STATISTICAL ANALYSIS PLAN

Phase IV

A Randomized Comparative Study Between Liquid (Tirosint®-SOL) and Tablet Formulations of Levothyroxine in Neonates and Infants with Congenital Hypothyroidism (CH)

PROTOCOL N° 20US-T414

NCT number: NCT05228184

Version: Final v. 2.0

Date: 24 MAR 2026

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SIGNATURES

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LIST OF ABBREVIATIONS

Abb.	Notes
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Max Index
BW	Body Weight
CH	Congenital Hypothyroidism
CI	Confidence Intervals
COVID-19	Coronavirus disease of 2019
CareCAT	Caregiver administered Children's Acceptance Tool
FAS	Full Analysis Set
FT4	Free Thyroxine
IWRS	Integrated Web Response System
LT4	Levothyroxine
MedDRA	Medical Dictionary for Regulatory Activities
PPS	Per Protocol Set
PSQ	Parents' satisfaction questionnaire
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Events
SAF	Safety Analysis Set
SAS	Statistical Analysis System
SOC	System Organ Calss
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
TFTs	Thyroid Function Tests
TH	Thyroid Hormone
TSH	Thyroid Stimulating Hormone
TT4	Total Thyroxine
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document outlines the statistical methods to be implemented in the analysis of the data of IBSA 20US-T414 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. In case of deviations from this updated statistical analysis plan, explanations will be provided in the statistical report.

2 VERSION HISTORY

Version Number	Summary/Reason for changes	Date Issued
Draft 0.1	First draft	13/08/2025
Final 1.0	First final version	15/10/2025
Draft 1.1	Section 7.1: LT4 medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and preferred drug name, separately from the prior and concomitant medications. Section 9.3: The demographic data analysis will be repeated stratified on neonates and infants. Section 9.4: The variables newly diagnosed neonates vs infants already on LT4 therapy and center will be removed from the analysis of covariances models. Interactions between visit and treatment group will be added to estimate the treatment effect at each visit. The visits included in the Parent Satisfaction Questionnaire analysis of covariance are specified. LT4 dose/kg, TSH and FT4 levels at each visit will be compared between treatment groups by Wilcoxon Mann-Whitney test. These comparisons will be repeated stratified on neonates and infants.	09/03/2026

	TSH values above 4.5 mU/L and FT4 values below the middle of the laboratory normal range will be analyzed also aggregate from Visit 2 to the last available visit. Summary descriptive statistics will be provided for Parents' Satisfaction Questionnaire score and the results at each visit will be compared between treatment groups by Wilcoxon Mann-Whitney test. Descriptive statistics on aggregate CareCAT results will also be provided. During the first week, the third week, and the eighth week of administration CareCAT will be analyzed by day in each week and by week comparing the treatment groups by means Cochran-Mantel-Haenszel chi² test. Descriptive statistics on aggregate CareCAT results overall and by week will also be provided.	
Final 2.0	Final version release. Section 9.4.2: added growth pattern comparison between treatment groups by Wilcoxon Mann-Whitney test.	24/03/2026

3 STUDY DESIGN

This is a multi-center, prospective, parallel-group, open-label, randomized clinical study in one hundred and twenty-six (126) subjects (neonates and infants diagnosed with congenital hypothyroidism (CH)).
Subjects will be randomized in a 2:1 ratio to Treatment (Tirosint®-SOL) or Control (levothyroxine sodium crushed tablets).
Newly diagnosed neonates will be randomly assigned to start therapy with Levothyroxine (LT4) at the initial dose recommended by the Standard of Care.
Infants already on LT4 therapy will continue at the same daily dose within the randomly assigned treatment group (dose adjustments are allowed, if needed based on laboratory parameters and clinical response).
Once enrolled, subjects will be treated and followed for 12 months (±1.5 months), participating in 7-8 study visits, consisting of 6-7 in-clinic and 1-2 (or more if follow-up

visits are required) telemedicine visits. The total number of visits depends on the age at inclusion as reported in the Tables 1 Schedule of Evaluations and Table 2 Outline of Visit Schedule based on Age of the study protocol.

In-clinic visits are performed between 3-4 weeks after randomization, when the subject is 4, 6, and 9 months of age, and then every 3 months as required depending on the age at the inclusion. Telemedicine visits will be performed between 1-2 weeks after randomization, when the subject is 2 months of age, if applicable, and any time an additional follow-up is required for TSH and thyroxine (T4) monitoring.

For further details refer to Study Protocol n. 20US-T414 final version v2.0, Release date: September 7, 2023.

The study was originally planned to enroll a total number of 126 subjects (84 Treatment and 42 Control), expected between September 2021 and July 2022. Despite the extension of the study timeline, a protocol amendament and the efforts by the sites, the enrollment (screening) was closed on 31 March 2024 with a total of 31 randomized subjects, since reaching the enrollment target appeared no longer practicable within reasonable timeframe.

3.1 STUDY OBJECTIVES

Primary objectives

The main objectives of this study are to compare the use of Tirosint®-SOL and conventional treatment with crushed LT4 tablets in terms of:

- LT4 dose required to maintain TSH in target range;
- hormonal (TFTs) profile;
- parent/caregiver reports of satisfaction and ease of administration; and
- subject's acceptance of the treatment.

Secondary objectives

The secondary objective is to compare the study drug and the control treatment by assessing frequency of dose adjustments, and growth patterns (length, BW, head circumference).

Exploratory objectives

An exploratory objective is to compare the study drug and the control treatment in neonates only for the time required to normalize TSH and FT4 into their target ranges.

3.2 SAMPLE SIZE

Subjects were randomized in a 2:1 ratio to Treatment (Tirosint®-SOL) or Control (conventional therapy with LT4 crushed tablets). Considering a mean value of 6 mcg/kg/day of LT4 dose at 12 months of age and a standard deviation of 2 mcg/kg, a sample size of 102 neonates and infants (68 Treatment and 34 Control) will have 80% power to detect a difference of 20% in the LT4 dose between the groups using an independent t-test with a 0.050 two-tailed significance level. To account for a drop-out rate of maximum 20%, 126 neonates and infants will be enrolled in the study (84 Treatment and 42 Control) (Peroni 2013).

3.3 RANDOMISATION

This study was not blinded, all study staff was aware of the treatment assigned.
All eligible subjects were randomly assigned at Visit 1. Subject randomization was 2:1 (Treatment:Control) and stratified by site through an Integrated Web Response System (IWRS). Randomization was stratified based on age:

- neonates newly diagnosed ≤ 28 days; and
- infants > 28 days already on therapy with LT4.

3.4 CHANGES FROM STUDY PROTOCOL

<u>Section 19.2 Population for analysis:</u>

The following subject populations were foreseen:

- Full Analysis Set (FAS): all randomized subjects;
- Per Protocol Set (PPS): all randomized subjects with no major protocol deviations; and
- Safety Analysis Set (SAF): all randomized subjects who received at least 1 dose of study medication.

Due to the premature termination of the study and the limited sample size the Per Protocol Set will not be considered for the final analysis.

Section 19.3.1 General Statistical Methods:

Due to the fast changing measurements in the specific population, in relation to growth, the last observation carried forward (LOCF) method will not be used to deal with missing data or in the case of early study discontinuation and missing data will not be replaced.

Section 19.3.2 Efficacy outcomes:

Due to the premature termination of the study and limited sample size all the efficacy analyses will be considered exploratory. LT4 dose/kg, laboratory parameters (TSH and FT4), "Parents' Satisfaction Questionnaire" will be analyzed with a mixed model adjusted with Kenward-Roger method and considering as first choice the unstructured covariate matrix (other matrixes will be considered if there will be convergence problems). Variables newly diagnosed neonates vs infants already on LT4 therapy and center will not be considered in the models. Normal distribution for LT4 dose/kg, laboratory parameters (TSH and FT4), "Parents' Satisfaction Questionnaire" will be tested with Shapiro Wilks, if data result not distributed as a normal distribution a log transformation will be applied. LT4 dose/kg, TSH and FT4 levels and Parents' Satisfaction Questionnaire score at each visit will be compared between treatment groups by Wilcoxon Mann-Whitney test.

Section 19.3.3 Exploratory outcomes:

Time to TSH and FT4 normalization in the neonates will not be evaluated between the treatment groups due to the low number of neonates enrolled (3 randomized to Tirosint-SOL and only 1 to Control).

4 DEFINITIONS AND DATA CONVENTIONS

Body Mass Index (BMI)

BMI will be computed using the following formula:

$$\text{BMI} = \text{Body Weight (kg)} / (\text{Height (m)})^2$$

Daily dosage

Daily dosage (mcg) will be computed for each patient as:

$$Daily\ Dosage = \left(\frac{\sum_{i=1}^{7}(daily\ dosage_i\ [mcg])}{7}\right)$$

where "i" is the day of the week.

Daily dosage/Body Weight

Daily dosage/Body Weight (mcg / kg) will be computed for each patient as:

$$Daily\ Dosage/Body\ Weight = \frac{\left(\frac{\sum_{i=1}^{7}(daily\ dosage_i\ [mcg])}{7}\right)}{Weight\ [kg]}$$

where "i" is the day of the week.

Previous medications

Medications reported with an end date before the first study treatment administration (end date < date of first study treatment administration).

Concomitant medications

Medications reported as ongoing or with an end date after the first study treatment administration (ongoing or end date ≥ date of first study treatment administration). Any medications with an unknown end date will be assumed to be concomitant medications.

Treatment-Emergent Adverse Events (TEAEs)
Treatment-Emergent Adverse Events are defined as follows:

- Adverse events which started on or after the first study treatment administration.
- Adverse events without start date and with an end date after the first study treatment administration.
- Adverse events without start date and reported as ongoing (for subjects who take at least one dose of study treatment).

Pre-Treatment Adverse Events (PTAEs)
Adverse events which start before the first study treatment administration (start date < date of first study treatment administration).

Serious Adverse Events (SAEs)
Adverse Event assessed as serious.

Drug related Adverse Events
Adverse Events with a relationship to treatment reported as "Certain", "Probable" or "Possible".

Adverse events leading to discontinuation
Adverse Events leading to discontinuation is an AE with action taken equal to “Drug withdrawn”.

Adverse events leading to death
Adverse Events leading to death is an AE with outcome equal to “Fatal”.

4.1 BASELINE DEFINITION

Unless stated otherwise, baseline will be defined for each subject as the last non-missing measurement (scheduled or unscheduled) obtained prior to the treatment start date.

5 ANALYSIS SETS

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Full Analysis Set (FAS): all randomized subjects;
- Safety Analysis Set (SAF): all randomized subjects who received at least 1 dose of study medication.

The FAS will be analyzed according to randomized treatment while the SAF will be analyzed according to the actual treatment received. The SAF will be the primary population for the analysis of safety endpoints.

5.1 PROTOCOL DEVIATIONS

Any protocol deviation (e.g., wrong inclusion, poor compliance, prohibited concomitant medications, etc.) has been discussed on a case-by-case basis with the clinical team and described in the data review document.
Protocol deviations will be listed for randomized patients, including information on theit classification as minor and whether they led to exclusion from any populations and their relation to COVID-19.

6 VARIABLES OF INTEREST

6.1 EFFICACY VARIABLES

6.1.1 Primary efficacy variables

LT4 dose required to maintain TSH in target range (unit: mcg/kg/day)
The LT4 dose is calculated based on the daily LT4 dose (mcg) used in the time period preceding the visit (or the average daily dose on a weekly basis if more than one strength is used over the course of the week) and the body weight (kg) measured during the visit.

6.1.2 Secondary efficacy variables

Laboratory parameters

- Thyroid Stimulating Hormone (TSH);
- Free Thyroxine (FT4);
- Number of events of TSH values above 4.5 mU/L;
- Number of events of FT4 values below the middle of the laboratory normal range

Frequency of dose adjustments
Percent number of subjects (%) who need a dose adjustment in the long-term follow up phase.

Parents' satisfaction questionnaire (PSQ)
The Parents' Satisfaction Questionnaire is completed by the parents/guardian in the eDiary:
at V1 only for infants who are already on TH therapy, and 0-3 days before in-clinic visits for all subjects.
Parents answer questions about the following topics:

- Coping and mental well-being;
- Drug preparation & administration;
- Treatment satisfaction; and
- Medication preference.

The PSQ score at each visit will be computed as sum of all questions scores assigned as reported in Appendix 3.

Caregiver administered Children's Acceptance Tool (CareCAT)
This questionnaire is completed within the eDiary during the first, the third and the eighth week of treatment.

Descriptors:
Swallows well – Medicine is swallowed down

- Observing the act of swallowing the medicine – '[I see that she] drinks the medicine and swallows'
- Ingesting the medicine in absence of negative behaviors – 'He swallows and does not give me a hard time'

Refusal – Resistance of the child (e.g. fighting, crying)

- Defensive behavior preventing the intake of medicine – 'By pushing the spoon' or 'fights with her hands' or 'turns away her head'
- Spitting up – Some medicine is coming out of the mouth immediately
- Forcing the medicine out actively – 'He spits or maybe blows the medicine out'
- Medicine passively leaving the mouth ('overflow' or 'spilling') – 'When the medicines runs down the mouth

Vomiting – Within 30 minutes after swallowing the medicine the child brings up something [vomits]

- 'She takes out the medicine after feeling nauseous, then vomits it with food'

Medication not taken – No medicine went into the mouth of the child

- No oral intake of medicine – 'She does not want [to take the medicine] until the medicine did not get in [the mouth]'
- Intake without ingesting – 'I have tried to give her but [the medicine] was still not swallowed

Growth assessments

The following variables about growth are collected: length (cm), weight (Kg) and head circumference (cm).

7 SAFETY AND TOLERABILITY VARIABLES

Signs and symptoms of hypo-/hyper-thyroidism

Total number of subjects experiencing hypothyroidism/hyperthyroidism signs and symptoms.

Physical examination

The following information about abnormalities found during the examination: body system, findings and clinical significance.

Vital signs

Vital signs that will be collected and recorded in the EDC are heart rate and temperature.

7.1 CONCOMITANT MEDICATIONS

All concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) and summarized by Anatomical Therapeutic Chemical (ATC) level 2 and preferred drug name. Concomitant medications will also be listed.
LT4 medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and preferred drug name, separately from the prior and concomitant medications.

7.2 LABORATORY DATA

Only the following laboratory data will be collected:

- Thyroid Stimulating Hormone (TSH);
- Free Thyroxine (FT4); and
- Total Thyroxine (TT4), optional.

Analysis is described under section 6.1.2.

8 HANDLING OF MISSING AND INCOMPLETE DATA

Missing values will not be replaced.

9 STATISTICAL METHODOLOGY

9.1 GENERAL METHODOLOGY

Descriptive statistics

Categorical variables will be summarized by frequency (n) and percentages (%) and quantitative (continuous) variables using measures of central tendency (mean, median) and dispersion (minimum & maximum; 95% confidence intervals; values defining the limits of the 2nd and 3rd quartiles (25th percentile, 75th percentile); and the standard deviation.

P-values and Type I error

All p-value(s) will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value is less than 0.050.
Two-sided 95% confidence intervals (CI) will be calculated.

9.2 PATIENT DISPOSITION

A complete screening disposition on screened subjects including the number of enrolled subjects, randomized subjects, screening failures and the reasons for screening failure will be provided.

Summary table of not met inclusion and exclusion criteria will also be provided.

A study disposition table on randomized subjects will be provided and it will include number of subjects who completed or discontinued the study and reasons for discontinuation.

Dispositions of randomized subjects who performed each visit and number of patients included in each analysis population will be provided too.

9.3 DEMOGRAPHIC AND SCREENING/BASELINE CHARACTERISTICS

Descriptive statistics of baseline characteristics will be presented for the Full Analysis Set (FAS).

Subjects baseline characteristics will include:

- Demographic data: age at screening, age at randomization, age class (infant or neonates), gestational age, weight at birth, sex, race, ethnicity, length at screening, weight at screening, BMI at screening, head circumference at screening, TSH (mIU/L) and T-4 FREE (pmol/L) levels at CH diagnosis.

- LT4 dose: LT4 dose (mcg/kg/day) at screening (for infants only)

- Hormonal status: TSH (mIU/L) and T-4 FREE (pmol/L) levels at screening (for infants only).

- Vital signs: pulse and temperature at screening.

- Physical examination: abnormal body systems at screening.

- Signs and symptoms of hypo and hyper thyroidism: category (hypothyroidism or hyperthyroidism) and sign or syntom at screening.

- Nutritional intake: breast milk, cow's milk, formula milk, baby food or adult-like food at screening.

- Medical History: those will be summarized by System Organ Class (SOC) and Preferred Term (PT).

- Previous Medications: All previous medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and preferred drug name.

Age at screening, age at randomization, gestational age, weight at birth, length at screening, weight at screening, head circumference at screening, TSH (mIU/L) and T-4 FREE (pmol/L) levels at CH diagnosis, TSH (mIU/L) and T-4 FREE (pmol/L) levels at screening (for infants

only), and LT4 dose (mcg/kg/day) at screening (for infants only) differences between treatment groups will be evaluated using Wilcoxon test.
Sex, ethnicity and race will be compared between treatment groups at each visit using a Chi-squared test or, when the expected values in any of the cells of a contingency table are below 5 or the total number of observations is less than 20, Fisher exact test as appropriate.

The demographic data analysis will be repeated stratified on neonates and infants.

9.4 ANALYSIS OF EFFICACY

All efficacy analyses will be considered explorative, due to the low number of subjects enrolled.
Efficacy analyses will be performed on Full Analysis Set (FAS).

9.4.1 Primary efficacy analysis

LT4 dose/kg

The LT4 dose/kg will be calculated based on the daily LT4 dose used in the time period preceding the visit and the body weight measured during the visit. When dosing schedules alternating strengths over the course of the week are used, the daily dose will be calculated as the average daily dose on a weekly basis.

The LT4 dose/kg required to maintain TSH in target range will be analyzed at 12 months of age visit (V8) and when the subject is 2, 4, 6, 9, 15, 18 and 21 months of age (V4, V5, V6, V7, V9, V10, V11) by means of analysis of covariance (mixed model), including treatment group, age at randomization and interactions between visit and treatment group as covariates. Treatment effect at each visit will be estimated.

Normal distribution for LT4 dose/kg will be tested with Shapiro Wilks, if data result not to be distributed as a normal distribution a log transformation will be applied.

The mixed model will be adjusted with Kenward-Roger method and the unconstructed covariance matrix will be used as first choice (other matrixes will be considered if there will be convergence problems).

Summary descriptive statistics will be provided for LT4 dose/kg and results at each visit will be compared between treatment groups by Wilcoxon Mann-Whitney test. This analysis will also be repeated stratified on neonates and infants.

9.4.2 Secondary efficacy analyses

Laboratory parameters (TSH and FT4)

Laboratory parameters (TSH and FT4) will be analysed at each time point by means of analysis of covariance (mixed model), including basal value, treatment group, age at randomization and interactions between visit and treatment group as covariate.

Normal distribution for TSH and FT4 will be tested with Shapiro Wilks, if data result not to be distributed as a normal distribution a log transformation will be applied.

The mixed model will be adjusted with Kenward-Roger method and the unconstructed covariance matrix will be used as first choice (other matrixes will be considered if there will be convergence problems).

Summary descriptive statistics will be provided for each laboratory parameter. TSH and FT4 levels at each visit will also be compared between treatment groups by Wilcoxon Mann-Whitney test. This analysis will also be repeated stratified on neonates and infants.

Laboratory data will also be listed with clinically significant information.

TSH values above 4.5 mU/L

The events of TSH values above 4.5 mU/L will be compared between treatment groups at each visit and aggregate from Visit 2 to the last available visit using a Chi-squared test or, when the expected values in any of the cells of a contingency table are below 5 or the total number of observations is less than 20, Fisher exact test as appropriate.

FT4 values below the middle of the laboratory normal range

The events of FT4 values below the middle of the laboratory normal range will be compared between treatment groups at each visit and aggregate from Visit 2 to the last available visit using a Chi-squared test or, when the expected values in any of the cells of a contingency table are below 5 or the total number of observations is less than 20, Fisher exact test as appropriate.

Parent satisfaction assessed by "Parents' Satisfaction Questionnaire"

Parent satisfaction assessed by "Parents' Satisfaction Questionnaire" score at V3, V5, V6, V7, V8, V9, V10, V11 will be analyzed by means of analysis of covariance (mixed model), including treatment age at randomization and interactions between visit and treatment group as covariate.

Normal distribution for Parents' Satisfaction Questionnaire score will be tested with Shapiro Wilks, if data results not be distributed as a normal distribution a log transformation will be applied.

The mixed model will be adjusted with Kenward-Roger method and the unconstructed covariance matrix will be used as first choice (other matrixs will be considered if there will be convergence problems).

Summary descriptive statistics will be provided for Parents' Satisfaction Questionnaire score and the results at each visit will also be compared between treatment groups by Wilcoxon Mann-Whitney test.

Caregiver Administered Children's Acceptance Tool (CareCAT)

The subject medicine acceptance assessed by "Caregiver Administered Children's Acceptance Tool (CareCAT)" will be analyzed during the first week, the third week, and the eighth week

of administration and analyzed by day in each week and by week comparing the treatment groups by means Cochran-Mantel-Haenszel chi² test. Descriptive statistics on aggregate CareCAT results overall and by week will also be provided.

Dose re-adjustment

The number of subjects who need a dose re-adjustement during the long-term follow-up phase (Visit 4 to Visit 11) of the study will be compared between treatment groups by means of Chi-squared test or, when the expected values in any of the cells of a contingency table are below 5 or the total number of observations is less than 20, Fisher exact test as appropriate.

Growth pattern

Summary descriptive statistics on length (cm), weight (Kg) and head circumference (cm) will be provided. Results at each visit for each parameter will be compared between treatment groups by Wilcoxon Mann-Whitney test.

Growth assessment parameters will also be listed with clinically significant information.

Signs and symptoms of hypo- and hyper-thyroidism

Number of subjects experiencing hypothyroidism/hyperthyroidism signs or symptoms will be summarized by hypothyroidism, hyperthyroidism and overall.

The number of subjects experiencing at least one sign or symptom will be compared between treatment groups using a Chi-squared test or, when the expected values in any of the cells of a contingency table are below 5 or the total number of observations is less than 20, Fisher exact test as appropriate.

10 ANALYSIS OF SAFETY

Safety analysis will be performed on Safety Analysis Set (SAF).

10.1 Tolerability parameters

10.1.1 Adverse Events

The total number and percentage of subjects with at least one Adverse Event (AE), treatment-emergent Adverse Event, serious Adverse Event, drug-related Adverse Event, Adverse Event leading to treatment discontinuation and Adverse Event leading to death will be summarized by treatment group.

The following summary tables by treatment group will also be provided:

- Adverse Events by System Organ Class (SOC) and Preferred Term (PT);
- Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT);
- Treatment-Emergent Adverse Events by System Organ Class (SOC) and Preferred Term (PT);
- Drug related Treatment-Emergent Adverse Events by System Organ Class (SOC) and Preferred Term (PT);

10.1.2 Vital signs

Summary descriptive statistics on heart rate and temperature will be provided by treatment group.
Vital signs will also be listed with clinically significant information.

10.1.3 Physical examination

Summary descriptive statistics on body systems and findings of abnormal physical examinations will be provided.
Abnormal physical examination information will also be listed with the following information: body system, abnormal finding and clinically significant.

10.1.4 Other tolerability parameters

Compliance

Compliance will be computed for each subject by visit considering as start date the first date of treatment after randomization reported on the LT4 treatment forms and as end date the Date of Last Study Drug Dose Taken reported in the end of study form.

The number of expected days of treatment will be computed by visit for each subject and the number of days of treatment will be computed based on the study medication diary considering the autofilled treatment day number with information about time of administration or strength not missing.

Due to the lack of adherence with the compilation of the daily diary, compliance will be calculated and reported for informative purposes only.

10.2 INTERIM ANALYSIS

No interim analysis is planned for this study.

10.3 SOFTWARE TO BE USED

All statistical analyses and data processing will be performed using SAS® Version 9.4 on a Windows operating system.

10.4 CODING DICTIONARIES

Adverse Events, medical history and previous and concomitant medications will be coded using the following dictionaries: MedDRA (version 24.0) and WHO Drug Dictionary (version March 1, 2021).

11 REFERENCES

Peroni E, Vigone M, Mora S, Bassi L, Pozzi C, Passoni A, Weber G (2013). Congenital Hypothyroidism Treatment in Infants: A Comparative Study between Liquid and Tablet Formulations of Levothyroxine. Hormone research in paediatrics. 81. 10.1159/000356047.

20US-T414 Clinical trial protocol V 1.0 final (2021)

20US-T414 Clinical trial protocol V 2.0 final (2023)

12 APPENDIX 1: LIST OF TABLES, LISTINGS AND FIGURES

Not applicable.

13 APPENDIX 2: SHELL TABLES, LISTINGS AND FIGURES

Not applicable.

14 APPENDIX 3: PARENTS' SATISFACTION QUESTIONNAIRE SCORES.