

Amendment No. 1

Levothyroxin und Iodid in der Strumatherapie Als Mono- oder Kombinationstherapie
LISA-Studie

Thyronajod® 75 Henning vs. L-Thyroxin Henning® 75 vs. Jodetten® 150 Henning vs. Placebo
in the treatment of nodular goitre.

Study No.	Study protocol HB TJ 01/03	Version	Amendment No. 1
		Date	05-Feb-2004
Sponsor	Sanofi-Synthelabo GmbH Geschäftsbereich Henning Berlin Potsdamer Straße 8 10785 Berlin		
Principal Investigator Leiter der Klinischen Prüfung according to AMG § 40	Prof. Dr. Martin Grußendorf Hospitalstr. 34 70174 Stuttgart		
Project Manager (Sponsor)	Dr. Renate Vaupel Sanofi-Synthelabo GmbH Geschäftsbereich Henning Berlin Potsdamer Straße 8 10785 Berlin		
Statistician	Prof. Dr. Karl Wegscheider Barstr. 9 10713 Berlin		
Author	Dr. Peter Schinnerling SocraTec-PFC GmbH Kreillerstr. 65 81673 Munich		
Drug Safety Department	Dr. Gernot Schreiber Sanofi-Synthelabo GmbH Geschäftsbereich Henning Berlin Potsdamer Straße 8 10785 Berlin		

Study Protocol - Clinical Study Phase IV

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SIGNATURE PAGE

Dr. M. Haring

Hauptabteilungsleiter Medical Affairs C
Sanofi-Synthelabo GmbH
Geschäftsbereich Henning

Date

Signature

Prof. Dr. med. M. Grußendorf

Principal Investigator

Date

Signature

Prof. K. Wegscheider

Statistician

Date

Signature

Dr. R. Vaupel

Project Manager
Sanofi-Synthelabo GmbH
Geschäftsbereich Henning

Date

Signature

Dr. P. Schinnerling

Project Manager and
author of the protocol
SocraTec-PFC GmbH

Date

Signature

Study protocol HB TJ 01/03

Amendment No. 1

Amendment No. 1 of February, 5th, 2004 with respect to the final study protocol of January 08, 2004, final version

The Amendment 1 of the Final Study Protocol became necessary after discussions at the Investigators' Meeting on January, 24th, 2004, 35 study centers participating. The study protocol - particularly the inclusion- and exclusion criteria - were previously discussed very carefully with several members of the "Sektion Angewandte Endokrinologie" and "Sektion Schilddrüse" of the German Society of Endocrinology. However, the opinions in Germany from what size goiters and nodules must definitely be treated vary within a broad, acceptable range. Therefore it was reasonable to take into account the entire spectrum of possible treatment options resulting in a consensus decision of the investigators present at the meeting. This is the reason for changing two inclusion criteria and one exclusion criterion. The following changes are to be implemented:

1. One inclusion criterion was revised (Page 11, 5.1 inclusion criteria)
2. One exclusion criterion was revised (Page 11, 5.2 exclusion criteria)
3. The time window between the baseline visit and visit 3 must be shortened (Page 16, 9. Methods and page 17, 9.1 Visit procedures)

For each change, the previous version and then the new modified version and rationale are listed below.

1. Inclusion criteria

1.a. Previous version:

in Protocol Section 5.1 Inclusion Criteria

- Caucasian
- Age 18 – 55 years (inclusive)
- Normal TSH value (target range between 0.6 – 3.0 mU/l)
- Nodular goitre (women > **25** ml, men > **30** ml but maximum 60 ml) and nodules diameter > 0.5 cm (without cyst component), for nodules > 1.0 cm the diagnosis must be performed according to the guideline for diagnostic standards of thyroid disorders
- Signed written informed consent

1.b. New version:

in Protocol Section 5.1 Inclusion Criteria

- Caucasian
- Age 18 – 55 years (inclusive)
- Normal TSH value (target range between 0.6 – 3.0 mU/l)
- Nodular goitre (women > **18** ml, men > **25** ml but maximum 60 ml) and **at least one** nodule (without cyst component) **with ≥ 1.0 cm** diameter, for nodules > 1.0 cm the diagnosis must be performed according to the guideline for diagnostic standards of thyroid disorders
- Signed written informed consent)

1.c. Rationale:

Instead of patients with a significantly increased thyroid volume (women > 25 ml and men > 30 ml) the above-normal thyroid volume value, using the WHO upper normal values (women < 18 ml, men < 25 ml) will be used. The nodular goitre volume limit for the study inclusion was reduced without impact on the study results.

In addition, since a decrease in volume in nodules with a diameter of only 0.5 cm is difficult to measure, one main nodule with a diameter of at least 1.0 cm is to be documented.

2. Exclusion criteria

2.a. Previous version:

in Protocol Section 5.2 Exclusion Criteria

- Thyroid therapy within the last 3 years
- Known focal or diffuse structure autonomous thyroid
- Presence of thyroid cysts
- Ioduria > 200 µg/dl
- Contraindication to iodine
- Concomitant treatment with iodine containing medication (i. e. amiodarone)
- Use of iodine-containing contrast medium within the last 6 weeks
- Presence of TPO antibodies (maximum twofold normal value)
- Symptomatic coronary heart disease
- Endocrine orbitopathy
- Known autoimmune thyreopathy
- Pregnancy
- Former radioiodine therapy or surgery
- Any acute or chronic illness or allergy
- Dermatitis herpetiformis
- Pathological laboratory results
- Patients who are unable to understand the written and verbal instructions, in particular regarding the risks and inconveniences they will be exposed to as a result of their participation in the study
- Participation in another clinical study with investigational medication within the last 30 days.

2.b. New version:

in Protocol Section 5.2 Exclusion Criteria

- Thyroid therapy within the last 3 years
- Known focal or diffuse structure autonomous thyroid
- Presence of thyroid cysts
- ~~Ioduria > 200 µg/dl~~
- Contraindication to iodine
- Concomitant treatment with iodine containing medication (i. e. amiodarone)
- Use of iodine-containing contrast medium within the last 6 weeks
- Presence of TPO antibodies (maximum twofold normal value)
- Symptomatic coronary heart disease
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- Any acute or chronic illness or allergy
- Dermatitis herpetiformis
- Pathological laboratory results
- Patients who are unable to understand the written and verbal instructions, in particular regarding the risks and inconveniences they will be exposed to as a result of their participation in the study
- Participation in another clinical study with investigational medication within the last 30 days.

2.c. Rationale:

Due to organisational reasons the result of the iodine determination will not be available immediately at visit 2 and therefore the exclusion criterion “Ioduria > 200 µg/dl” will be deleted. The urine samples for the measurement of iodine amount in urine at the baseline visit (visit 2) and at the study end visit (visit 5) will be shipped in bulk to this central lab. There is no safety issue if the patients have an ioduria.

3. Time Windows

3.a. Previous version:

in Protocol Section 9. METHODS

Table 2: Study Procedures Flowchart

Procedures	Screening	Baseline	Control		Study end
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Study day	within - 4 weeks	0	3 months ± 7 days	6 months ± 7 days	12 months ± 14 days
Written informed consent	●				
Medical history	●				
Physical examination		●			●
Vital signs (blood pressure, pulse)	●	●	●	●	●
Sonography	●	●	●	●	●
Clinical laboratory ^a	●				●
TSH	● ^a	● ^b	● ^b	● ^b	● ^b
TPO antibodies ^a	●				●
Iodine determination in urine ^c		●			●
Study medication supply		●	●	●	
Study medication return			●	●	●
Adverse event questioning			●	●	●
Concomitant medication	●	●	●	●	●

^a = each site

^b = central lab in Stuttgart

^c = central lab in Würzburg

in Protocol Section 9.1 Visit procedures

Visits 3 and 4 (Control):

The following evaluations are to be completed after 3 and 6 months. Study visits are to be completed within **± 7 days** of the protocol-specified visit date calculated from the baseline visit.

3.b. New version:

in Protocol Section 9. METHODS

Table 2: Study Procedures Flowchart

Procedures	Screening	Baseline	Control		Study end
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Study day	within - 4 weeks	0	3 months - 14 days	6 months ± 7 days	12 months ± 14 days
Written informed consent	●				
Medical history	●				
Physical examination		●			●
Vital signs (blood pressure, pulse)	●	●	●	●	●
Sonography	●	●	●	●	●
Clinical laboratory ^a	●				●
TSH	● ^a	● ^b	● ^b	● ^b	● ^b
TPO antibodies ^a	●				●
Iodine determination in urine ^c		●			●
Study medication supply		●	●	●	
Study medication return			●	●	●
Adverse event questioning			●	●	●
Concomitant medication	●	●	●	●	●

^a = each site

^b = central lab in Stuttgart

^c = central lab in Würzburg

in Protocol Section 9.1 Visit procedures

Visits 3 and 4 (Control):

The following evaluations are to be completed after 3 and 6 months. Study visits are to be completed **for visit 3 within 14 days and for visit 4** within ± 7 days of the protocol-specified visit date calculated from the baseline visit.

3.c. Rationale:

To ensure that the subject has no interruption in medication, the subjects should not visit the investigator later than 3 months after receiving their last supply. This allows time for sending the patient-specific supply after receiving their TSH lab result.