Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Contents

I. Investigator and Trial Personnel List

ClinicalTrials.gov identifier: NCT00277589

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II. Supplementary Methods

Logarithmic approach

As suggested by previous data and pre-specified in the study protocol, total nodule volumes and thyroid volumes were log-transformed. Inferential statistics were performed on the resulting log values. Estimated means were transformed back to the original scales and are reported as geometric means. Individual as well as mean changes are reported as percent increase or reduction. The logarithmic approach was chosen because pre-study data revealed skewed distributions of volumes and suggested that changes in nodule or thyroid size are better described in terms of relative changes than in terms of absolute changes. Meanwhile, logarithmic approaches are frequently used for the analysis of nodule and thyroid volumes by other authors as well since they are judged to be more appropriate (see 30).

Justification of the statistical approach

The primary analysis of the study as specified in the study protocol was focused to the comparison of T4+I to each of its components and placebo with respect to total nodule volume, taking the perspective of studying a combination therapy. However, while the study was running, this approach was challenged by methodological discussions that emphasize the requirement of head-to-head studies for fair symmetric comparisons of different therapeutic approaches under real-world conditions. These comparative effectiveness studies (1,2 (Suppl. Ref.)) should preferentially be performed as randomized trials (3 (Suppl.Ref.)). Since many physicians routinely use T4 alone or iodine as first-line therapy or choose a wait-and-see strategy, the symmetric perspective was found to be more appropriate than the original selective analysis with comparisons to the combination alone. However, the price to be paid is the requirement to further adapt the test levels to the increased number of comparisons, resulting in a slight loss of power for the comparisons with the combinations. Taking the loss of power into regard, the steering committee while still blind to cumulative results found it justified to enlarge the perspective of the primary analysis to gain further insight. We therefore present all six possible pairwise t-test comparisons between randomization groups and report raw (unadjusted)

p values along with p values adjusted for multiplicity of tests by applying the appropriate closure test (28). Significance was stated if adjusted p values were below 0.05. The closure test procedure is the optimal (most powerful) test strategy to keep an experiment-wise error rate if all pairwise comparisons are of interest. Actually, in the present case the loss of power as compared to the original strategy was almost negligible.

Sensitivity analyses

Three sensitivity analyses were performed to study the influence of definitions on the primary results. At first, the primary analysis was performed as defined in the original study protocol where only comparisons to the combination therapy were to be performed, using a Bonferroni-Holm correction for multiplicity adjustment. At second, the primary analysis was repeated with inclusion of the centers that were excluded because of data quality and documentation problems. The third analysis was in complete cases only to study the potential influences of imputation.

Statistical model building for the analysis of covariate effects and treatment effect modification

Multilevel models with change in log total nodule volume or log thyroid volume as dependent variables and random groups and baseline values as covariates were used to study associations of potentially influential variables with outcome or treatment effects. We studied the involvement of the following variable: age, gender, family history, body mass index, baseline TSH >1.0 mU/l, baseline Iodine excretion <100 µg/l, baseline thyroid volume >25ml for men and >18ml for women, baseline nodular volume >2ml, the presence of multiple nodules at baseline, and <20% cystic largest nodules. In a first step, all variables were included simultaneously in the model to receive regression coefficients that reflect the independent predictive information contributed by each variable. In a second step, the same covariates were used for interaction terms with treatment to study potential effect modification. Again, all interactions were studied simultaneously. The interaction analysis, however, was restricted to the comparison of T4+I versus the pooled P and I groups for nodule volume and for the pooled T4+I and T4 group versus placebo since the strongest effects were expected for these comparisons. Repeated measurement multilevel longitudinal models allowing for heteroscedasticity and first-order autocorrelation were applied to study the development of parameters

visit by visit. To preserve the intention-to-treat approach, for these analyses missing values were imputed by direct maximum likelihood methods (4 (Suppl. Ref.)).

In a post hoc analysis for explanation and further exploration of the observed treatment effects, individual changes in total nodule volume or in thyroid volume were regressed to iodine changes from baseline and TSH changes from baseline averaged over the follow-up determinations (only complete patients, n=600). We report changes in the group-specific estimates of treatment effects by adjustment to one or both of these variables in order to find out whether these two components could explain the observed differential volume reductions.

III. Supplementary Results

Sensitivity analyses

If the primary analysis would have been restricted to the comparisons of T4+I to P, I and T4 as originally planned, Bonferroni-Holm adjusted p values were <0.001, 0.002 and 0.018 as compared to <0.001, 0.003 and 0.018 in the presented primary analysis extended to 6 two-group comparisons. Thus, the result would not have changed qualitatively with respect to T4+I.

In patients excluded for documentation gaps nodule volume reductions were significantly larger than in the analysis population. This effect was observed in each of the four random groups. If these patients were added to the analysis population, change rates were -18.3% to -30.5%, but the relative differences between groups did not change substantially. Due to the increased centre effect, residual variances more than doubled and p values increased with the difference of T4+I and P as only significant effect after adjustment for multiplicity (multiple p=0.043).

Restriction of the analysis population to complete cases resulted in marginal changes only. Significances and conclusions remained identical.

IV. Supplementary References

1. Volpp KG, Das A: Comparative effectiveness--thinking beyond medication A versus medication B. N Engl J Med. 2009 Jul 23;361(4):331-3.

2. Garber AM, Hlatky MA: The confirmatory trial in comparative-effectiveness research. N Engl J Med. 2009 Oct 8;361(15):1498-9.

3. Iglehart JK: Prioritizing comparative-effectiveness research-IOM recommendations. N Engl J Med. 2009 Jul 23;361(4):325-8.

4. Molenberghs G, Kenward MG: Missing Data in Clinical Studies. (2007) John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester,West Sussex PO19 8SQ, England

V. Supplementary Tables

Supplemental Table 1: Study Procedures

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[b]		●			●
Study medication supply		●	●	●	
Study medication return			●	●	●
Adverse event questioning			●	●	●
Concomitant medication	●	●	●	●	●

[a] lab of study center, [b] central lab

Supplemental Table 2: Percent of patients within TSH ranges, by randomization group and visit (only patients with complete follow-up).

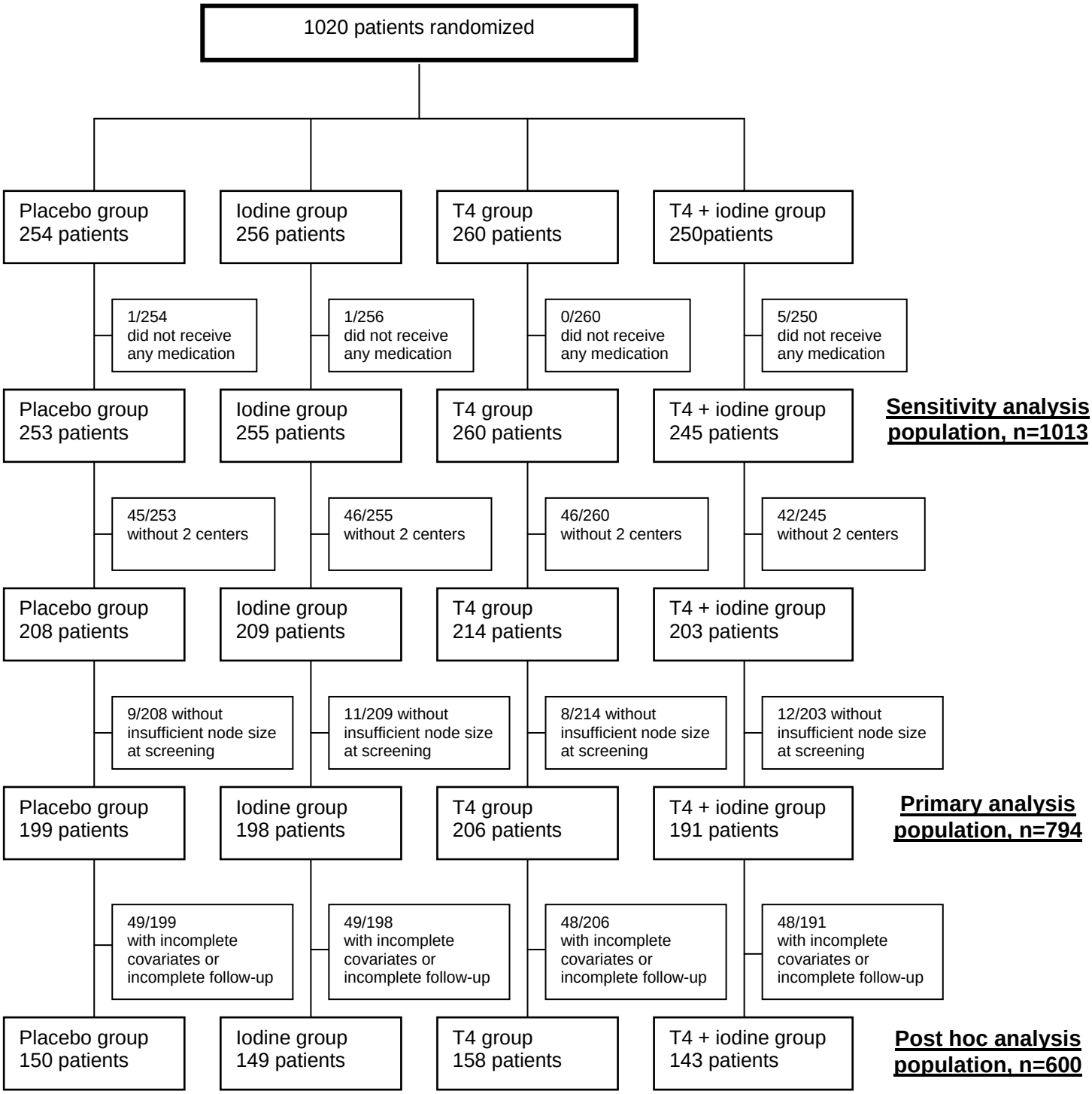
Visit	TSH	Placebo	Iodine	T4	T4+Iodine
Baseline	<0.2 mU/l	0%	0%	0%	0%
	0.2-0.8 mU/L	23.7%	23.7%	21.1%	29.3%
	>0.8 mU/l	76.4%	76.3%	78.9%	70.7%
After 3 months	<0.2 mU/l	0.7%	0.6%	39.2%	40.1%
	0.2-0.8 mU/L	22.3%	26.9%	40.3%	53.1%
	>0.8 mU/l	77.0%	72.4%	20.5%	6.8%
After 6 months	<0.2 mU/l	0.7%	0%	6.6%	17.0%
	0.2-0.8 mU/L	25.0%	30.8%	59.6%	58.5%
	>0.8 mU/l	74.3%	69.2%	33.7%	24.5%
After 12 months	<0.2 mU/l	1.4%	1.3%	4.8%	6.8%
	0.2-0.8 mU/L	29.7%	27.6%	57.2%	55.8%
	>0.8 mU/l	68.9%	71.1%	38.0%	37.4%

Supplemental Table 3: Classification of nodular volume changes according to direction of change

	Change in nodule volume, qualitative			
	Decrease	No change	Increase	Total
Placebo	101	14	84	199
	50.75%	7.04%	42.21%	
Iodine	108	16	74	198
	54.55%	8.08%	37.37%	
T4	115	15	76	206
	55.83%	7.28%	36.89%	
T4+Iodine	126	14	51	191
	65.97%	7.33%	26.70%	
Total	450	59	285	794
	56.68%	7.43%	35.89%	100.00%

VI. Supplementary Figure

Supplementary Figure 1: Patient flow



F I N A L

(**L**evothyroxin und **I**odid in der **S**trumatherapie **A**ls 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**	Final
		Date	08-Jan-2004

Sponsor	**Sanofi-Synthelabo GmbH** Geschäftsbereich Henning Berlin Potsdamer Straße 8 10785 Berlin
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Study Protocol - Clinical Study Phase IV

SIGNATURE PAGE

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1. SYNOPSIS

Study Title	**L**evothyroxin und **I**odide in der **S**trumatherapie **A**ls 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 Objective	To evaluate if the effect of a 12-month Thyronajod (levothyroxine/iodide combination) in the treatment of nodular goitre is superior to the effect after 12-month reference treatments with either levothyroxine or iodide monotherapies or placebo Each patient will start with a standard dosage Thyronajod® 75 Henning or L-Thyroxin Henning® 75 or Jodetten® 150 Henning or Placebo. After 3 months a dosage adjustment will be done due to the TSH result. It is aimed with study medication to get a target range of TSH between 0.2 – 0.8 mU/l
Study Medication	• 1 tablet Thyronajod® 75 Henning (depending on the TSH result after 3 months' Thyronajod® 50 Henning or Thyronajod® 100 Henning or • 1 tablet L-Thyroxin Henning® 75 (depending on the TSH result after 3 months' L-Thyroxin Henning® 50 or L-Thyroxin Henning® 100 or • 1 tablet Jodetten® 150 Henning or • 1 tablet Placebo all taken orally once daily
Project code	HB TJ 01/03
Indication	Nodular goitre
Study phase	IV
Study design	Prospective, randomised, double-blind, placebo-controlled, multicentre, 4 arms
Duration of treatment per patient	12-month double-blind treatment
Patient population	1000 male and female patients, 250 patients per group
Number of study centres	Minimum 30
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

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, which 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
Study criteria	<u>Primary objective:</u> Change in total volume of all nodules <u>Secondary objectives:</u> Change in goitre volume after a 12-month treatment, number of nodules, echogenity of nodules
Statistical methods	Bonferroni adjusted two-sample t-test comparisons (Mann-Whitney U test for count data) for test vs. reference treatments (one of the two active controls or placebo), analysis of covariance
Blood samples per patient	5 blood samples per patient within 12 months
Technical and analytical determinations	Determination of TSH, in a central laboratory Measurement of TPO antibodies at each site at screening and after a 12-month treatment Sonography with a 7.5 MHz ultrasound head or higher (a 3.5 MHz sonographic head is necessary in addition for large goitres) by experienced and proficient sonographic personnel.
Principal Investigator (“Leiter der klinischen Prüfung according to § 40 of the German Drug Law ”	Professor Dr.med. M. Grussendorf (Stuttgart)
Planned recruitment	January 2004 – January 2005
First patient out	February 2005
Planned study end	June 2006

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3. Choice of sample size: Executive Summary of July 7, 2003

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2. INTRODUCTION / STUDY RATIONALE

The pathogenesis of goiter is not completely understood. An important role has been attributed to endogenous thyrotropin (TSH) and other growth factors, mainly induced by iodine deficiency (in iodine deficient countries like Germany) [Mazzaferri, 1993; Giuffrida, 1995]. Levothyroxine (L-T4) therapy has been used to suppress the action of TSH and to reduce successfully the size of nodules (solitary solid nodules) in a portion of the patients. But controversial results in a number of studies indicated that a number of factors are involved. One of the major factors identified for the development of goitre is inadequate alimentary iodine supply. Iodine deficiency together with the action of different growth factors has a great proliferative effect on the thyroid resulting in hyperplasia. TSH boosts the hypertrophy of the thyroid cells and is, contrary to former interpretations, not the primary triggering factor of thyroid growth.

The worldwide incidence of iodine deficiency and the associated diseases, which primarily is goitre, is estimated to be about 11 % of the total population. Thyroid related illness is common in Germany. While Germany is known as an iodine-deficient country, goitre is still endemic although iodine prophylaxis has been established stepwise since the 1980s. Many patients remain undetected for a long period of time. Currently about 70 % of the general population in Germany is supplied with sufficient amounts of dietary iodine, whereas the others still have deficiency and need iodine supplementation [Gärtner, 2001; Meng, 2002]. According to WHO recommendations the daily iodine intake should be 150 – 300 µg; the average intake in the German population is estimated to be 100 – 120 µg [Gärtner, 2001; Feldkamp, 1998].

The thyroid gland compensates iodine deficiency with growth and/or development of nodules, which are either non-functional (cold nodules) or produce hormones (hot nodules).

Studies have been conducted with Levothyroxine and iodine either alone or in combination for treatment of diffuse and nodular goitre caused by iodine deficiency [Hintze, 1989; Saller, 1991].

Monotherapy with iodine in adults bears the risk of hyperthyreosis and the formation of autoantibodies due to the high doses needed [Koutras, 1986]. The combination therapy of L-T4 and iodine interact synergistically and may allow one to reduce the dose of iodine as well as L-T4. The use of L-T4 causes a reduction of the hypertrophic degeneration of the follicle cells and simultaneously iodine inhibits proliferation of follicle cells and causes a hyperplasia reduction. In general nodular goitre will be treated conservatively.

The treatment of euthyroid goitre with the combination levothyroxine and iodine was examined in several studies. In general, the combination therapy proved to be superior to the monotherapies in reducing the thyroid volume [Grussendorf, 1996; Klemenz, 1998; Kreissl, 2001; Hotze, 2002].

However, performing a meta-analysis Richter et al. [Richter, 2002] found that most of the studies, especially in iodine-deficient countries had inadequate sample size, lack of randomized assignments of patients, inappropriate control visit schedules, an open design and only short follow-up periods. In several of the studies the initial nodule size was not defined, the nodule size was inaccurately evaluated, and suppressive treatment of TSH was insufficient [Giuffrida 1995; Gharib, 1997]. The authors conclude that a carefully designed long-term study is needed to evaluate the benefit of L-T4 and iodine therapy in patients with goitre.

In a nation-wide thyroid screening initiative ("Schilddrüsen-Initiative Papillon") epidemiological data were collected by measuring sonographic changes of the thyroid in a large number of working adults of both sexes between the ages of 18 and 65.

Thyroid sonography is a relatively simple non-invavsive method to obtain information on size and characteristics of the thyroid gland. The first results of this epidemiological trial show that more than 30 % of the subjects exhibit a pathological thyroid finding (e.g. goitre or nodular thyroid changes). None of the screened subjects expressed any clinical findings of a thyroid disease. The incidence of pathological findings increased with age and was more prevalent in male subjects as expected.

STUDY RATIONALE

Though the data concerning medical treatment of endemic goitre in iodine-deficient regions as Germany are very inconsistant and controversial, millions of patients are treated with thyroid hormones or iodine (e.g. L-Thyroxine is one of the most frequently prescribed medicines in Germany) without any evidence-based guidelines for the prescribing physician. It is not proven until now, that a patient with nodular goitre will receive any benefit from the different treatment regimens with iodine, L-Thyroxine or a combination of both.

Therefore, a study with a high statistical level is needed to compare the different therapy regimens; the design of this study (prospective, double blind and randomized) and the high number of included patients will deliver evidence-based results, which will have an influence on the treatment of a widespread disease – not only in Germany.

3. STUDY OBJECTIVES

The aim of this study is to evaluate if the effect of Thyronajod (levothyroxine/iodine combination) is superior to each of the monotherapies (levothyroxine or iodide or placebo) in the 12-month treatment of nodular goitre.

- **Primary Objective:**
  - The primary objective is to compare the change in total volume of all nodules after 12 months Thyronajod treatment to the change after 12 month of each of the reference treatments (one of the two active controls or placebo)

- **Secondary Objectives:**
  - The change in goitre volume after Thyronajod treatment will be compared to that after each reference treatment after 12 months' treatment
  - Additionally, the change in the number of nodules after Thyronajod treatment will be compared to each reference treatment after 12 months' treatment
  - Echogenity of the nodules after Thyronajod treatment will be compared to each reference treatment after 12 months' treatment

4. STUDY DESIGN

The study is a national multicentre, prospective, double-blind, randomised, placebo controlled assessment of the efficacy and safety of 3 orally administered thyroid medications for goitre therapy and a placebo as control group for a period of 12 months. After 1 year, the patients will end their study medication treatment and the investigator will discuss further treatment with the patient.

A total of 1000 patients will be randomly assigned to one of the following 4 parallel groups:

- Thyronajod® 75 Henning, tablets, combination of 75 µg levothyroxine and 150 µg iodine
- L-Thyroxin Henning® 75, tablets, containing 75 µg levothyroxine
- Jodetten® 150 Henning, tablets, containing 150 µg iodine
- Placebo

After 3 months a dosage adjustment in the Thyronajod- and L-Thyroxin groups will be done based on the TSH result. The target range for TSH is between 0.2 – 0.8 mU/l.

5. PATIENT SELECTION

Patients of both gender, between 18 to 55 years of age with TSH levels within the upper normal range will be enrolled in this study. Patients will be selected by practicing thyroidologists in accordance with the inclusion and exclusion criteria (see section 5.1 and 5.2).

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

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.

Number of patients and study sites

It is planned to involve a minimum of 30 thyroid specialists to recruit a total of 1000 patients. Each site should be able to recruit 50 patients within 1 year. If necessary, to obtain the required number of patients, the sites could offer a voluntary thyroid screening initiative according to the "Schilddrüsen-Initiative Papillon" to recruit further patients.

6. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the final version of the study protocol, the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and Sommerset West), ICH-GCP guidelines, and the legal requirements of the German Drug Law (Arzneimittelgesetz, AMG) and the Federal data protection law (Bundesdatenschutzgesetz BDSG).

6.1 Patient Information and Consent

Every patient must to be informed verbally and in writing by the patient information, which has been approved by the respective ethics committee. The written informed consent form must be signed and personally dated by the patient and by the physician, who conducted the informed consent discussion, prior to performance of any study-specific procedures.
The date on which consent was obtained will be recorded on the case report form as well as in the patient's medical chart.

Every patient has the right to refuse participation in the study at any time and without giving any reason. Data protection, according to the stipulations of the German Data Protection Law, confidentiality and anonymity of the patients are assured.

6.2 Patient Insurance

Every patient is insured in accordance with the German Drug Law § 40 (3) against damage to health, which might occur during the conduct of the study and the material damages which might occur in connection thereto.

The sponsor is the holder of an annual ALLIANZ global risks third party liability insurance policy covering clinical trials worldwide. The insurance certificate contract number is IHA 10/445/9900017/220.

6.3 Ethics Committee (EC)

The study protocol and any subsequent amendments will be submitted first for review to the Principal Investigator's ("Leiter der Klinischen Prüfung" LKP) responsible Ethic's Committee (EC). This will be the Ethics Committee of the Landesärztekammer Baden-Württemberg.

The investigators must submit the final protocol and proposed informed consent document to their local Ethics Committee, which complies with the ICH Guideline for Good Clinical Practice. The EC will provide the investigator with a written decision regarding the conduct of the study at that site and a copy of the document will be forwarded to the Project Manager. The study will not be initiated and patients will not be enrolled until the appropriate documentation of EC approval of the study protocol and the informed consent have been received by the Project Manager.

Amendments to the protocol or any other written information, which is given to the patient, as well as any advertisements used for patient recruitment must be approved by the EC before implementation. The investigator will make appropriate and timely reports to the EC as required by applicable government regulations and EC policy. In addition to progress reports, all known information regarding serious and unexpected adverse events, whether observed at their clinical site or at another site participating in a clinical investigation with the study product, will be reported to the EC.

It is the investigator's obligation to provide the sponsor and/or its designees with copies of all study-related correspondence with the EC in a timely fashion and to retain originals in a study file. The investigator's file, including this EC correspondence will be made available upon request to appropriate Sponsor designees for monitoring or quality assurance review and to governmental regulatory representatives

It is the Sponsor's and/or its designee's responsibility to inform the investigator of serious and unexpected events observed at other investigational sites.

7. STUDY MEDICATION

7.1 Description of Study medication

The study products Thyronajod® 75 Henning, L-Thyroxin Henning® 75, and Jodetten® 150 Henning are currently marketed for goitre therapy. Batches selected for the study are to be manufactured and be released by the sponsor according to GMP standards. After 3 months, depending on the TSH result, a dosage adjustment (50 µg Levothyroxine-Na or 100 µg Levothyroxine-Na) will be made for Thyronajod and L-Thyroxin. As this study will be conducted in a double-blind fashion, two additional batches for Jodetten and Placebo will also be labelled to ensure that a balanced study medication supply is established.

Table 1: Study medications (to be labelled as Thyroid medication 1 -12)

Thyronajod

Product name	Thyronajod® 75 Henning	Thyronajod® 50 Henning	Thyronajod® 100 Henning
Formulation	tablets	tablets	tablets
Dosage active ingredient	75 µg Levothyroxine-Na and 196.2 µg KJ 196 µg KJ=150 µg Iodide	50 µg Levothyroxine-Na and 196.2 µg KJ 196 µg KJ =150 µg Iodide	100 µg Levothyroxine-Na and 196.2 µg KJ 196 µg KJ =150 µg Iodide
Manufacturer	Sanofi-Synthelabo GmbH		
Expiry date	……..	……..	……..

L-Thyroxin

Product name	L-Thyroxin Henning® 75	L-Thyroxin Henning® 50	L-Thyroxin Henning® 100
Formulation	tablets	tablets	tablets
Dosage active ingredient	75 µg Levothyroxine-Na	50 µg Levothyroxine-Na	100 µg Levothyroxine-Na
Manufacturer	Sanofi-Synthelabo GmbH		
Expiry date	……..	……..	……..

Jodetten

Product name	Jodetten® 150 Henning
Formulation	tablets
Dosage active Ingredient	196.2 µg KJ, 196 µg KJ = 150 µg Iodide
Manufacturer	Sanofi-Synthelabo GmbH

Expiry date	……..	……..	……..

Placebo

Product name	**Placebo**		
Formulation	tablets		
Ingredients	calcium phosphate, microcrystalline cellulose, maize starch, silicium dioxide, magnesium stearate		
Manufacturer	Dragenopharm Apotheker Püschl GmbH & Co. KG		
Expiry date	01/2007	01/2007	01/2007

7.2 Allocation of study medication

Patients will be assigned a consecutive “Screening number” at the time of written consent. Once eligibility has been confirmed (including the results of laboratory tests) the patient will be given a consecutive “Patient number”. The patient number will be given consecutively, in ascending order, according to a site-specific randomisation list, which allocates one of the four treatment groups.

7.3 Packaging and labelling of the study medication

Dragenopharm Apotheker Püschl GmbH & Co. KG will package and label the study medication. The study medication will be released by Sanofi-Synthelabo GmbH.

The study tablets are packaged in individual small “Duma” containers containing 35 tablets for one month’s supply.

The study medications will be labelled in accordance with the German Drug Law (AMG) § 10. The text of the label will be as follows:

Zur klinischen Prüfung bestimmt!

Für Kinder unzugänglich aufzubewahren!

1 Tablette enthält: Schilddrüsenmedikation

Menge: 1 Dose enthält 35 Tabletten zum Einnehmen

Studien-Nr.: HB TJ 01/03

Ch.-B.: .....

Verwendbar bis: .....

Zentrums-Nr.: .....

Patienten-Nr.: .	.....
Hersteller:	Sanofi-Synthelabo GmbH, 10898 Berlin

Nicht über 25°C lagern!

Vor Licht und Feuchtigkeit geschützt aufbewahren !

The batch numbers for the 12 study medications will be as follows:

(1) 011-161-113, (2) 021-112-221, (3) 103-141-311, (4) 103-151-511, (5) 116-011-811, (6) 116-113-311, (7) 181-110-144, (8) 221-111-211, (9) 511-911-811, (10) 611-711-130, (11) 711-101-119, (12) 911-811-115

Each site will be provided with an initial shipment of a 3-month study medication supply for 12 patients. Further shipments will be sent as needed.

7.4 Dosage and administration

First, each patient will start with a standard dosage i.e. Thyronajod® 75 Henning, L-Thyroxin Henning® 75, Jodetten® 150 Henning or Placebo. Depending on the TSH result (target normal value 0.2 – 0.8 mU/l under therapy) a dosage adjustment will be performed after 3 months. SocraTec-PFC will deliver the appropriate study medication and dosage for each patient to the site, which will in turn forward the medication to the patient.

One tablet of the study medication is to be swallowed whole with sufficient water, once daily 30 min before breakfast.

7.5 Breaking treatment codes

Every attempt must be made to keep the study blind intact. However, if in the investigator's opinion an emergency situation requires knowledge of the randomization code, Sponsor Project Manager, Dr. Vaupel or Socratec-PFC Project Manager Dr. Schinnerling should be contacted **immediately.** The investigator must submit the date and reason(s) for breaking the blind in writing to Dr. Vaupel or Dr. Schinnerling, within 24 hours.

7.6 Storage, dispensing and return of study medication

All study supplies are to be stored in a locked area separately from normal practise stocks and stored at room temperature. The site will confirm receipt and disposition of study medication in writing.

The study medication will be given to the patient at the baseline visit. At visits 2 and 3 (see flow chart, section 9) a blood sample will be taken to determine the TSH level and afterwards, after the TSH result is available, the appropriate dosage of the same study medication will be sent to the patient. Patients will be instructed to return unused study medication in the original Duma container at each study visit. After medication reconciliation is complete at the end of the study, all study medication containers (used and unused) received by the investigator will be collected by the monitor.

7.7 Patient Compliance

Compliant patients are defined as those, who have taken at least 80% of the prescribed dose.

8. CONCOMITANT THERAPY

Permitted concomitant medication

Concomitant medication treatment may be necessary. Depending on the type and duration of treatment, the investigator may decide whether this is acceptable for further study participation or whether the patient needs to be withdrawn for his own safety. A concomitant medication (documented by generic name), the dosage and each change in the dosage as well as the start and end dates of therapy are to be documented in the case report form.

If any of the medications, below, are required, then with specific caution:

- Salicylate, dicumarole, furosemide, clofibrate replace levothyroxine from the plasma-protein linkage
- Phenytoin: fast i.v. application may produce increased plasma level of levothyroxine and liothyronine and favor in some cases a development of cardiac arrythmia
- Antacids with aluminium and ferric salts, because resorption of levothyroxine could be reduced
- Antidiabetics and coumarin derivates: dosages of these drugs must be adapted and the laboratory parameters glucose and blood coagulation must be controlled

Not permitted concomitant medication

- Amiodarone: due to high iodine concentration, amiodarone could initiate hyperthyreosis as well as hypothyreosis
- Any other iodine-containing medication

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

9.1 Visit procedures

In order to check inclusion and exclusion criteria each patients will undergo a pre-study examination (screening).

Screening (Visit 1): Day -28 (max.) to Day -1

The following procedures and assessments must be performed prior to receiving the first dose of the study medication:

- Informed consent: study related details will be carefully discussed with the patient, and the patient will be asked to sign the approved Informed Consent Form. Signed Informed Consent must be obtained before proceeding with other evaluations.
- Medical history
- Vital signs (Blood pressure and pulse)
- Clinical laboratory: leukocytes, erythrocytes, haemoglobin, haematocrit, potassium, calcium, creatinine, γ-GT, GPT, AP
- Determination of TSH and antithyroidal antibodies (anti-TPO) at each site; for all other visits TSH determination will be measured by using the central laboratory
- Ultrasound examination of the thyroid gland, for nodules > 1.0 cm the diagnosis must be performed according to the guideline for diagnostic standards of thyroid disorders

Visit 2 (Baseline): Day 0

- Complete physical examination, including weight and height
- Ultrasound examination of the thyroid gland
- Vital signs
- Determination of TSH
- Iodine determination in urine
- Review inclusion and exclusion criteria
- Study medication dispensing according to the consecutive patient number
- The patient will be instructed to take the study medication with water the next morning 30 minutes before breakfast and to return the Duma bottles at the next visit

Visits 3 and 4 (Control):

The following evaluations are to be completed after 3 and 6 months. Study visits are to be completed within $\pm$ 7days of the protocol-specified visit date calculated from the baseline visit. Regularly scheduled evaluations will be made for all patients, even if they may have discontinued the study medication treatment.

- Review of AEs and changes in concomitant medication
- Study medication return (Drug accountability will be done by the monitor and not by the investigator or study staff)
- Vital signs
- Determination of TSH
- Ultrasound examination of the thyroid gland
- The site will forward the appropriate study medication to the patient after the receipt of the TSH result

Visit 5 (Study end):

End of study visit has to be completed within 12 months (± 14 days) calculated from the baseline visit.

- Review of AEs and changes in concomitant medication
- Study medication return (Drug accountability will be done by the monitor)
- Physical examination
- Vital signs
- Clinical laboratory: leukocytes, erythrocytes, haemoglobin, haematocrit, potassium, calcium, creatinine, γ-GT, GPT, AP
- Determination of TSH
- Antithyroidal antibodies (anti-TPO)
- Iodine determination in urine
- Ultrasound examination of the thyroid gland

9.2 Laboratory methods

The patients must be instructed to come to each visit in a fasted state before the blood sample is taken. Specific instructions for handling TSH samples will be given by the central laboratory. TSH will be measured by commercial assays in a central laboratory for all visits, except for the screening visit which will be determined at each site's laboratory. At screening and at the study end visit the TPO antibodies will be determined by the site's laboratory. The site's laboratory will also perform the clinical laboratory analysis.

The iodine determination in urine at the baseline visit and at the study end visit will be done at the University of Würzburg.

9.3 Normal ranges for laboratory variables

Each site must send SocraTec-PFC / Sponsor a current list of normal values of the chemistry parameters and the lab certificates prior to shipment of study medication. SocraTec-PFC / Sponsor shall be informed immediately about any change in normal values during the study.

9.4 Efficacy measurements

Efficacy measurements will be done as follows:

- Ultrasonography with 7.5 MHz or higher (a 3.5 MHz sonographic head is necessary in addition for large goitres) by an experienced and proficient examiner, who is masked to treatment assignment. **Each patient examination should be performed by the same examiner to reduce variability.**
- Calculation of the goitre and nodule volumes will be done by the published method of Brunn and Block [Brunn J, 1981] according to the following formula:
  - Male: Lobe volume (ml) = 0.50 length x depth x width (in cm)
  - Female: Lobe volume (ml) = 0.48 length x depth x width (in cm)

10. TIME SCHEDULE

After the LKP EC approval the German Health Authority will be notified and the local authority will be informed about the investigator participation of each “Bundesland”. It is planned to initiate the first sites in January 2004. After a 12-month recruitment time, and a 12-month treatment period, the first patient will complete the clinical study part in June 2006.

11. DRUG SAFETY

11.1 Definition of Adverse Events (AEs)

An **adverse event** is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) or symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

11.2 Definition of Serious Adverse Events (SAEs)

A **serious adverse event** is defined as any untoward medical occurrence that at any dose

- results in death, or
- is life-threatening, or
- requires hospitalisation or prolongation of existing hospitalisation, or
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Examples of such events are intensive treatment in an emergency unit or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The term „life threatening“ in the definition refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe. Hospitalisation for rehabilitation or surgery already planned before the start of the study period is not a serious AE. Such an event meets the definition of „no case“.

11.2.1 Definition of unexpected Adverse Events

An AE/SAE, whose nature or severity is not consistent with the applicable product information, (Investigator´s Brochure, local product information sheet) is an **Unexpected AE/SAE.**

11.3 Causality

Classification of causality of adverse events to the study drug

Every AE experienced during the clinical trial must be evaluated for its relation to the investigational medication administered. The causal relationship of an adverse event with the investigational product(s) will be classified as follows:

Probable	When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
Possible	When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, e.g., due to missing data or insufficient evidence.
No causal relationship	When there is sufficient information to accept a lack of a causal relationship in the sense of impossible and improbable.
Unclassified	When the causal relationship is not assessable for whatever reason, e.g. due to insufficient evidence, conflicting data or poor documentation.

11.4 Recording of AEs

Adverse events are to be documented on the appropriate case report form including information about type of AE (description, diagnosis), time course of AE (date and time of onset and end) and evaluation of seriousness and all measures resulting from the AE. Furthermore, the outcome of the AE and the relationship with the study medication (causality) is to be classified. After termination of the clinical trial phase, any adverse event having occurred will be listed and described in the report including a judgement about the relation of the AE to the treatment.

Classification of adverse events with regard to (maximum) intensity

The intensity of an adverse event is to be classified according to the following criteria

Mild	The AE impairs the normal functional level of the patient only slightly, if at all.
Moderate	The AE impairs the normal functional level of the patient to a certain extent.
Severe	The AE represents a clear-cut, marked impairment of the patient's normal functional level.

Each degree of intensity occurring within the course of observation of an untoward medical occurrence is to be documented and evaluated as a single adverse event.

Specification of the outcome of adverse events
The outcome of an adverse event is to be classified as follows:

recovered

recovered with sequelae

not yet recovered

death

unknown

The sponsor should expedite the reporting to all concerned investigator(s)/institution(s) and to the regulatory authority(ies) of all AEs that are both serious and related. Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Safety data will be summarised in the final report. Listing of individual values and descriptive statistical evaluation will be given for all measured values including clinical laboratory parameters, heart rate and systolic/diastolic blood pressure. Furthermore, AEs will be described and judged considering medical relevance

11.5 Reporting of AEs

SAEs are to be documented in detail on the SAE form in addition to the regular AE documentation on the case report form. Each Investigator must report SAEs within 24 hours, at the latest the next working day, to the Drug Safety Department of the sponsor.

Dr. Gernot Schreiber
Sanofi-Synthelabo GmbH
Geschäftsbereich Henning
Potsdamer Straße 8
10785 Berlin
Telephone 030/2575-2170 / Fax 030/2575-2295

SAEs which, according to present knowledge, might be caused by the study drugs require immediate, thorough medical assessment by the Principal Investigator. The decision regarding termination of the entire study will be taken on the basis of this assessment and in accordance with the German Drug Law (AMG) and the legal requirements of other involved countries.

The relevant ethics committee as defined by the AMG § 40 must be informed, if the AEs

- are serious and related, or
- are unexpected and might jeopardise the safety of the subjects or the conduct of the study

11.6 Monitoring of patients with AEs

Any AE that occurs in the course of the study must principally be monitored and followed up until

- it receeded

- pathological laboratory findings have returned to normal

- exclusion of a relationship to the study medication

AEs, which are still present at the end of the study are to be followed up until a final assessment is possible. All deaths, regardless of cause or relationship, must be reported for subjects on study and for deaths occurring within 30 days of last study medication dose or within 30 days of last study evaluation, whichever is longer.

11.7 Overdosage and intoxication with the study medications

The investigational products contain levothyroxine and/or iodine as active ingredient.

Adverse effects of **L-T4** are related to overdosage and generally correspond to symptoms of hyperthyroidism. These adverse effects usually disappear after dosage reduction or temporary discontination of treatment. Thyroid crisis has occasionally been reported following massive or chronic intoxication [Roti, 1993]. Single large doses of L-T4 up to 3 mg in healthy individuals appear to be safe and lack clinical toxicity [Wenzel, 1977; Spencer, 1995; Wenzel, 1974; Wallack, 1970]. In former studies with about 400 drug exposures single oral L-T4 doses of 600-700 µg/d were tolerated without any serious adverse reaction; only rarely mild effects like heat intolerance, nervousness, and sleep disorders were observed that could be attributed to L-T4 [Walter-Sack, 2003]. Further effects, which can occur, are tachycardia, palpitations, cardiac arrythmia, chest pain, muscular weakness, muscle cramps, hyperhidrosis, fever, tremor, vomiting, diarrhea, weight loss, headache, Pseudotumor cerebri and menstruation disorders [Product information of L-Thyroxin Henning, 2003].

Thyroid agents are contra-indicated in untreated thyrotoxicosis and should be used with caution in patients with cardiovacular disorders including heart failure and hypertension [Product information of Thyronajod 2003]. Thyroid replacement therapy should be introduced only very gradually in elderly patients and those with long-standing hypothyroidism to avoid any sudden increase in metabolic demands. L-T4 should not be given to patients with adrenal insufficiency without adequate corticosteroid coverage. Otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis [Toft, 1994].

Iodine supplementation for prevention of goitre in otherwise healthy individuals can be scheduled as daily intake of the required amounts or as a larger single iodine dose up to 1500 µg once per week [Product information of Jodetten, 2003]. Extrathyroidal adverse effects of iodine are uncommon. The most frequently encountered adverse reaction is sialoadenitis, but this occurs only after the administration of large doses of iodine. Drug sensitivity rashes, including dermatitis herpetiformis and hypocomplementemic vasculitis, can occur after iodine exposure, but are rare. In addition, fever, ocular itching and burning, dry cough, diarrhea, or headache can occur.

With respect to intrathyroidal effects, single doses of 450 to 900 µg iodine can be regarded as safe in normal individuals. However, subtle effects on thyroid function are possible. Large doses of iodine (40 to 150 mg per day) can cause small but significant rise in TSH. Smaller quantities of iodine (1500 to 4500 µg/d) administered to normal individuals, who resided in iodine-replete areas resulted in significant decreases in serum TT4 and fT4,but not in serum TT3 concentrations, whereas TSH concentrations increased [Gardner, 1988]. The smallest quantitiy if iodine that did not affect thyroid function after prolonged administration was 500 µ/d [Paul, 1988].

In small other studies, however, this small quantity of iodine enhanced the TSH response to TRH and in a few patients also increased the basal serum TSH concentration above the normal range. Thus, iodine administration of about 500 µg/d above the normal diet in iodine-sufficient areas might cause subtle changes in thyroid function.

In particularly susceptible persons, iodine exposure may also cause three primary types of intrathyroidal effects.

1. Iodine thyroiditis, which sometimes causes painful inflammation of the thyroid that occurs after intake of large doses of iodine
2. Iodine goitre with hypothyroidism or more commonly goitre alone without hypothyroidism

   This also usually occurs after prolonged exposure to dietary iodine or drugs containing iodine.
3. Iodine-induced thyrotoxicosis, which is seen after excess iodine exposure in four patient groups:

   - patients from areas of endemic goitre
   - patients with known goitre
   - euthyroid patients with autonomous hyperactive nodules or a history of previous hyperthyroidism or Grave's disease

   This has been rarely observed in patients with no underlying thyroid disorders [Nuovo, 2001; Roti, 1996].

12. STATISTICS

12.1 Analysis populations

The primary analysis population is the ITT population. The ITT (intention-to-treat) population consists of all randomised patients, who received at least one dose of study medication.

Further analyses will be performed in the PP population. The PP (per protocol population) consists of all patients of the ITT population, who met the inclusion critieria and did not meet the exclusion criteria, did not experience any protocol violation and were in particular treated with the study medication according to the standard procedure as defined in the study protocol.

12.2 Primary endpoint

12-month difference from baseline in sonographically determined log total volume of all nodules with a diameter of >0.5 cm.

12.3 Secondary endpoints

- 12-month difference from baseline in log thyroid volume, number of nodules, number of nodules with high/normal/low echogenity and log maximal nodule volumes

12.4 Randomization and Sample Size

250 patients per group will be randomized. The rationale for the choice of the sample size is given in the Appendix 3 (Executive Summary of July 7, 2003). While the calculations in appendix 3 concern the total thyroid volumes, it is assumed based on unpublished data that the differences in log total nodule volumes behave sufficiently similar to allow the demonstration of relevant therapeutic differences with the same sample sizes. With these sample sizes, the probability will be at least 80% that a true difference of 0.06 log units between test and one of the reference treatments will be detected, assuming that the true within-group standard deviation of the primary variable is 0.2 log units and the drop-out rate is below 15%.

12.5 Description of statistical analysis

The primary analysis will consist of the three two-arm comparisons (test vs. one of the two active controls or placebo) of the primary variable, using two-sample t-tests. The level of the t-tests will be 0.0167 two-sided in order to guarantee a multiple test level of 0.05, according to the Bonferroni procedure.

Further analysis include the corresponding analyses of the secondary variables (the numbers of nodules will be analysed using the Mann-Whitney U test, as this is a count variable). Analysis of covariance will be applied additionally, in order to adjust for baseline measurements and demographic parameters. A detailed statistical analysis plan will be prepared before unblinding of the study.

12.6 Coding Procedures

The body systems of the medical conditions will be coded according to MedDRA. The specific conditions will be coded according to WHO dictionary.

12.7 Data handling procedures

The CRFs will be logged in, entered in a double-data fashion and checked using computerised and manual means to identify inconsistencies (validation plan). DMSys Version 5.0 software will be used for data entry and automated checks. Queries will be issued, e.g. on missing data, inconsistencies, illegibilities, illegal values and improperly corrected items (e.g. without initials, date of change or a clear reason for change). Answers to queries, which have to be signed by the investigator, will be implemented in the database and kept together

with the original CRF. When the two databases are 100% concordant, inconsistencies etc. are resolved and data sets are clean, the database will be locked and will be provided to the statistician to perform the statistical analysis.

13. STUDY MANAGEMENT

13.1 Data Handling

Data required according to this protocol are to be recorded for each patient on the appropriate Case Record Form (CRF). Entries on the CRF must be legible and made using a black ball-point pen. Pencils and correction fluids are not allowed. If corrections are necessary, they will be entered by a member of the site study team in the following manner: the wrong CRF entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to the error. Corrections must be initialled and dated by an authorised study team member. For corrections concerning AEs or a primary variable, a reason must be provided.

13.2 Monitoring

In accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor will review the signed informed consent, the patient medical record, the Investigator File, study medication storage and check the medication compliance due to the study medication accountability form. The monitor must have direct access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.3 Audits

Any study may be selected for audit at any time by the sponsor, its designee or by a regulatory body. The investigator and his team should be available when the auditors visit and the auditors will need direct access to the patient data.

14. CHANGES

14.1 Amendments to the study protocol

All protocol amendments will be issued by the sponsor and must be signed and dated by the LKP, by each investigator and approved by the Ethics Committee and Regulatory Agency prior to implementation of the amendment.

14.2 Deviations from the study protocol

In situations requiring a departure from the protocol, the investigator or other physician in attendance will contact the monitor by fax or telephone. If possible, this contact will occur before implementing any departure from protocol. The CRF and source documentation must describe any departure from the protocol and the circumstances.

14.3 Premature discontinuation of Patients

The investigator or the sponsor may prematurely discontinue an individual patient from the study at any time for the following reasons:

- If a patient suffers an adverse event that, in the judgment of the investigator or sponsor, presents an unacceptable risk to the patient
- If a patient develops an illness or complication that is not consistent with the protocol requirements or which justifies withdrawal from the study
- Non-adherence to the study conditions or relevant deviations from procedures as established in the study protocol
- Withdrawal of consent
- If a patient has used a prohibited medication or treatment, or otherwise fails to comply with protocol requirements
- The patient shows signs of a hypersensitivity reaction
- Pregnancy

If a patient is prematurely withdrawn from the study, the procedures foreseen for Visit 3 (end of study) will be performed at the time of patient discontinuation.
The investigator must document the reason for patient discontinuation on the patient "Premature Discontinuation" page of the CRF. The patient should also complete a follow-up visit within 1 month for the safety aspects and study medication return whenever possible.

If not possible, a follow-up telephone call will be made to the patient within 1 month after the date of discontinuation to document resolution of any outstanding adverse events or to record any new adverse events. All adverse events will be followed up by phone or in person until resolution or until a stable clinical endpoint is reached.

In the event a patient discontinues due to an adverse event, the investigator should notify the SocraTec-PFC's Project Manager by telephone, fax or email within 48 hours of discontinuation.

14.4 Replacements of patients

Patients who prematurely discontinue participation will be not replaced.

14.5 Premature discontinuation of the study / of a center

- Serious adverse events (SAEs)
- Occurrence of AEs unknown to date in respect of their nature, severity and duration or the unexpected incidence of known AEs
- Insufficient recruitment of patients
- Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Sanofi-Synthelabo GmbH, Geschäftsbereich Henning, and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

14.6 Confidentiality and investigator agreement

The methods of data collection and processing are designed to safequard the confidentiality of the parties. The results of this study are considered to be the property of Sanofi-Synthelabo GmbH, Geschäftsbereich Henning Berlin. The confidentiality agreement will be part of the investigator study contract. An investigator statement will be also implemented in the investigator study contract that the investigator has read the protocol, including all appendices, and has agreed that it contains all necessary details for them and the staff to conduct this study as described. The investigator will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. The investigator will provide all study personnel under his/her supervision copies of the protocol and access to all information provided by the sponsor. The investigator will discuss this material with them to ensure that they are fully informed about the study medications and the study.

15. STUDY REPORT AND PUBLICATION

After conclusion of the study and without prior written approval from Sanofi-Synthelabo GmbH, Geschäftsbereich Henning Berlin, investigators in this study may communicate, orally present, or publish in scientific journals after the results of the study in their entirety have been publicly disclosed by or with the consent of Sanofi-Synthelabo GmbH, Geschäftsbereich Henning Berlin in an abstract, manuscript, or presentation form.

15.1 Record keeping

Any study documents must be retained for at least 15 years after the completion of the overall clinical study report The sponsor will inform the investigator about developments which could affect the required storage period.

16. REFERENCES

1. Mazzaferri EL, Management of a solitary nodule. N. Engl J Med 1993; 328:553-559.

2. Giuffrida D, Gharib H, Controversies in the management of cold, hot and ocult thyroid nodules.
   Am J Med 1995; 99:642-650.

3. Gärtner R, Manz F, Grossklaus R, Representative data of iodine intake and urinary excretion in Germany. Exp Clin Endocrinol Diabetes 2001; 109:2-7.

4. Meng W, Scriba PC, Jodversorgung in Deutschland. Dtsch Ärztebl 2002; 99:B2185-9.

5. Feldkamp J, Röher HD, Scherbaum WA., Rezidivprophylaxe und medikamentöse Therapiestrategien nach Operationen an der Schilddrüse. Dtsch Ärztebl 1998; B1821-5.

6. Hintze, G., D. Emrich und J. Köbberling, Treatment of endemic goiter due to iodine deficiency with iodine, levothyroxine or both. Results of a multicenter trial.
   Eur J Clin Invest 1989;19: 527-534.

7. Saller B, Hoermann R, Ritter MM, Morell R, Kreisig T, Mann K, Course of thyroid iodine concentration during treatment of endemic goitre with iodine and a combination of iodine and levothyroxine. Acta Endocrinol (Copenh). 1991; 125:662-7.

8. Koutras, D. A., Karaiskos, K. S., Piperingos, G. D., et al., Treatment of endemic goitre with iodine and thyroid hormones, alone or in combination.
   Endocrinol. Exp. 1986; 20:57–65.

9. Grussendorf M, Therapie der euthyreoten Jodmangelstrum. Wirksamkeit der Kombination aus L-Thyroxin und 150 µg Jodid im Vergleich zu Mono-L-Thyroxin.
   Med. Klinik 1996; 91:489-493.

10. Klemenz B, Förster G, Wieler G et al., Studie zur Kombinationstherapie der endemischen Struma mit zwei unterschiedlichen Thyroxin/Jodkombinationen.
    Nuklearmedizin 1998; 37:101-106.

11. Kreissl M, Tiemann M, Hänscheid H et al., Vergleich der Wirksamkeit zweier verschieden-dosierter Levo-Jodid-Kombinationen in der Therapie der euthyreoten diffusen Struma. Dtsch Med Wochenschr 2001; 126:227-231.

12. Hotze L-A, Wegscheider K, Therapieverlauf bei euthyreoter Jodmangelstruma: Vergleich der Wirksamkeit und Verträglichkeit von zwei Levothyroxin-Jodid-Kombinationen.
    Fortschritte der Medizin 2002; Originalien 120 Jg. No.11:37-41.

13. Richter B, Neises G, Clar C., Pharmacotherapy for thyroid nodule, A systematic review Meta analysis Endocrinol Metab Clin North Am. 2002 Sep; 31(3):699-722.

14. Gharib H, Management of thyroid nodules; another look.
    Thyroid Today 1997; 20(1):1-11.

15. Brunn J, Block U, Ruf G et al., Volumetrie der Schilddrüsenlappen mittels Real-Time-Sonographie. Dtsch Med Wschr 1981; 106:1338-1340.

16. Roti E, Minelli R, Gardini E, Braverman LE, The use and misuse of thyroid hormones endocrine rev 1993; 14:401-423.

17. Wenzel KW, Kirschsieper HE, Aspects of the absorption of oral L-thyroxine in normal man Metabolism 1977; 26:1-8.

18. Spencer CA, LoPresti JS, Nicoloff JT, Dlott R, Schwarzbein D, Multiphasic thyrotropin responses to thyroid hormone administration in man. J Clin Endocrinol Metab 1995; 80:854-9.

19. Wenzel KW, Meinhold H, Evidence of lower toxicity during thyroxine suppression after a single 3-mg L-thyroxine dose: Comparison to the classical l-triiodothyronine test for thyroid suppressibility. J Clin Endocrinol Metab 1974; 38:902-5.

20. Wallack MS, Adelberg HM, Nicoloff JT. A thyroid suppression test using a single dose of L-thyroxine. N Engl J Med 1970; 283:402-5.

21. Walter-Sack I, Clanget C, Ding R, Goeggelmann C, Hinke V, Lang M, Pfeilschifter J, Tayrouz Y, Wegscheider K, Assessment of levothyroxine bioavailability: recommendations for an improved methodology based on the pooled analysis of eight identically designed trials with 396 drug exposures. Clin Pharmacokinet 2003.

22. L-Thyroxin Henning® [Product information dated October 2003]

23. Thyronajod® 50, 75, 100, 125 Henning [Product information dated February 2003]. Sanofi-Synthelabo GmbH, Geschäftsbereich Henning Berlin.

24. Toft AD, Thyroxine therapy. N Engl J Med 1994; 331:174-80.

25. Jodetten® Henning, [Product information dated April 2003]. Sanofi-Synthelabo GmbH, Geschäftsbereich Henning Berlin.

26. Gardner DF, Centor RM, Utiger RD, Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol (Oxf) 1988 ;28:283-288.

27. Paul T, Meyers B, Witorsch RJ, Pino S, Chipkin S, Ingbar SH, Braverman LE, The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 1988; 37:121-124.

28. Nuovo JA, Wartowsky L; Adverse effects of iodide. In Principles and Practise of Endocrinology and Metabolism, K.L. Becker Editor, Lippincott Williams and Wilkins, Philadelphia 2001, pp.360-266.

29. Roti E, Vagenakis AG, Effect of excess iodide: clinical aspects. In Werner and Ingbar's The Thyroid; Braverman LE, Utiger RD, Editors, Philadelphia: Lippincott–Raven;1996:316-27.

17. ABBREVIATIONS

AE	Adverse Event
AMG	Arzneimittelgesetz, German Drug Law
AP	Alkaline Phophatase
BDSG	Bundesdatenschutzgesetz
CRF	Case Report Form
GCP	Good Clinical Practice
γ-GT	γ-Glutamyltransferase
GPT (ALAT)	Glutamate pyruvate transaminase (alanine-aminotransferase)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
SAE	Serious Adverse Event
TPO-Ab	Anti Thyroid Peroxidase-Antibodies
TPO	Thyroid Peroxidase
TRH	Thyroid Releasing Hormone
TSH	Thyroid Stimulating Hormone

HENNING BERLIN

Amendment No. 1

Levothyroxin und **I**odid in der **S**trumatherapie **A**ls 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
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Statistician	**Prof. Dr. Karl Wegscheider**
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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Principal Investigator

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Dr. P. Schinnerling

Project Manager and
author of the protocol
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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
- 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.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.

Amendment No. 2

Levothyroxin und **I**odid in der **S**trumatherapie **A**ls 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. 2**
		Date	29-Sep-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
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Study Protocol - Clinical Study Phase IV

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Study protocol HB TJ 01/03

Amendment No. 2

Amendment No. 2 of September 17th, 2004 with respect to the final study protocol of January 08th, 2004, final version and Amendment No. 1 of February 05th, 2004

The Amendment 2 of the amended Study Protocol became necessary after discussions with the Principal Investigator, other investigators and proposals of some Ethics Committees. The crucial point was: In a nation-wide thyroid screening initiative ("Schilddrüsen-Initiative Papillon") epidemiological data were collected in a large number of “healthy” working adults. A total of 96278 employees 18-65 years of age from 214 companies or other private or public institutions voluntarily underwent ultrasonographic examinations of the thyroid by experienced investigators. The result was: Nodular goiter was found in 9,1 % of the examined population and nodules without enlarged thyroid in 14,3 %. (These results are accepted for publication in “Thyroid”). All these abnormal findings have to be treated. So it was decided by the Principal Investigator, to delete the limitation of the thyroid gland.

Therefore it was reasonable to take into account the entire spectrum of possible treatment options resulting in a consensus decision of the investigators who participated in the discussion. This is the reason for changing two inclusion criteria and one exclusion criterion. The following changes are to be implemented:

1. Two inclusion criteria were revised (Page 11, 5.1 inclusion criteria)
2. One exclusion criterion was revised (Page 11, 5.2 exclusion criteria)

3. On closer inspection a discrepancy was conspicuous between the patient information and the study protocol. In the study protocol a change of food at the patient groups is not planned but in the patient information.

   As a result the patient information has been revised.

4. Furthermore the CRO was changed. The study will be attended to a new CRO.

   New CRO: IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH.

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 1 Synopsis

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 ...
Exclusion criteria	Thyroid therapy within the last 3 years Known focal or diffuse structure autonomous thyroid Presence of thyroid cysts Contraindication to iodine ...

1.a. New version:

in Protocol Section 1 Synopsis

Inclusion criteria	Caucasian Age 18 – **65** years (inclusive) Normal TSH value (target range between 0.6 – 3.0 mU/l) Thyroid nodules in a normal sized or enlarged thyroid~~(women > 18 ml, men > 25 ml but maximum 60 ml),~~ at least one nodule **(≤ 20% of volume with cystic change)** 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 ...
Exclusion criteria	Thyroid therapy within the last 3 years Known focal or diffuse structure autonomous thyroid ~~Presence of thyroid cysts~~ Contraindication to iodine ...

1.b. Previous version:

in Protocol Section 5 Patient Selection

Patients of both gender, between 18 to 55 years of age with TSH levels within the upper normal range will be enrolled in this study. Patients will be selected by practicing thyroidologists in accordance with the inclusion and exclusion criteria (see section 5.1 and 5.2).

1.b. New version:

in Protocol Section 5 Patient Selection

Patients of both gender, between 18 to **65** years of age with TSH levels within the upper normal range will be enrolled in this study. Patients will be selected by practicing thyroidologists in accordance with the inclusion and exclusion criteria (see section 5.1 and 5.2).

1.c. Previous version:

in Protocol Section 5.1 Inclusion Criteria

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. New version:

in Protocol Section 5.1 Inclusion Criteria

5.1 Inclusion Criteria

- Caucasian
- Age 18 – **65** years (inclusive)
- Normal TSH value (target range between 0.6 – 3.0 mU/l)
- ~~Nodular goitre~~ Thyroid nodules ~~(women > 18 ml, men > 25 ml but maximum 60 ml)~~ in a normal sized or enlarged thyroid, at least one nodule ~~(without cyst component)~~ **(≤ 20% of volume with cystic change)** 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

2.a. Previous version:

in Protocol Section 5.2 Exclusion Criteria

5.2 Exclusion Criteria

- Thyroid therapy within the last 3 years
- Known focal or diffuse structure autonomous thyroid
- Presence of thyroid cysts
- Contraindication to iodine
- ...

2.a. New version:

in Protocol Section 5.2 Exclusion Criteria

5.2 Exclusion Criteria

- Thyroid therapy within the last 3 years
- Known focal or diffuse structure autonomous thyroid
- ~~Presence of thyroid cysts~~
- Contraindication to iodine
- ...

3.a. Previous version:

Patient Information, Page 1

Sehr geehrte Patientin, sehr geehrter Patient,

Ihr behandelnder Arzt hat Sie gefragt, ob Sie an dieser klinischen Studie teilnehmen möchten, und Ihnen dieses Informationsblatt überreicht, um Sie über das Ziel und die Durchführung dieses Forschungsvorhabens zur Behandlung einer knotigen Struma (Kropf) zu informieren.

3.a. New Version:

Patient Information, Page 1

Sehr geehrte Patientin, sehr geehrter Patient,

Ihr behandelnder Arzt hat Sie gefragt, ob Sie an dieser klinischen Studie teilnehmen möchten, und Ihnen dieses Informationsblatt überreicht, um Sie über das Ziel und die Durchführung dieses Forschungsvorhabens zur Behandlung von Schilddrüsenknoten mit oder ohne Vergrößerung der Schilddrüse ~~einer knotigen Struma (Kropf)~~ zu informieren.

3.b. Previous version:

Patient Information, Page 2

Studienziel

- Vergleich der verschiedenen medikamentösen Therapiemöglichkeiten mit einer alleinigen Ernährungsumstellung.

Studienteilnehmer

Patienten mit vergrößerter Schilddrüse, in der sich Knoten gebildet haben (medizinischer Fachbegriff: Struma nodosa)

Studienmedikation

- Ernährungsumstellung allein, als Medikament wird ein Placebo (Scheinmedikament ohne Wirkstoff) gegeben

Studienrisiken

Durch die Teilnahme an dieser Studie wird die Entwicklung Ihrer Struma und/oder der Knoten eng überwacht. Trotz der durch die medikamentöse Therapie zu erwartenden Verbesserung Ihrer Erkrankung können in seltenen Fällen bekannte Nebenwirkungen durch die Studienmedikamente hervorgerufen werden. Über mögliche Nebenwirkungen werden Sie ausführlich durch Ihre/-n betreuende/-n Studienärztin/-arzt und dieses Informationsblatt aufgeklärt.

3.b. New version:

Patient Information, Page 2

Studienziel

- Vergleich der verschiedenen medikamentösen Therapiemöglichkeiten mit Placebo ~~mit einer alleinigen Ernährungsumstellung.~~

Studienteilnehmer

Patienten mit <u>normal großer oder</u> vergrößerter Schilddrüse, in der sich Knoten gebildet haben (medizinischer Fachbegriff: Struma nodosa)

Studienmedikation

- ~~Ernährungsumstellung allein, als Medikament wird ein~~ Placebo (Scheinmedikament ohne Wirkstoff) ~~gegeben.~~

Studienrisiken

Durch die Teilnahme an dieser Studie wird die Entwicklung ~~Ihrer Struma und/oder der Knoten~~ der Größe Ihrer Schilddrüse und der Schilddrüsenknoten eng überwacht. ~~Trotz der durch die medikamentöse Therapie zu erwartenden Verbesserung Ihrer Erkrankung können~~ In seltenen Fällen können bekannte Nebenwirkungen durch die Studienmedikamente hervorgerufen werden. Über mögliche Nebenwirkungen werden Sie ausführlich durch Ihre/-n betreuende/-n Studienärztin/-arzt und dieses Informationsblatt aufgeklärt.

3.c. Previous version:

Patient Information, Page 3, last paragraph

Beschreibung der Erkrankung und Ziel der Studie

Denn trotz der Häufigkeit dieser Erkrankung fehlen nach wie vor große Studien, die einen Vorteil einer der unterschiedlichen medikamentösen Therapien, verglichen mit ausreichender Jodzufuhr aus jodiertem Speisesalz, bei einer vergrößerten Schilddrüse mit Knoten eindeutig belegen. Solche Studien werden schon seit längerer Zeit von vielen Ärzten und Behörden gefordert. Das Ziel *dieser* jetzt geplanten, groß angelegten Studie ist es, zu überprüfen, ob eine Kombinationstherapie aus Schilddrüsenhormon *und* Jod gegenüber einer sog. Monotherapie (nur mit Schilddrüsenhormon *oder* nur mit Jod) oder aber einer alleinigen Jodzufuhr aus der Nahrung in der Behandlung der Knotenstruma überlegen ist.

3.c. New version:

Patient Information, Page 3, last paragraph

Beschreibung der Erkrankung und Ziel der Studie

Denn trotz der Häufigkeit dieser Erkrankung fehlen nach wie vor große Studien, die einen Vorteil einer der unterschiedlichen medikamentösen Therapien, verglichen mit ausreichender Jodzufuhr aus jodiertem Speisesalz, bei einer vergrößerten Schilddrüse mit Knoten eindeutig belegen. Solche Studien werden schon seit längerer Zeit von vielen Ärzten und Behörden gefordert. Das Ziel *dieser* jetzt geplanten, groß angelegten Studie ist es, zu überprüfen, ~~ob~~ wie sich eine Kombinationstherapie aus Schilddrüsenhormon *und* Jod gegenüber einer sog. Monotherapie (nur mit Schilddrüsenhormon *oder* nur mit Jod) oder ~~aber einer alleinigen Jodzufuhr aus der Nahrung~~ einem Placebo auf die Größe von Schilddrüsenknoten einer normal großen oder vergrößerten Schilddrüse auswirkt, und ob es zu einer Reduktion der Schilddrüsengröße kommt ~~in der Behandlung der Knoten in der Schilddrüse mit einer eventuellen Struma überlegen ist~~.

3.d. Previous version:

Patient Information, Page 4, first paragraph

Beschreibung der Erkrankung und Ziel der Studie

An dieser Studie werden ca. 30 Studienzentren in Deutschland teilnehmen, wobei insgesamt 1000 Patienten in die Studie aufgenommen werden sollen.

Studienmedikation

Gruppe 4: Ernährungsumstellung allein, gegeben wird ein Placebo (Scheinmedikament ohne Wirkstoff), 1 Tablette täglich

Studiendurchführung

Nachdem bei Ihnen eine Knotenstruma festgestellt wurde und Sie sich für eine Studienteilnahme entschieden haben, werden Sie - außer an der heutigen Untersuchung (Visite 1) - an 4 weiteren Untersuchungen (Visiten) über einen Zeitraum von 12 Monaten teilnehmen.

Während der **Visite 1**, bei der die Knotenstruma bei Ihnen diagnostiziert wurde, wurden - wie bei jeder ärztlichen Erstuntersuchung - Ihre allgemeinen Daten (Alter, Größe, Gewicht) sowie bisherige Erkrankungen, Allergien, Medikamenten-Unverträglichkeiten, die Einnahme Ihrer aktuellen weiteren Medikamente und eventuelle Schilddrüsenerkrankungen in Ihrer Familie erfaßt.

3.d. New version:

Patient Information, Page 4, first paragraph

Beschreibung der Erkrankung und Ziel der Studie

An dieser Studie werden ca. ~~30~~ 60 Studienzentren in Deutschland teilnehmen, wobei insgesamt 1000 Patienten in die Studie aufgenommen werden sollen.

Studienmedikation

Gruppe 4: ~~Ernährungsumstellung allein, gegeben wird ein~~ Placebo (Scheinmedikament ohne Wirkstoff), 1 Tablette täglich

Studiendurchführung

Nachdem bei Ihnen ~~eine Knotenstruma~~ Schilddrüsenknoten mit oder ohne Vergrößerung der Schilddrüse festgestellt wurde und Sie sich für eine Studienteilnahme entschieden haben, werden Sie - außer an der heutigen Untersuchung (Visite 1) - an 4 weiteren Untersuchungen (Visiten) über einen Zeitraum von 12 Monaten teilnehmen.

Während der **Visite 1**, bei der Schilddrüsenknoten ~~Knotenstruma~~ bei Ihnen diagnostiziert wurden, werden - wie bei jeder ärztlichen Erstuntersuchung - Ihre allgemeinen Daten (Alter, Größe, Gewicht) sowie bisherige Erkrankungen, Allergien, Medikamenten-Unverträglichkeiten, die Einnahme Ihrer aktuellen weiteren Medikamente und eventuelle Schilddrüsenerkrankungen in Ihrer Familie erfaßt.

3.e. Previous version:

Patient Information, Page 5, 2nd paragraph

Studiendurchführung

Bei der **Visite 2** liegen die Ergebnisse der Blutuntersuchungen der Visite 1 vor und es werden die Ein- und Ausschlusskriterien für die Studienteilnahme erneut überprüft. Außerdem wird eine körperliche Untersuchung, eine Blutdruck- und Pulsmessung sowie eine weitere Sonographie zur präzisen Bestimmung der Größe Ihrer Schilddrüse und der Knoten durchgeführt, eine Blutprobe (ca. 10 ml) für die Messung des TSH-Wertes abgenommen und Urin zur Bestimmung der

Jodausscheidung gesammelt. Danach erhalten Sie eines der vier, auf Seite 4 erwähnten, möglichen Studienmedikamente für die Einnahme in den ersten 3 Monaten. Die Studienmedikation befindet sich in 3 kleinen Dosen, die jeweils 35 Tabletten enthalten (im Schnitt eine Dose pro Monat). Weder Ihre Studienärztin/Ihr Studienarzt noch Sie wissen, welcher der 4 unterschiedlichen Behandlungsgruppen Sie zugeordnet werden. Dieses Verfahren nennt man „doppelblind“. Natürlich nehmen auch die Patienten der Gruppe 4 (= Ernährungsumstellung) eine Tablette (Placebo) ein, damit das "Doppelblindverfahren" aufrechterhalten werden kann. Die Zuteilung wird vom Computer berechnet, erfolgt zufallsbedingt und kann auch nicht beeinflußt werden. Dies hat den Zweck, eine möglichst hohe wissenschaftliche Aussagekraft der Untersuchung zu erreichen.

Patient Information, Page 5, 4th paragraph

Da der TSH-Wert in einem Zentrallabor bestimmt wird und daher nicht sofort am Tag der Kontrolluntersuchung vorliegt, wird Ihnen die Studienmedikation nachträglich von Ihrer Studienärztin/Ihrem Studienarzt zugeschickt. Den Empfang dieser Studienmedikamente müssen Sie unter Angabe des Datums auf einer beiliegenden Postkarte bestätigen und diese zurückschicken. Auf der Postkarte ist nur Ihre Patienten-Nummer angegeben und nochmals ein Hinweis für den Beginn der Einnahme der ersten Tablette vermerkt.

3.e. New version:

Patient Information Page 5, 2nd paragraph

Studiendurchführung

Bei der **Visite 2** liegen die Ergebnisse der Blutuntersuchungen der Visite 1 vor und es werden die Ein- und Ausschlusskriterien für die Studienteilnahme erneut überprüft. Außerdem wird eine körperliche Untersuchung, eine Blutdruck- und Pulsmessung sowie eine weitere Sonographie zur präzisen Bestimmung der Größe Ihrer Schilddrüse und der Schilddrüsenknoten durchgeführt, eine Blutprobe (ca. 10 ml) für die Messung des TSH-Wertes abgenommen und Urin zur Bestimmung der Jodausscheidung gesammelt. Danach erhalten Sie eines der vier, auf Seite 4 erwähnten, möglichen Studienmedikamente für die Einnahme in den ersten 3 Monaten. Die Studienmedikation befindet sich in 3 kleinen Dosen, die jeweils 35 Tabletten enthalten (im Schnitt eine Dose pro Monat). Weder Ihre Studienärztin/Ihr Studienarzt noch Sie wissen, welcher der 4 unterschiedlichen Behandlungsgruppen Sie zugeordnet werden. Dieses Verfahren nennt man „doppelblind“. Natürlich nehmen auch die Patienten der Gruppe 4 ~~(= Ernährungsumstellung)~~ eine Tablette (Placebo) ein, damit das "Doppelblindverfahren" aufrechterhalten werden kann. Die Zuteilung wird vom Computer berechnet, erfolgt zufallsbedingt und kann auch nicht beeinflußt werden. Dies hat den Zweck, eine möglichst hohe wissenschaftliche Aussagekraft der Untersuchung zu erreichen.

Patient Information, Page 5, 4th paragraph

Da der TSH-Wert in einem Zentrallabor bestimmt wird und daher nicht sofort am Tag der Kontrolluntersuchung vorliegt, wird Ihnen die Studienmedikation nachträglich von Ihrer Studienärztin/Ihrem Studienarzt zugeschickt oder persönlich ausgehändigt. ~~Den Empfang dieser Studienmedikation müssen Sie unter Angabe des Datums auf einer beiliegenden Postkarte bestätigen und diese zurückschicken. Auf der Postkarte ist nur Ihre Patienten-Nummer angegeben und nochmals ein Hinweis für den Beginn der Einnahme der ersten Tablette vermerkt.~~ Nach dem Erhalt der neuen Studienmedikation nehmen Sie bitte ab sofort diese, wie mit Ihrem Arzt besprochen, ein.

3.f. Previous version:

Patient Information, Page 7, 4th paragraph

Risiken und Nutzen der Studie

Durch die Teilnahme an dieser Studie wird die Entwicklung Ihrer Struma und der beobachteten Knoten eng überwacht. Es ist sehr wahrscheinlich, daß sich Ihr Zustand durch die Teilnahme an dieser Studie verbessert und daß durch diese Studie bewiesen werden kann, ob eine Kombinationstherapie aus Levothyroxin und Jodid oder die jeweiligen Monotherapien oder die alleinige Jodzufuhr aus der Nahrung bei der Behandlung der Struma überlegen ist und somit zukünftig Patienten vorrangig diese Behandlung erhalten sollen.

3.f. New version:

Patient Information, Page 7, 4th paragraph

Risiken und Nutzen der Studie

Durch die Teilnahme an dieser Studie wird die Entwicklung ~~Ihrer Struma und der beobachteten Knoten~~ der Größe Ihrer Schilddrüse und der Schilddrüsenknoten eng überwacht. Es ist sehr wahrscheinlich, ~~daß sich Ihr Zustand durch die Teilnahme an dieser Studie verbessert und~~ daß durch diese Studie gezeigt wird ~~bewiesen werden kann~~, welche Therapie ~~ob eine Kombinationstherapie aus Levothyroxin und Jodid oder die jeweiligen Monotherapien und somit eines der Medikamente oder Placebo~~ ~~Struma~~ den günstigsten Einfluß auf diese Veränderung in der Schildrüse nehmen kann, und daß somit zukünftige Patienten von den Ergebnissen dieser Studie profitieren könnten. ~~vorrangig diese Behandlung erhalten sollen.~~

3.g. Previous version:

Patient Information, Page 9, last paragraph

Studienbezogene Versicherung

Die Allgemeinen Versicherungsbedingungen können Sie jederzeit einsehen oder erhalten Sie auf Anfrage bei Ihrer Studienärztin / Ihrem Studienarzt.

3.g. New version:

Patient Information, Page 9, last paragraph

Studienbezogene Versicherung

Die Allgemeinen Versicherungsbedingungen ~~können Sie jederzeit einsehen oder erhalten~~ bekommen Sie als Kopie ~~auf Anfrage bei~~ von Ihrer Studienärztin / Ihrem Studienarzt zu Beginn der Studie ausgehändigt.

3.h. Previous version:

Patient Information, Page 10, 4th paragraph

Studienbezogene Versicherung

Eine Gesundheitsschädigung, die als Folge der klinischen Studie eingetreten sein kann, muss der Studienpatient unverzüglich der Versicherung: Allianz Versicherungs AG, Kaiser-Wilhelm-Ring 31, 50672 Köln, (Versicherungspolice-Nr.: IHA 10/445/9900017/ 220), anzeigen. Dabei sollte die Hilfe der Studienärztin/des Studienarztes in Anspruch genommen werden.

3.h. New version:

Patient Information, Page 10, 4th paragraph

Studienbezogene Versicherung

Eine Gesundheitsschädigung, die als Folge der klinischen Studie eingetreten sein kann, muss der Studienpatient unverzüglich der Versicherung: **Allianz Versicherungs AG, Kaiser-Wilhelm-Ring 31, 50672 Köln, Telefon-Nr.: 0221/57312410 (Versicherungspolice-Nr.: IHA 10/445/9900017/ 220)**, anzeigen. Dabei sollte die Hilfe der Studienärztin/des Studienarztes in Anspruch genommen werden.

4.a. Previous version:

in protocol Page 7 "RESPONSIBILITIES AND CONTACT ADDRESSES"

Monitoring	SocraTec-PFC GmbH	Kreillerstr. 65 81673 Munich Telephone +49 89/999977-33 Fax +49 89/999977-44

4.a. New version:

in protocol Page 7 "RESPONSIBILITIES AND CONTACT ADDRESSES"

Monitoring	IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH.	c/o Z. Katharina 6 45307 Essen Telephone +49 201/8990-0 Fax +49 201/8990-101

4.b. Previous version:

in protocol Page 15, "Dosage and administration"

SocraTec-PFC will deliver the appropriate study medication and dosage for each patient to the site, which will in turn forward the medication to the patient.

4.b. New version:

in protocol Page 15, "Dosage and administration"

~~SocraTec-PFC~~ IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH will deliver the appropriate study medication and dosage for each patient to the site, which will in turn forward the medication to the patient.

4.c.Previous version:

in protocol Page 15, "Breaking treatment codes"

However, if in the investigator's opinion an emergency situation requires knowledge of the randomization code, Sponsor Project Manager, Dr. Vaupel or Socratec-PFC Project Manager Dr. Schinnerling should be contacted **immediately.**

4.c. New version:

in protocol Page 15, "Dosage and administration"

However, if in the investigator's opinion an emergency situation requires knowledge of the randomization code, Sponsor Project Manager, Dr. Vaupel or ~~SocraTec-PFC Profect Manager Dr. Schinnerling~~ IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH Project Manager Andreas Klein should be contacted **immediately.**

4.d.Previous version:

in protocol Page 18, "Normal ranges for laboratory variables"

Each site must send SocraTec-PFC / Sponsor a current list of normal values of the chemistry parameters and the lab certificates prior to shipment of study medication. SocraTec-PFC / Sponsor shall be informed immediately about any change in normal values during the study.

4.d. New version:

in protocol Page 18, "Normal ranges for laboratory variables"

Each site must send IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH ~~SocraTec-PFC~~ / Sponsor a current list of normal values of the chemistry parameters and the lab certificates prior to shipment of study medication. IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH ~~SocraTec-PFC~~ / Sponsor shall be informed immediately about any change in normal values during the study.

4.e.Previous version:

in protocol Page 25, " Premature discontinuation of Patients "

In the event a patient discontinues due to an adverse event, the investigator should notify the SocraTec-PFC's Project Manager by telephone, fax or email within 48 hours of discontinuation.

4.e. New version:

in protocol Page 25, " Premature discontinuation of Patients "

In the event a patient discontinues due to an adverse event, the investigator should notify the ~~SocraTec-PFC´s~~ IFE Institut für Forschung und Entwicklung an der Universität Witten/Herdecke GmbH Project Manager by telephone, fax or email within 48 hours of discontinuation.