool*

4.2 *Secondary endpoint: TSH and FT4 drawn 8-weeks post intervention*

4.3 *Tertiary endpoint: linear growth (height), weight gain, and head circumference growth*

5.0 Study Design

5.1 **Study Design:** This is a single-center, pilot, randomized, open-label, cross-over study to determine satisfaction of standard LT4 tablets compared to liquid stable LT4 (Tirosint® -SOL) therapy and biochemical comparability in 22 participants diagnosed with Trisomy 21 and congenital or acquired hypothyroidism already on levothyroxine (LT4). Participants will be randomized in a 1:1 ratio to treatment (Tirosint®-SOL) or control (conventional therapy with LT4 tablets) for 8 weeks, at which point they will then crossover to receive the treatment arm they were not initially randomized to receive.

Participants will continue their same daily dose of LT4 or Tirosint®-SOL within the randomly assigned treatment group. Dose adjustments are allowed as needed, based on laboratory results and clinical response. Once enrolled, participants will be treated for 16 weeks total. The study will involve up to 3 in-person visits and 2 safety phone calls. Enrollment visit may be done via approved CMH video conferencing platform.

5.2 Table of Events:

Procedures	Enrollment/Baseline[a] 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

6.0 Study Intervention/Investigational Agent

6.1 Description: Tirosint®-SOL (levothyroxine sodium) is a ready-to-use clear, colorless to slightly yellow oral solution containing LT4. It is supplied in 1 mL white single-dose ampules. Inactive ingredients are glycerol and water. IBSA Pharma Inc. will provide Tirosint®-SOL for the study at the following strengths (mcg/mL): 13, 25, 38, 50. Commercially available LT4 tablets will also be used in the study. Inactive ingredients vary between formulations. LT4 tablets for the study will be supplied in the following strengths (mcg): 25, 50, 75. Children's Mercy IDS Pharmacy will store, handle, and dispense the study drug per Research Pharmacy SOP for the Control of Investigational Drugs.

6.2 Drugs or Biologics:

Drug/Biologic Name	FDA Approval Status and Use in this Study
Tirosint®-SOL	FDA approved, and being used within FDA labeling
Levothyroxine sodium	FDA approved, and being used within FDA labeling

PARTICIPANT MANAGEMENT

7.0 Inclusion and Exclusion Criteria

7.1 Eligibility Criteria:

Inclusion Criteria

- *Participant is at least 2 months old and less than 10 years of age*
- *Prior confirmed diagnosis of Trisomy 21*
- *Prior confirmed diagnosis of congenital or acquired hypothyroidism*
- *Currently takes levothyroxine sodium by mouth*
- *Gestational age >35 week*

Exclusion Criteria

- *Gestational age ≤35 weeks*
- *Participant currently takes anticonvulsant medication*
- *Participant takes medication through G-tube or another parenteral route*
- *Participant has more than 2 missed SOC clinic visits in the last 2 years*
- *Participant has documented history of noncompliance with levothyroxine*
- *Participant is currently in foster care or state custody*

7.2 Vulnerable Populations: *Check any vulnerable populations that are being targeted for enrollment into the study: (Members of the following populations may not be included as participants in the research unless selected here.)*

☒ Children/Minors (under 7 years of age)
☒ Children/Minors (7-17 years of age)
☐ Neonates (infants less than 30 days old)
☐ Neonates of Uncertain Viability (infants less than 30 days old)
☐ Non-Viable Neonates (infants less than 30 days old)
☐ Wards of the State
☐ Fetuses
☐ Pregnant Women
☐ Adults with impaired decision-making capacity
☐ CM Employees
☐ CM Students/Residents/ Fellows
☐ Economically or Educationally Disadvantaged Persons
☐ Prisoners

- We will enroll children between the ages of 2 months and < 10 years, therefore meeting the definition of children as a vulnerable population. Participants may also have developmental delays. Study rationale, procedures, risks, and benefits will be explained prior to enrollment by one of the study team members using plain English with minimal medical terminology. The research staff will ensure that the potential participant's parent(s)/LAR understand that participation is voluntary. Parent/LAR will be assured that their child's research records will be kept confidential and will only be available to study personnel. To minimize coercion, parent(s)/LAR will be reassured that participation in no way influences or impacts their child's medical treatment. This research does not include other vulnerable populations including neonates, pregnant women, prisoners, or cognitively impaired adults. It is possible that a CMH employee's child may be eligible for this study. In this event, they will be allowed to participate. The employee will be reassured that participation is voluntary. If the research involves enrolling CM employees or students, indicate how the potential for employees/students to feel coerced or unduly influenced to participate will be minimized. For example, the risk of coercion may be minimized by ensuring that employees will not be recruited or enrolled by their direct supervisor.

8.0 Local Number of Participants

8.1 A total of 22 subjects will be enrolled in this study. Study participation will last approximately 4 months.

9.0 Identification and Recruitment of Potential Participants

9.1 Identification of Potential Participants: Patients may be identified from the CMH Endocrine Clinic outpatient visit schedule, by a list of potential eligible patients through a batch medical chart review from IT, individual chart review, or through outside referrals. Research staff may approach parent(s)/LAR of eligible patients during Endocrine Clinic visits, by phone, or by email. Patients may also be referred by Downs Syndrome Clinic providers. Baseline visit may occur in Downs Syndrome Clinic with approval of Down Syndrome Clinic Medical Director. Potential participants may also self-refer in response to posted advertisements. Study team members may contact potential participants no more than three times to determine interest in this study. Contact attempts and refusals will be documented in the pre-screening log. Refusals will not be approached further.

9.2 Pre-Screening prior to HIPAA Authorization: In accordance with 45 CFR 164.512(i)(1)(ii), qualified participants will be identified and recorded initially by creation of a pre-screening log. The pre-screening log will be maintained to aid in participant identification and eligibility status. This will aid key study personnel in efficiently and effectively attending clinic visits for optimal recruitment. PHI may be collected and stored in pre-screening log and may contain, names (participant and

parents/LAR), address, phone number, email address, medical record number, date of birth, age, clinic visit date, clinic location, clinic provider & appointment time, diagnoses, as well as coordinator/investigator notes regarding eligibility/scheduling. A Waiver of HIPAA is being requested for recruitment purposes only. Data from subjects who are determined ineligible or chose not to participate will be kept until the completion of enrollment to avoid approaching them multiple times. When enrollment is complete, this data will be deleted for patients that did not enroll.

9.3 Recruitment of Potential Participants: IRB-approved recruitment flyers may be distributed at the CMH Endocrine and Down Syndrome Clinics and the Down Syndrome Guild of Greater Kansas City. The study may also be advertised using the recruitment flyer in the employee announcement bulletin board (Scope), internal employer website, or email.

10.0 Procedures

11.0 Surveys:

12.0 Sharing of Results with Participants

12.1 Results of study labs will be provided to parents of subjects. No other study data will be shared with subjects

13.0 Risks to Participants

13.1 The risk 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. 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. These reactions are very rare. Participants will be on levothyroxine regardless of study participation, so there is no increased risk with study participation

13.2 The researchers believe the risks involved in this study are not greater than minimal risk

14.0 Potential Benefits

14.1 Patients may benefit from improved tolerability of administration of the study drug. Subject may have improved biochemical response and absorption to medication, evaluated by TSH & LT4 lab results.

16.0 Payment, Reimbursement and Tangible Property provided to participants

17.0 Economic Burden to Participants

18.0 Permission/Assent/Consent Process

18.1 Indicate below all methods of Permission/Consent that will be used in this study:

18.2 Assessment of Ability to Assent: Study staff will ask parent(s)/LAR if their child has been diagnosed with any developmental or cognitive delay. If yes, study staff will ask if parent(s)/LAR feel the participant is at or above the cognitive and development level of an average 7-year-old. Any child 7 years and older and at a cognitive or developmental level typical of an average 7-year-old will be assented. Study staff reserve the right to withhold assent on any participant deemed ineligible due to cognitive or development level based solely on the assessment of the study staff. Assessment of ability to assent will be documented in consent note per CMH research policy.

18.3 Permission/Assent/Consent Discussion: Consent and assent discussion may take place in one of the CMH Endocrine Clinic locations, by phone, or approved CMH video conferencing platform per CMH research policy. Consent discussions conducted in person will be held in a private room. Consent and assent will be presented by designated study staff to parent(s)/LAR. Parent(s)/LAR and participants will be reminded that research is voluntary and will be provided ample time to read, review, and ask questions about participating in the research study. Parent(s)/LAR and participant will be provided and allowed the opportunity to meet with the PI privately to discuss consent if requested. Parent(s)/LAR and participant will be provided a copy of the consent to take home to allow for more time if needed. Person giving consent and assent will utilize teach back to confirm understanding prior to

signing of consent and assent. Parental consent and participant assent will be verbally confirmed prior to performing study procedures at every visit.

19.0 HIPAA and Confidentiality

19.1 Full Written HIPAA Authorization will be obtained withing the permission/consent from. A Partial Waiver of HIPAA Authorization for Recruitment Only will be requested as described in section 9.2.

19.2 Research staff will emphasize that participate in research is voluntary and that participants may withdraw at any time without penalty. Verbal permission to continue participation in study will be obtained at the beginning of every study visit. All procedures will be explained with an opportunity for parent(s)/LAR to ask questions prior to proceeding with study procedures

20.0 Provisions to Protect the Privacy Interests of Participants

21.0 Withdrawal of Participants

21.1 Participants may be withdrawn by study staff at any time for an issue with study compliance, any concerns of harm to the participant, or if study labs reveal that the participant no longer needs levothyroxine (at the discretion of the PI). Participants may also be withdrawn if the study staff or CMH Research Compliance discover any issues that could compromise the safety of the participants or the integrity of the study data. Any participant withdrawals will be discussed with the PI and documented by the study coordinator in a research note in the electronic medical record.

21.2 All data collected prior to participant withdrawal will be retained by the study. Participants will be asked to return all study medication, both unused and empty packaging to the study coordinator to be returned to IDS Pharmacy for drug accountability. Participants will be instructed to continue their regular care with their Endocrine provider

22.0 Data Collection

23.0 Adverse Events and Unanticipated Problems

23.1 **Monitoring:** Parent(s)/LAR of participants will be asked at every study visit if there have been any changes to the participant's health status since the last contact. Any change in medical history after enrollment visit will be considered an AE and will be documented. Any open AE/SAE at the end of study will only be followed if the PI has determined it is related to study participation.

Open AE/SAEs attributed to study participation will be followed until resolved or the discretion of the PI.

24.0 Statistical Analysis

25.0 Data and Specimen Management

26.0 Setting & Location

26.1 This study will be conducted at any of the CMH Endocrine Clinics or virtually through a CMH approved video conferencing platform. No community advisory boards will be involved in the research study. No study procedures will be conducted outside of the CMH organization. Participants will be given contact information for both the PI and lead Nurse Coordinator. If laboratory results reflect a need in dose change, the child's provider will be consulted for that decision. No other anticipated medical or psychological resources are anticipated.