These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**Clinicaltrials.gov Identifier:**	NCT00277589
		Study Code:	L_9133
Generic drug name:	Levothyroxin Sodium	**Date:**	25 November 2009

Title of the study:	Levothyroxin und Iodide in der Strumatherapie Als Mono- oder Kombinationstherapie – LISA-Studie Thyronajod® 75 Henning vs. L-Thyroxin Henning® 75 vs. Jodetten® 150 Henning vs. Placebo in the treatment of nodular goitre	
Principal Investigator:	Prof. Dr. M. Grußendorf, Sophienstraße 40, 70178 Stuttgart	
Study centers:	58 active centers in Germany	
Publications (reference):	Not applicable.	
Study period: Date first patient enrolled: 11-May-2004 Date last patient completed: 10-Dec-2008		Phase of development: IV
Objectives:	Primary: The primary objective was 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: The change in goiter volume after Thyronajod treatment was compared to that of each reference treatment after 12 months treatment. Additionally, the change in the number of nodules after Thyronajod treatment was compared to each reference treatment after 12 months treatment.	
Methodology:	Prospective, randomized, observer-blind, placebo-controlled, multicentre, 4 arms study Each patient started with a standard dosage Thyronajod® 75 Henning or L-Thyroxin Henning® 75 or Jodetten® 150 Henning or Placebo, 1 tablet taken once daily. After 3 months, a dosage adjustment was performed dependent on the thyroid stimulating hormone (TSH) result. It was aimed with the study medication to get a target range of TSH between 0.2 – 0.8 mU/l by means of the study medication	
Number of patients:	Planned: 1000	Randomized: 1024

Evaluated:	A total of 1013 patients were defined as "intention to treat" (ITT). The per protocol (PP) set comprised 615 patients, 834 patients were included in the primary analysis population (ITT-PAP).
Diagnosis and criteria for inclusion:	Main Inclusion criteria: Patient with thyroid nodules in a normal sized or enlarged thyroid, at least one nodule (≤ 20% of volume with cystic change) with ≥ 1.0 cm diameter and normal TSH values (0.6 – 3.0 mU/l), aged 18-65 years
Investigational product: Dose: Administration:	Thyronajod® 75 Henning or Thyronajod® 50 Henning or Thyronajod® 100 Henning (depending on the TSH result after 3 month) 75 (or 50 or 100) µg Levothyroxine-Na and 196.2 µg KJ 196 µg KJ=150 µg Iodide Tablets, orally, once daily
Duration of treatment: 12 months	Duration of observation: 12 months
Reference therapy: Dose: Administration:	Placebo calcium phosphate, microcrystalline cellulose, maize starch, silicium dioxide, magnesium stearate Tablets, orally, once daily
Single treatment regimen: Dose: Administration:	L-Thyroxin Henning® 75 or L-Thyroxin Henning® 50 or L-Thyroxin Henning® 100 (depending on the TSH result after 3 month) 75 (or 50 or 100) µg Levothyroxine-Na Tablets, orally, once daily
Single treatment regimen: Dose: Administration:	Jodetten® 150 Henning 196.2 µg KJ, 196 µg KJ = 150 µg Iodide Tablets, orally, once daily
Criteria for evaluation	
Efficacy: Safety:	<u>Primary objective:</u> To compare the difference from baseline in sonographically determined log total volume of all nodules with a diameter of > 0.5 cm to the 12-months follow-up <u>Secondary objectives:</u> To compare the 12-month difference from baseline in log thyroid volume, number of nodules, and log maximal volume Adverse events (AEs) noted by the investigator. Standard hematology and blood chemistry.

Statistical methods:	The primary analysis consisted 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 was 0.0167 two-sided in order to guarantee a multiple test level of 0.05, according to the Bonferroni procedure. The ITT-PAP dataset was used (LOCF imputed data without centre 18 and centre 54.). The secondary analysis consisted of the three two-arm comparisons (test between one of the two active controls vs Placebo) of logarithmized volume of nodules at 12 months, using two-sample t-tests, and the number of nodules analyzed using the Mann-Whitney-U test, as this was a count variable. Each test was performed at a significance level of alpha = 5%. The ITT-PAP dataset was used. *Sensitivity analysis* For the analysis of the primary endpoint an investigation concerning the sensitivity of the results was carried out.
	Per-protocol analysis The primary analysis was replicated using the PP dataset. *Extended analyses* To adjust for baseline measurements analysis of covariance was applied. All extended analyses were regarded as exploratory and were based on the ITT and/or PP dataset.
	The first extended analysis for the primary and secondary endpoint calculated the mean treatment effect using a mixed model included the center identity as random effect and the baseline log thyroid volume > 0.5 cm as covariate. This model was extended with the additional baseline covariates. The potential effect was explored by backward selection with 0.05 as significance limit. For continuous outcomes, generalized linear mixed models were applied. For ordinal variables mixed Poisson regression was used. Each test was performed at a significance level of $\alpha = 0.05$. The model was further extended to include interim follow-up timepoints. For an improved understanding of an optimal placement of control examinations, three - level mixed models were fitted to the data, allowing autocorrelation and heteroscedasticity.
Summary:	The demographic data of the study population were raised as follows: Demographic data (ITT-PAP, N = 834)

Demographic variable		Overall
Age [years], mean (SD)		46.9 (10.2)
Height [cm], mean (SD)		169.6 (8.7)
Weight [kg], mean (SD)		78.4 (16.8)
BMI [kg/m^2]		27.2 (5.3)
Gender N [%]	female	582 (69.8)
	male	251 (30.1)
Family history of thyroid disease N [%]		330 (39.6)
Goiter N [%]		467 (56.0)
Presence of accompanying disorders N [%]		541 (64.9)

N: number of patients; SD: standard deviation

Efficacy results:	In the primary endpoint analysis, the highest reduction in log total volume was achieved in the Thyronajod group with a mean difference of -0.24 to baseline, compared to -0.13 in the L-Thyroxin (LT4) group, -0.09 in the Jodetten group and -0.05 in the Placebo group. Between-group comparisons revealed that the reduction in the Thyronajod group was statistically significant higher compared to the Placebo- and Jodetten group and however, without statistical significance compared to the LT4 group. Sensitivity analyses carried out for the ITT set showed that the exclusion of non-compliant centers led to overall lower values, higher variability, and loss of some significances, without altering the conclusion of the primary result. In addition, analyses for data without LOCF and for the PP dataset showed overall the same results as those obtained in the primary analysis. Results obtained from the extended analyses revealed no differences to the primary analysis but showed a significant center effect. This indicates that geographic or environmental differences might have contributed to the therapeutic success in the pharmacotherapy of thyroid nodules. As also shown in the unadjusted analysis, the difference between the Thyronajod- and Jodetten group and Thyronajod- and Placebo group remained statistically significant. As secondary endpoints, the difference to baseline in log thyroid volume, number of nodules, and log maximal nodule volumes were investigated. Analogously to the primary endpoint variable, differences to baseline were highest for the Thyronajod group also in log thyroid volume, number of nodules, and log maximal nodule volumes. Regarding the log thyroid volume, the reduction was obviously higher in the Thyronajod group (mean: -0.11) compared to the LT4 group (mean: -0.07) and was of statistically significant difference between the Thyronajod- and Placebo and Thyronajod- and Jodetten group. Similar results were observed concerning log maximal nodule volume. Also for 'number of nodules', the reduction was highest for the Thyronajod group, however, statistically significant differences between the treatment groups could not be shown. This is possibly due to the fact that this study was not adequately powered for this calculation and therefore the number of patients was simply not sufficient to gain statistically significant results. Within the extended analyses, again a center effect was observed, except for the investigation of 'number of nodules'. Results were similar to the primary analysis, with statistically significant differences between the Thyronajod- and Placebo group and Thyronajod- and Jodetten group, but without significant difference between the Thyronajod- and LT4 group.
Safety results:	During the course of this study, AEs were observed in overall 524 patients (51.2%), no difference was found regarding patients' gender (p: 0.8172) or treatment group (p: 0.4374). Serious adverse events (SAEs) occurred in overall 39 patients (3.8%) without statistical difference regarding patient gender (0.6817) or treatment group (p: 0.4087). No patient died during the course of this study.
Date of report:	17-Nov-2009