CONFIDENTIAL

A PROSPECTIVE, MULTICENTER OBSERVATIONAL STUDY TO EVALUATE THYROID FUNCTION OF PEDIATRIC SUBJECTS FROM BIRTH TO 3 YEARS EXPOSED TO ISOVUE® (IOPAMIDOL INJECTION)

IOPAMIDOL

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Bracco Diagnostics Inc.
[redacted]

Protocol Title

A PROSPECTIVE, MULTICENTER OBSERVATIONAL STUDY TO EVALUATE THYROID FUNCTION OF PEDIATRIC SUBJECTS FROM BIRTH TO 3 YEARS EXPOSED TO ISOVUE® (IOPAMIDOL INJECTION)

Protocol No.

This study is being conducted under protocol number: IOP-120
IND number: 16,272

Objectives

Primary Objective(s)

- To evaluate the proportion of subjects, 0 to 3 years of age, with abnormal TSH values at either one month or two months after intravascular administration of ISOVUE.

Secondary Objective(s)

- To evaluate the proportion of subjects, 0 to 3 years of age, with hypothyroidism regardless of the need for thyroid hormone replacement therapy at either one month or two months after intravascular administration of ISOVUE.
- To estimate the proportion of subjects initiated on thyroid hormone replacement therapy

Investigational Plan

Overall Study Design Description

This is a Phase IV prospective, multicenter, observational study. Subjects 0 to 3 years of age who are required to undergo a radiologic procedure with intravascular administration of ISOVUE as part of their standard of care will be enrolled in the study. The specific iodine concentration and volume of ISOVUE used during the radiologic procedure will depend on the type of procedure and the standards in place at the site where the procedure is performed.

All subjects enrolled in the study will have thyroid function tests (TFT) which include serum TSH, total triiodothyronine (T3), total thyroxine (T4) and free T4 (fT4) assessed at baseline, at one month and two months following administration of ISOVUE. If TSH values are abnormal at either the one month or two month time points, further follow-up will be required at 6 and 12 months after the administration of ISOVUE to monitor subject's response and treatment (if any). Follow-up at 6 and 12 month post-dose time points will be performed using a pre-defined questionnaire.

The study will be conducted at approximately 10-20 sites in the United States.

Discussion of Study Design

The proposed study is designed as an intra-subject comparison of TSH, T3, and T4 values before and after administration of ISOVUE and will enroll pediatric subjects 0 to 3 years of age, who require a radiologic procedure with intravascular administration of ISOVUE as part of their standard of care.

The primary endpoint of this study is to evaluate the proportion of subjects exhibiting abnormal values of TSH following intravascular administration of ISOVUE. Thyroid function test data will be collected prospectively. Serum thyroid function testing at baseline, one month and two month post-dose time points will be performed at a local laboratory.

Abnormal TSH findings for subjects enrolled in the study will be compared to a reference population. As recommended by the FDA, the reference population for the study is represented by 3,214 infants who received potassium iodide prophylaxis on the second day of life at the time of the Chernobyl nuclear accident; 12 of the 3,214 infants (p=0.003734, 95% CI 0.002025, 0.006339) showed a transient increase of serum TSH levels and a decrease of fT4 levels after administration of potassium iodide. [1]

As per FDA recommendation, sample size estimation for the current study has utilized the threshold incidence rate (p=0.003734) as the clinically meaningful value to rule out a safety concern about the proportion of children with abnormal TSH after exposure to ISOVUE.

Following FDA recommendations to be complied with:
- abnormal TSH in the study is defined as any TSH value above the normal age/gender-specific reference range provided by the respective local laboratories.

- hypothyroidism is defined as a TSH > 10 mIU/L (independent of fT4) or as a TSH above the normal age-specific reference range and an fT4 below the lower limit of the normal range.

Risk-Benefit Considerations

This study will enroll subjects who require a radiologic procedure with intravascular administration of ISOVUE as part of their standard of care; therefore, inclusion in the present clinical trial will not add any risk to the subject. Three blood draws of approximately 2.0 ml each will be performed in all subjects as part of the study, to assess serum TFTs before and after administration of ISOVUE.

Although subjects enrolled in the study will not directly benefit from this clinical trial, study results may be beneficial for pediatric subjects 0 to 3 years of age who will be exposed to iodinated contrast agents.

Study Duration

All subjects enrolled in the study will undergo the radiologic examination with administration of ISOVUE, as part of their standard of care; TFTs will be assessed at baseline, one month and two months post-dose.

If TSH values are abnormal at either the one month or two month time points, follow-up will be required at 6 and 12 months after the administration of ISOVUE to monitor subject's response and treatment (if any). Follow-up at the 6 and 12 month post-dose time points will be performed using a pre-defined questionnaire. Each follow-up will take no longer than 20 minutes.

Study Population

The study will be conducted in pediatric subjects 0 to 3 years of age, who are scheduled to undergo a radiologic procedure with intravascular administration of ISOVUE as part of their routine standard of care.

It is planned to enroll approximately 1,560 subjects in order to obtain 1,482 evaluable subjects.

Inclusion Criteria

Enroll a subject in this study if the subject meets the following inclusion criteria:

1. Is male or female from 0 to 3 years of age;
2. Is scheduled to undergo a radiologic examination that requires intravascular administration of ISOVUE as part of his/her standard of care;
3. Has normal baseline thyroid function tests (TSH, total T3, total T4, and fT4) performed at a local laboratory with blood sample obtained within one week prior to ISOVUE administration;
4. Written informed consent is obtained from the subject's parent(s) or legally acceptable representative(s) (according to local regulations) who are willing to comply with the protocol requirements.

Exclusion Criteria

Exclude a subject from this study if the subject does not fulfill the inclusion criteria, or if any of the following conditions are observed:

1. Has any known allergy to one or more of the ingredients of ISOVUE;
2. Has been diagnosed with congenital hypothyroidism;
3. Has undergone radiation treatments to the head or neck;
4. Is currently on thyroid replacement therapy;
5. Is on therapy with dopamine or any treatment which may affect the thyroid function testing results;
6. Has been exposed to any topical iodinated product within 30 days prior to enrollment in the present study;
7. Has been exposed to an iodinated contrast agent within 1 year prior to enrollment in the present study, including any administration of iodinated contrast agents during placement of a central line;
8. Has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study and/or post-dose follow-up examinations.

Discontinuation Criteria

Clearly document the reason for the subject's discontinuation on the Case Report Form. Discontinued subjects are not replaced. Discontinue a subject from the study if the subject:

- Withdraws consent;
- No longer meets the Inclusion Criteria;
- Is lost to Follow Up

Investigational Products

The investigational product is ISOVUE® (Iopamidol Injection).

ISOVUE will not be provided to the participating sites since the study will enroll subjects undergoing a radiologic examination with intravascular administration of the contrast agent as part of their standard of care.

Methodology

Subject Evaluations

Demographic Information

Collect the following demographic information for subject's enrolled in the study:

- Date of Birth
- Gender
- Race
- Height (cm)
- Weight (kg)

Medical History

Obtain a complete medical history of subjects enrolled in the study, within 24 hours prior to the administration of ISOVUE. Report any clinical condition that might predispose to thyroid function abnormalities such as

- pre-term birth
- low or very low birth weight
- mother's exposure to iodinated contrast agents, iodine containing medications (e.g., Amiodarone, Potassium iodide), or topical iodinated product during pregnancy
- diagnosis of Down's Syndrome or other chromosomal abnormalities, congenital diseases, or Type I diabetes
- results of neonatal screening of thyroid function testing
- previous exposure to iodinated contrast agent (greater than 12 months prior enrollment in the present study).

Concomitant Medications

Record all medications (prescription and over-the-counter) taken within 24 hours prior to investigational product administration in the Concomitant Medication section of the Case Report Form. Additionally, record newly prescribed pharmacological treatments up to 1 week after administration of ISOVUE.

Safety Assessments

Monitor for any untoward medical occurrences that occur in the subject during the timeframe associated with the ISOVUE administration.

Laboratory Evaluations

A local laboratory will perform evaluation for the analytes listed in Table A.

A screening/baseline assessment of TFTs specified in Table A will be collected within 7 days prior to the administration of ISOVUE. Results must be obtained prior to enrollment into the study. Only subjects with normal TFT values will be enrolled into the study.

Blood samples for assessment of TFTs specified in Table A below will be collected at one month and two months post-dose.

Table A: Laboratory Analytes

Thyroid function test
TSH (Thyroid Stimulating Hormone)
fT4 (free Thyroxine)
Total T3 (total Triiodothyronine)
Total T4 (total Thyroxine)

Follow-up

If TSH is abnormal at either the one month or two month time points, the subject will undergo follow-up at 6 and 12 months after the administration of ISOVUE using a pre-defined questionnaire. Clinical data to be collected at 6 and 12 month follow-up will include, among the others:

- development of new symptoms which were considered to be related to the abnormal TFT values by the subject's physician;
- need for treatment related to the abnormal TFT values observed after the administration of ISOVUE; in case of treatment, the type of treatment, dosage, dose adjustments, start date and current status of treatment (i.e. ongoing, completed, stop date, etc.) will be collected and reported in the CRF;
- results of any additional TFT assessment performed in the interval time since the previous visit;
- results of thyroid ultrasound examinations, if any performed in the interval time since the previous visit;
- exposure to any iodinated contrast agent in the interval time since the previous visit;
- exposure to any topical iodinated product in the interval time since the previous visit.

A more detailed description of clinical data to be collected during follow-up will be provided in the questionnaire which will be a part of the CRF.

Imaging Procedures

Report the following information about the radiologic examination with intravascular administration of ISOVUE:

- type and indication of the radiologic examination (such as CT of the chest, urography, etc)
- date of examination
- contrast administration protocol, including route of administration (venous or arterial), iodine concentration (mgI/mL), and volume (mL) of ISOVUE administered.

Statistical Methods

In general, summary statistics (mean, median, standard deviation, minimum, and maximum) will be provided for continuous variables, and the number and percentage of each category will be provided for categorical data. Any changes in the original statistical methodology will be documented in the statistical analysis plan (SAP). All data collected will be presented in the listings.

All statistical analyses will be performed using SAS® software.

Subject Disposition and Demographic and Baseline Characteristics

Summary tables will be provided for the number of subjects who have been enrolled and completed according to the protocol. The number of subjects who prematurely discontinued the study and the reasons for their discontinuation will be summarized.

Summary statistics will be presented for demographic and baseline characteristics, including age, sex, race, height, weight, BMI, medical history, and other relevant study entry criteria.

Analysis Population

The safety population will consist of all enrolled subjects who had intravascular administration of ISOVUE. The analysis population will include subjects who received ISOVUE with TSH assessment at 1 month or two months post-dose. For subjects who received ISOVUE but do not have TSH assessment at 1 month or two months post-dose, the reasons for not having TSH assessment at 1 month or two months post-dose will be recorded and listed.

Concomitant Medications

Frequencies of concomitant medication use will be tabulated by World Health Organization (WHO) class, level I and level II.

Imaging Procedure

Data pertaining to the description of imaging procedure (type and indication of the radiologic examination) will be summarized.

Extent of Exposure

Descriptive statistics will be presented to summarize the concentration (mgI/ml) and volume (mL) of ISOVUE administered. The route of administration (venous or arterial) will also be summarized.

Primary Endpoint - Analysis for Abnormal TSH

The primary endpoint of this study is to evaluate the proportion of subjects, 0 to 3 years of age, with abnormal TSH values at either one month or two months after administration of ISOVUE. Following FDA recommendations, abnormal TSH in the study is defined as any TSH value above the normal age/gender-specific reference range provided by the respective local laboratories.

Abnormal TSH findings for subjects enrolled in the study will be compared to a reference population. As recommended by the FDA, the reference population for the study is represented by 3,214 infants who received potassium iodide prophylaxis on the second day of life at the time of the Chernobyl nuclear accident; 12 of the 3,214 infants (p=0.003734, 95% CI 0.002025, 0.006339) showed a transient increase of serum TSH levels and a decrease of fT4 levels after administration of potassium iodide.[1]

The study hypothesis will be:

H_0: $p \geq 0.003734$

H_A: $p < 0.003734$

The proportion of subjects with abnormal TSH at either one month or two months after administration of ISOVUE and its 95% confidence interval will be estimated. Confidence interval will be calculated based on the approximate normal distribution:
$95\%\ CI = p \pm 1.96*(p*(1-p)/n)^{1/2}$

The number of subjects with shift in serum TSH (with respect to normal reference range) after exposure to ISOVUE will be cross tabulated and summarized separately. Each subject will serve as his/her own control, with the pre-dose values representing their baseline or control values.

Secondary Endpoint - Analysis for Hypothyroidism

The secondary endpoint is to evaluate the proportion of subjects, 0 to 3 years of age, with hypothyroidism regardless of the need for thyroid hormone therapy at either one month or two months after administration of ISOVUE.

Hypothyroidism is defined as a TSH > 10 mIU/L (independent of fT4) or as a TSH above the normal age/gender-specific reference range and a fT4 below the lower limit of the normal range.

The proportion of subjects with hypothyroidism at either one month or two months after administration of ISOVUE will be estimated and the 95% confidence interval will be presented.

For those subjects with hypothyroidism, follow-up data will be summarized by monitoring time points (6 months and 12 months).

Secondary Endpoint - Analysis for Thyroid Hormone Replacement Therapy

The proportion of subjects initiated on thyroid hormone replacement therapy will be estimated with 95% confidence interval.

Analysis for Other Safety Issues

Serious adverse events and non-serious adverse drug reactions will be summarized and listed.

Sample Size

The threshold incidence rate (p=0.003734) obtained from the Nauman and Wolff publication[1] will be used as the clinically meaningful value to rule out a safety concern about the proportion of children with abnormal TSH after exposure to ISOVUE. Using confidence interval method for the probability of observing a rare event, when no case is observed out of n, the upper 95% confidence limit of the incidence rate can be estimated by 3/n. If no cases were observed in the sample size of 1,482, there is 95% confident to rule out an incidence rate of 0.002025 or higher. Considering a 5% drop out rate, 1,560 subjects will be enrolled in the study.

Interim Analyses

No interim analysis is planned.

References

1 Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. Am J Med. 1993 May;94(5):524-32.