Clinical Trial Report

Protocol Identification No.:	EMR 200125-002
Title:	An open-label, single-dose, randomized, three-period, six sequence crossover, single-center trial to assess dosage form proportionality of 600 µg levothyroxine new formulation administered orally as either 12 white tablets of 50 µg or 6 white tablets of 100 µg or 3 white tablets of 200 µg in healthy volunteers
Short Title:	Dosage Form Proportionality of Levothyroxine New Formulations (50 µg, 100 µg, and 200 µg Tablets) in Fasted State
Development Phase:	Phase I
Investigational Product:	Levothyroxine, 600 µg (3 dosage forms of new formulation): Treatment A: 12 tablets of 50 µg Treatment B: 6 tablets of 100 µg Treatment C: 3 tablets of 200 µg
Treatment Duration:	Three (3) single administrations separated by a wash-out period of at least 35 to maximal 38 days between each administration
Indication:	Not applicable
Trial Design:	Phase I, open-label, randomized, three-period, six sequence crossover, single-center trial
Trial Initiation Date:	19 Nov 2013 (first subject screened)
Trial Completion Date:	14 Mar 2014 (last subject last visit)
Principal Investigator:	Dr. med. [redacted] t Early Phase Clinical Unit – Berlin PAREXEL International GmbH Spandauer Damm 130, Haus 18 14050 Berlin, Germany
Sponsor:	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany

Levothyroxine **Dosage Form Proportionality of Levothyroxine New Formulations (50 µg, 100 µg, and 200 µg Tablets) in Fasted State**

EMR 200125-002

Sponsor Contact:
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Date of Report: 18 Dec 2014, Version 1.0

This trial was performed in compliance with Good Clinical Practice (GCP).

1 Approval Page

Clinical Trial Report: EMR 200125-002

An open-label, single-dose, randomized, three-period, six sequence crossover, single-center trial to assess dosage form proportionality of 600 µg levothyroxine new formulation administered orally as either 12 white tablets of 50 µg or 6 white tablets of 100 µg or 3 white tablets of 200 µg in healthy volunteers

Signatures may be found in Appendix 16.1.5.

[1]Dr. med

Trial Director

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[1] Note: Dr. med. Matthias Grossmann was indicated as the medical responsible person, per protocol. However, Dr. med. Wolfgang Uhl (Trial director) assumed this responsibility during the conduct of the trial.

2 Synopsis

Title of Trial:

An open-label, single-dose, randomized, three-period, six sequence crossover, single-center trial to assess dosage form proportionality of 600 µg levothyroxine new formulation administered orally as either 12 white tablets of 50 µg or 6 white tablets of 100 µg or 3 white tablets of 200 µg in healthy volunteers

Trial Number:

EMR 200125-002

Investigator:

Dr. med.

Trial Center:

Early Phase Clinical Unit - Berlin
PAREXEL International GmbH
Klinikum Westend, Haus 31
Spandauer Damm 130
14050 Berlin, Germany

Publication (reference):

None

Trial Period (years):

19 Nov 2013 (first subject screened) to 14 Mar 2014 (last subject last visit)

Phase of Development:

Phase I

Objectives:

- The primary objective of the trial was to demonstrate dosage form proportionality of 3 dosage forms of the new formulation in healthy subjects by estimating the relative bioavailability (BA) and by pairwise bioequivalence (BE) testing (3 BE tests for each set of primary endpoints).
- The secondary objective of the trial was to assess the safety and tolerability of 600 µg levothyroxine.

Methodology:

This was a Phase I, open-label, randomized, three-period, six sequence crossover, single-center trial of 600 µg of levothyroxine new formulation given as single dose of either 12 tablets of 50 µg (Treatment A), 6 tablets of 100 µg (Treatment B), or 3 tablets of 200 µg (Treatment C) in healthy subjects. For logistic reasons the subjects were dosed in several cohorts.

Screening was performed within 21 days before first Investigational Medicinal Product (IMP) administration.

Investigation period
If eligibility was confirmed, subjects were randomized to a treatment sequence on Day 1 prior to IMP administration in the first treatment period. There was a 35 to 38-day wash-out period between the 3 trial periods, respectively.

Subjects stayed in the unit until the morning of Day 2, but needed to come back for regular ambulatory visits on Days 2, 3, and 4 in each treatment period.

Follow-up period
The Follow-up (FU) Visit was performed 14 to 18 days after last IMP administration in the final treatment period. Subjects that were not considered eligible at admission to Period 2 or 3 were allowed to come back within 3 days for another eligibility check. If they were not considered eligible 38 days after previous IMP administration, they were to be discontinued from the trial and they were to have an FU Visit as soon as possible.

Number of Subjects:

Planned:	42 subjects
Screened:	103 subjects
Randomized:	42 subjects (19 males and 23 females)
Completed:	37 subjects (17 males and 20 females)
Withdrawals:	5 subjects (2 males and 3 females)

Diagnosis and Main Criteria for Inclusion:

Healthy, non-smoking male and female subjects (every effort was made to balance gender), aged 18 to 50 years, having a body weight of 49 to 95 kg for women and 55 to 95 kg for men and a body mass index (BMI) of 18.5 to 29.9 kg/m^2, inclusive (subjects must have been within 15% of ideal body weight for their height and build), and who were certified as healthy by clinical assessment.

Main exclusion criteria included any medical condition or concomitant medication use that may have significantly influenced the results and conduct of the trial. The relatively high screening

failure rate is typical for studies where stringent inclusion / exclusion criteria were employed to ensure subject safety.

Test Product: Dose and Mode of Administration, Batch Number(s):

The Test IMP was a 600 µg administration of new formulation levothyroxine, provided in three (3) dosing strengths (50 µg, 100 µg, and 200 µg). The following three (3) treatments were administered as single dose in three treatment periods:

Treatment A: 12 tablets of 50 µg

Treatment B: 6 tablets of 100 µg

Treatment C: 3 tablets of 200 µg

Levothyroxine sodium tablets was taken orally with 240 mL water in fasted state in the morning of Day 1 in Periods 1, 2, and 3.

	50 µg Levothyroxine	**100 µg Levothyroxine**	**200 µg Levothyroxine**
Batch numbers:	015635	015639	015642
Packaging number:	MSC1014774A	MSC1014774A	MSC1014774A
Lot number:	165113	165119	165127

Duration of Treatment:

- Screening up to 21 days before start of IMP administration
- Treatment Period 1 (over 5 days), start of single IMP administration on Day 1
- Washout period of 35–38 days after dosing on Day 1
- Treatment Period 2 (over 5 days), start of single IMP administration on Day 1
- Washout period of 35–38 days after dosing on Day 1
- Treatment Period 3 (over 5 days), start of single IMP administration on Day 1
- Follow-up period of 14–18 days after last IMP administration

Total duration (range) per subject: 97–127 days.

Reference Therapies, Dose and Mode of Administration, Batch Numbers:

Not applicable.

Criteria for Evaluation:

Efficacy:

Not applicable

Pharmacokinetics:

Primary PK endpoints:

- Set 1: Area under the plasma concentration time curve (AUC) from time zero to 72 hours postdose (AUC_{0-72}) and maximum plasma concentration as observed (C_{max}) of total thyroxine (T4)

- Set 2: Area under the plasma concentration time curve from time zero to 72 hours postdose, adjusted for baseline ($AUC_{0-72,adj}$, i.e., AUC_{0-72} - 72*mean baseline level) and maximum of total T4 concentrations, adjusted for baseline ($C_{max,adj}$, i.e., C_{max} minus mean baseline level).

Secondary PK endpoints:

- For total T4: For total T4: area under the plasma concentration time curve from time zero to infinity, adjusted for baseline ($AUC_{0-\infty,adj}$), area under the plasma concentration time curve from time 72 hours postdose to infinity, adjusted for baseline ($AUC_{extra,adj}$), area under the plasma concentration time curve from time zero to 48 hours postdose (AUC_{0-48}) and adjusted for baseline ($AUC_{0-48,adj}$), time to reach the maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), apparent terminal elimination rate constant (λ_z), apparent total body clearance of drug from plasma (CL/F), and volume of distribution (V_z/F).

- Total triiodothyronine (T3) PK parameters: C_{max}, AUC_{0-48}, AUC_{0-72}, and t_{max}

Safety:

Secondary endpoints:

- Standard laboratory hematology and biochemical parameters, treatment-emergent adverse events (TEAEs), vital signs (body temperature, systolic and diastolic blood pressure [BP], and pulse rate), and electrocardiogram (ECG) parameters.

Pharmacodynamics:

Not applicable.

Statistical Methods:

Pharmacokinetics:

The primary variables, AUC_{0-72} and C_{max} (Set 1) and $AUC_{0-72,adj}$ and $C_{max,adj}$ (Set 2) of total T4 in plasma, were log-transformed and estimated according to non-compartmental standard methods. A generalized linear model was applied to each set of primary endpoints including effects for treatment, period, sequence and subject within sequence. Differences Test minus Reference was estimated, and based on the residual (within-subject) variation 95% confidence intervals (CI) for

the differences were calculated. Back transformation resulted in Test/Reference ratios and corresponding 95% CIs.

According to the defined BE limits [0.80 to 1.25], for each set of primary endpoints null and alternative hypotheses were:

- H_0: $\mu_T / \mu_R \leq 0.8$ or $1.25 \leq \mu_T / \mu_R$;

  for at least one of the primary endpoints AUC_{0-72} or C_{max} in at least one of 3 possible Test/Reference comparisons.

- H1: $0.8 < \mu_T / \mu_R < 1.25$;

  for AUC_{0-72} and C_{max} in all 3 Test/Reference comparisons.

μ_T and μ_R are the means under Test and Reference treatment, respectively.

Comparison 1

Test treatment: 600 µg levothyroxine as 6 tablets of 100 µg (Treatment B)

Reference treatment: 600 µg levothyroxine as 12 tablets of 50 µg (Treatment A)

Comparison 2

Test treatment: 600 µg levothyroxine as 3 tablets of 200 µg (Treatment C)

Reference treatment: 600 µg levothyroxine as 12 tablets of 50 µg (Treatment A)

Comparison 3

Test treatment: 600 µg levothyroxine as 3 tablets of 200 µg (Treatment C)

Reference treatment: 600 µg levothyroxine as 6 tablets of 100 µg (Treatment B)

Dose-form-proportionality was confirmed, if the 95% CI for the ratios of geometric means for both AUC_{0-72} and C_{max} of total T4 in plasma, were included in the interval 0.8 to 1.25 in all three pairwise comparisons.

The same approach was applied to set 2, i.e. $AUC_{0-72,adj}$ and $C_{max,adj}$.

All other secondary PK endpoints and all safety parameters were analyzed descriptively. For t_{max} only n, median, Minimum, and Maximum were presented.

The PK parameters were presented in a descriptive way per treatment (number [N], mean, standard deviation [SD], standard error of the mean [SEM], arithmetic and geometric coefficient of variation percentage (CV%), median, minimum (min) and maximum (max) values, geometric means, and 95% CI of geometric means). Graphs were produced as appropriate.

Safety

Safety parameters were secondary endpoints and included standard laboratory hematology and clinical chemistry parameters, TEAEs, vital signs (body temperature, systolic BP, diastolic BP, and pulse rate) and ECG parameters. All safety analyses were performed using the safety population.

Summary and Conclusions:

Subject Disposition:

Overall, 103 subjects were screened for inclusion in this trial. Of these, 42 subjects were randomized to treatment sequence. A total of 37 subjects completed the trial.

- Five (5) subjects were discontinued from the trial prematurely:
    - Subjec Sequence: BCA) – Completed Treatment B and was withdrawn due to positive drug screen [opiates] at predose Treatment C (200 µg)
    - Subject Sequence: ACB) – Completed Treatment A (50 µg) before subject was withdrawn due to SAE (deep vein thrombosis)
    - Subject Sequence: BCA) – Completed Treatment B (100 µg) before subject was withdrawn due to AE (vomiting)
    - Subject (Sequence: BAC) – Completed Treatment B (100 µg) before subject withdrew consent
    - Subject equence: CBA) – Completed Treatment C (200 µg) before subject withdrew consent

There were no major protocol violations reported during the trial.

Demographics and Baseline Characteristics:

Of all 42 healthy male and female subjects included in the trial 23 (54.8%) subjects were female and 19 (45.2%) subjects were male. All subjects (100.0%) were Caucasian and of "Not Hispanic" ethnicity. For all randomized subjects, the mean age (±SD) was 34.9±10.13 years, the mean (±SD) height was 173.3±7.68 cm, the mean weight (±SD) was 69.11±9.369 kg, and the mean (±SD) BMI was 22.95±2.119 kg/m^2; similar distribution was observed between all treatment sequences.

Pharmacokinetic Results:

The geometric LS mean ratios for total T4 $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 6 x 100 µg tablets and levothyroxine 12 x 50 µg tablets were 99.3% and 103.8%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 12 x 50 µg tablets were 104.1% and 103.2%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 6 x 100 µg tablets were 104.8% and 99.4%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 6 x 100 µg tablets and levothyroxine 12 x 50 µg tablets were 100.1% and 101.8%, respectively, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 12 x 50 µg tablets were both 101.7%, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 6 x 100 µg tablets were 101.5% and 99.9%, respectively, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

Safety Results:

Overall, treatment with all three dosage forms (50 µg, 100 µg and 200 µg) at a total dose of 600 µg of the new formulation levothyroxine as investigated in this trial can be considered as safe and well tolerated. The safety and tolerability of the three dosage forms were similar between treatment periods.

The incidence of TEAEs was similar for all three dosage forms of the new formulation levothyroxine. In total, 27 (64.3%) subjects reported 85 TEAEs; 11 (28.9%) subjects reported 27 TEAEs during 12 tablets of 50 µg treatment, 16 (40.0%) subjects reporting 27 TEAEs during 6 tablets of 100 µg treatment, and 13 (33.3%) subjects reporting 31 TEAEs during 3 tablets of 200 µg treatment. Slightly more than one third (37.6%) of all reported TEAEs (32 of 85 TEAEs) were considered related to IMP by the Investigator: Five (13.2%) subjects reported 9 IMP-related TEAEs during 12 tablets of 50 µg treatment, 6 (15.0%) subjects reported 10 IMP-related TEAEs during 6 tablets of 100 µg treatment, and 7 (17.9%) subjects reported 13 IMP-related TEAEs during 3 tablets of 200 µg treatment.

Headache was the most commonly reported TEAE (22 of 85 TEAEs) (reported by >12% of subjects during 6 tablets of 100 µg treatment and 3 tablets of 200 µg treatment, respectively). In addition, nausea (10 of 85 TEAEs) was reported by >12% subjects during 3 tablets of 200 µg treatment. All TEAEs except one were considered mild or moderate in intensity; Subject 1040

(6 tablets of 100 µg treatment) had a severe TEAE of vomiting considered unrelated to IMP (the event commenced approximately 8 days following 6 tablets of 100 µg treatment).

There were no deaths reported during the trial. In total, two subjects (Subject 1033 and Subject 1048) were withdrawn from the trial for safety reasons. Subject 1033 (12 tablets of 50 µg treatment) was withdrawn from the trial due to a serious adverse event (SAE) of moderate deep vein thrombosis, considered unrelated to IMP. Subject 1048 (6 tablets of 100 µg) was withdrawn from the trial due to an AE of mild vomiting, considered related to IMP.

Compared with predose values none of the safety laboratory, vital sign or ECG parameters showed any clinically relevant changes after treatment.

Conclusions:

The primary objective of the trial was to demonstrate dosage form proportionality of three dosage forms of the new formulation in healthy subjects by estimating the relative BA and by pairwise BE testing.

The three dosage forms (50 µg, 100 µg, and 200 µg tablets) of the new levothyroxine formulation administered as 600 µg single doses were determined to be dose proportional as the relative BA for total T4 AUC_{0-72} and C_{max} with and without baseline adjustment ranged from 99.3% to 104.8%, and the 95% CIs for the pairwise comparisons for BE were within the predefined margin of 0.8 to 1.25.

Treatment with all three dosage forms of the new formulation levothyroxine (12 tablets of 50 µg, 6 tablets of 100 µg, or 3 tablets of 200 µg) could be considered as safe and well tolerated. No new safety signals were observed as a result of the safety analysis.

Date of Report/Version No.: 18 Dec 2014, Version 1.0

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4 List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification
AUC_{0-48}	AUC from time zero to 48 hours postdose
$AUC_{0-48,adj}$	Baseline-adjusted AUC from time zero to 48 hours postdose
AUC_{0-72}	AUC from time zero to 72 hours postdose
$AUC_{0-72,adj}$	Baseline-adjusted AUC from time zero to 72 hours postdose
$AUC_{0-\infty}$	AUC from time zero to infinity
$AUC_{0-\infty,adj}$	Baseline-adjusted AUC from time zero to infinity
AUC_{extra}	Extrapolated part of $AUC_{0-\infty}$
$AUC_{extra,adj}$	Baseline-adjusted extrapolated part of $AUC_{0-\infty}$
BA	Bioavailability
BE	Bioequivalence
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent total body clearance of drug from plasma
C_{max}	Maximum observed concentration in plasma
CRF	Case Report Form
CRO	Contract Research Organization
CV%	Coefficient of variation percentage
ECG	Electrocardiogram

EPCU	Early Phase Clinical Unit
GCP	Good Clinical Practice
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
PK	Pharmacokinetics
PR	Time from the onset of the P wave to the start of the QRS complex
QRS	ECG interval from start of Q wave until end of S wave
QT	Time from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia method
RR	ECG interval, the time between successive R wave peaks
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOP	Standard operating procedure
$t_{½}$	Apparent terminal half-life
T3	triiodothyronine
T4	thyroxine
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach the maximum plasma concentration
V_z/F	Volume of distribution
λ_z	Apparent terminal elimination rate constant

5 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Prior to commencement of the trial, the clinical trial protocol, clinical trial amendment and all applicable documentation were reviewed and approved by the relevant Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

Details for the IEC, including the name of the committee chair can be found in Appendix 16.1.3.

5.2 Ethical Conduct of the Trial

The trial was conducted in accordance with the clinical trial protocol and the ethical principles that have their origin in the Declaration of Helsinki, as well as with the principles set forth in the Guidelines of the International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP). The trial was also carried out in keeping with applicable regulatory requirements.

5.3 Subject Information and Consent

An unconditional prerequisite for a subject's participation in the trial was the subject's written informed consent. The subject's written informed consent to participate in the trial was to be given before any trial-related activities were carried out.

Adequate information must therefore have been given to the subject by the Investigator before informed consent was obtained. A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) was provided by the Investigator for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate informed the subject verbally of all pertinent aspects of the trial. The language used in doing so was chosen so that the information could be fully and readily understood by lay persons.

The Informed Consent Form was signed and personally dated by both the subject and the Investigator. One original of the signed form was provided to the subject and the other original remained at the Early Phase Clinical Unit (EPCU), and was safely archived by the Investigator so that the forms could be retrieved at any time for monitoring, auditing or inspection purposes. An original of the signed and dated information and Informed Consent Form was provided to the subject prior to participation.

For a copy of the sample Informed Consent form, refer to Appendix 16.1.3.

6 Investigators and Trial Administrative Structure

Trial Center	Early Phase Clinical Unit - Berlin PAREXEL International GmbH Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany Phone: +49 30 30685 100 Fax: +49 30 30685 299

Sponsor Personnel

Medical Lead	Dr. med. \ Merck KGaA
Clinical Trial Lead	Merck KGaA
Drug Safety Responsible	Merck KGaA
Biostatistician	Merck KGaA
Legal Representative	Merck KGaA Frankfurter Str 250 64293 Darmstadt, Germany

PAREXEL's Personnel

Principal Investigator	Dr. med Early Phase Clinical Unit Berlin PAREXEL International GmbH Spandauer Damm 130, Haus 18 14050 Berlin, Germany Phone: Fax: E-Mail:
Sub-Investigator	Early Phase Clinical Unit Berlin PAREXEL International GmbH Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: E-Mail:

Medical Responsible	[2]Dr. med. Early Phase Scientific Affairs Berlin PAREXEL International GmbH Klinikum Westend, Haus 17 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: + E-Mail:
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Statistical Processing	Early Phase Clinical Unit - Berlin PAREXEL International GmbH Klinikum Westend, Haus 17 Phone: E-Mail:

[2] Note: Dr. med. Matthias Grossmann was indicated as the medical responsible person, per protocol. However, Dr. med. Wolfgang Uhl (Trial director) assumed this responsibility during the conduct of the trial.

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Urinalysis, Drug Screen	Early Phase Clinical Unit – Berlin PAREXEL International GmbH Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: E-Mail:
Bioanalytical Laboratory	Esther Kruger Early Phase Clinical Unit - Bloemfontein PAREXEL Bioanalytical Services Division Kampuslaan Suid University of the Free State 9301 Bloemfontein South Africa Phone: E-Mail:
Medical Writing	Early Phase Scientific Services – Bloemfontein Kampuslaan Suid University of the Free State 9301 Bloemfontein South Africa Phone: E-Mail:

External Personnel

Monitoring (under responsibility of PAREXEL)	Monitoring Systems Wolfgang Feth GmbH Möckernstrasse 112 D-10963 Berlin, Germany

Responsible Pharmacist

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Phone:
Fax:
E-Mail:

A list and description of investigators and other important participants in the trial is provided in Appendix 16.1.4. For signatures of the Principal Investigator, and the Sponsor's Trial Director and biostatistician, refer to Appendix 16.1.5.

7 Introduction

7.1 Background Information

Levothyroxine is sold worldwide for the treatment of hypothyroidism. First registration is dated 1972. Merck KGaA has marketing authorizations worldwide (registered in over 100 countries, marketed in most of them) as originator in the majority of countries.

All preparations represent immediate release tablets of proportional composition in terms of the excipients.

Various strengths covering an overall dose range from 25 µg to 200 µg per tablet are marketed; however, the portfolio differs between the countries.

The new formulation shall meet potency specifications of 95.0 to 105.0% at release and over the envisaged shelf-life of at least 2 years at the storage condition of 25°C. This is to comply with the changing potency requirements for levothyroxine tablets, e.g., the revised United States Pharmacopeial (USP) monograph for levothyroxine sodium tablets of 3 October 2009 and in 2012 by Agence Nationale de Sécurité du Médicament et des Produits de Santé, France that increasing numbers of countries are adopting.

7.2 Known and Potential Risks and Benefits to Human Subjects

Before starting therapy with thyroid hormones or before performing a thyroid suppression test, the following diseases or medical conditions should be excluded or treated: coronary failure, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency, and thyrotoxicosis. Thyroid autonomy should also be excluded or treated before starting therapy with thyroid hormones.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases.

In the case of secondary hypothyroidism the cause must be determined before replacement therapy is given and if necessary replacement treatment of a compensated adrenal insufficiency must be commenced.

Where thyroid autonomy is suspected a thyrotropin-releasing hormone test should be carried out or a suppression scintigram obtained before treatment.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, supra-physiological plasma levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely.

Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during antithyroid drug treatment of hyperthyroidism. Euthyrox® contains lactose, and therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Where the individual tolerance limit for levothyroxine sodium is exceeded or after overdose it is possible that the following clinical symptoms typical of hyperthyroidism may occur: cardiac arrhythmias (e.g., atrial fibrillation and extrasystoles), tachycardia, palpitations, angina conditions, cephalalgia, muscular weakness and cramps, flushing, fever, vomiting, disorders of menstruation, pseudotumor cerebri, tremor, restlessness, insomnia, hyperhidrosis, weight loss, and diarrhea. In case of hypersensitivity to any ingredients of Euthyrox® allergic reactions particularly of the skin and the respiratory tract may occur. Cases of angioedema have been reported.

8 Trial Objectives

Primary

- To demonstrate dosage form proportionality of 3 dosage forms of the new formulation in healthy subjects by estimating the relative bioavailability (BA) and by pairwise bioequivalence (BE) testing for each set of primary endpoints.

Secondary

- To assess the safety and tolerability of 600 µg levothyroxine.

9 Investigational Plan

9.1 Overall Trial Design and Plan: Description

This is a Phase I, open-label, randomized, three-period, six sequence crossover, single-center trial. Primary and secondary endpoints are described in Section 9.7.1.2. The treatments studied are described in Section 9.4.1.

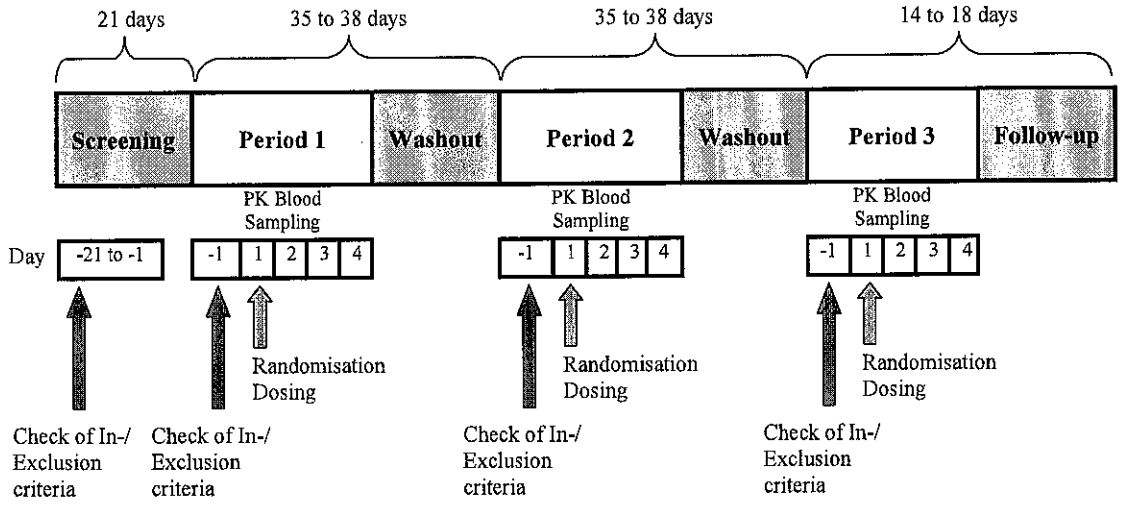
The trial was to be conducted in 3 periods. Assuming a drop-out rate of 20%, forty-two (42) subjects (7 subjects per sequence) were enrolled in the trial. The replacement of drop-outs was to be considered in consultation with the Sponsor in case the drop-out rate was higher than assumed. For logistic reasons, the subjects were dosed in several cohorts.

The usual one-sided alpha of 0.05 is adjusted to 0.025, corresponding to a confidence level of 95% since dosage form proportionality was tested for two sets of parameters. Refer to Section 9.7.1.4.

The trial scheme is shown in

Figure 9.1.

Figure 9.1 Trial Schematic



PK = pharmacokinetics

Subjects who met all of the inclusion criteria and none of the exclusion criteria were sequentially randomized to a treatment sequence. The estimated total duration of a subject's participation in the trial, from screening to follow-up visit was approximately 12–16 weeks.

The order and duration of the trial phases (see

Figure 9.1) were as follows:

Screening

To determine overall eligibility screening took place no more than 21 days before starting Investigational Medicinal Product (IMP) administration. Eligibility was rechecked at admission to each treatment period.

The screening period was defined from signature of the informed consent until first IMP administration.

Dosing and wash-out period

If eligibility was confirmed, the subjects were randomized to receive 600 µg levothyroxine on Day 1 of each treatment period. There was a wash-out period of 35 to a maximum of 38 days between administrations of IMP in each treatment period.

Subject eligibility was re-confirmed prior to IMP administration in Periods 2 and 3. Subjects who were not eligible were allowed to return within 3 days for another eligibility check. If not eligible 38 days after the previous IMP dose, the subject was discontinued from the trial and had the scheduled FU Visit as soon as possible after consultation with the Investigator.

End of Trial

Subjects returned for an FU Visit 14-18 days after administration of IMP in Treatment Period 3.

9.2 Discussion of Trial Design

The trial design was in line with the Food and Drug Administration (FDA) Guidance for Industry, Center of Drug Evaluation and Research (CDER) 2000 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071946.pdf), accessed 22 June 2014. The time points chosen for blood sampling for PK until 48 hours postdose were in line with the FDA guideline. The additional 72 hours postdose time point was added according to the European Union (EU) Guideline on Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Revision 1, dated Jan 2010.

Baseline correction is required by EU Guideline but not by the FDA Guideline, and for the primary endpoints it was agreed to provide both, baseline corrected and uncorrected values.

No safety concerns were raised in the previous Merck KGaA trials. The dose was in line with the FDA guideline which requires a multiple of the highest tablet strength to achieve a total dose of 600 µg. According to Sanford Bolton "Bioequivalence Studies for Levothyroxine" (http://www.aapsj.org/articles/aapsj0701/aapsj070106/aapsj070106.pdf accessed on 22 June 2014), a dose of 600 µg is the appropriate dose that ensures proper plasma concentrations to allow full characterization of the PK profile of levothyroxine without too much interference from endogenous levothyroxine levels.

The use of 600 µg of levothyroxine as the minimal dose resulting in robust PK parameters was also confirmed in previous Merck KGaA trials. Six BA/BE trials conducted with identical total levothyroxine doses of 600 µg administered in all trial periods were provided. In 3 of those (436-99-263, 436-99-264, and 436-99-277) different formulations or strengths were compared, also with an oral solution.

9.3 Selection of Trial Population

9.3.1 Inclusion Criteria

For inclusion in the trial, subjects had to fulfill all of the following inclusion criteria:

1. Healthy male and female subjects aged 18 to 50 years (every effort was made to aim gender balance)

2. Written informed consent provided before any trial-related activities were carried out

3. Body weight of 49 to 95 kg for women and 55 to 95 kg for men and body mass index (BMI) of 18.5 to 29.9 kg/m^2, inclusive (subjects should have been within 15% of ideal body weight for their height and build)

4. Vital signs in the following normal range (after 10 minutes in supine position):

    - systolic blood pressure (BP): 90 to 140 mmHg
    - diastolic BP: 50 to 90 mmHg
    - pulse rate: 45 to 90 beats per minute (bpm)
    - oral body temperature: 35.0°C to 37.5°C

5. Had a normal electrocardiogram (ECG). Abnormalities, even if non-clinically relevant, were also not permitted (e.g., time from the onset of the P wave to the start of the QRS complex [PR], ECG interval from start of Q wave until end of S wave [QRS], Time from the onset of the QRS complex to the end of the T wave [QT], heart rate [HR] corrected QT interval [QT corrected with Fridericia method {QTcF}] should have been within normal range, with no conduction abnormalities etc.)

6. Non-smoker for at least 3 months

7. Total and free thyroxine (T4), total and free triiodothyronine (T3) and thyroid-stimulating hormone (TSH) must have been within normal ranges

8. Female subjects must have been postmenopausal or surgically sterile. Females of childbearing potential must have been willing to use additional non-hormonal contraception (e.g., condoms or occlusive cap [diaphragm or cervical/vault cap] with spermicide, non-hormonal intra-uterine device with a Pearl index of less than 1% for at

least 1 month before the screening, previous sterilization of subject or her partner, being sexually inactive) from Day 1 and until the end of the trial

9.3.2 Exclusion Criteria

Subjects were not eligible for this trial if they fulfilled any of the following exclusion criteria:

1. Any surgical or medical condition, including findings in the medical history or in the pretrial assessments that in the opinion of the Investigator, constituted a risk or a contraindication for the participation of the subject in the trial or that could have interfered with the trial objectives, conduct, or evaluation
2. Any clinically relevant abnormality in the safety laboratory parameters
3. Had positive results from serology examination for Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV), or Human Immunodeficiency Virus (HIV)
4. History or presence of tumors of the pituitary gland or hypothalamus, thyroid or adrenal gland dysfunction or cardiac disease
5. Subjects with a concurrent medical condition known to interfere with the absorption or metabolism of thyroid hormones
6. Any contraindication to treatment with levothyroxine according to the current Summary of Product Characteristics
7. Should not have been pregnant or breast-feeding a child
8. Definite or suspected personal history or family history of adverse drug reaction or hypersensitivity to drugs with a similar chemical structure to levothyroxine
9. Subjects with a history or presence of asthma, any serious allergy (requiring hospitalization or prolonged systemic treatment), clinically relevant heart diseases or any food allergy or intolerance which in the opinion of the Investigator represented a safety risk (e.g., iodine allergy, etc.) were excluded
10. History or presence of drug or alcohol abuse. Alcohol abuse is defined as: an average daily intake of more than 3 units or a weekly intake of more than 21 units where 1 unit equals 340 mL of beer, 115 mL of wine or 43 mL of spirits
11. Positive test for drug of abuse (including alcohol)
12. Positive test of pregnancy at Screening and on Day -1 of each period (serum)
13. Whole blood donation or loss (equal to or more than 400 mL) within 90 days prior to first drug administration

14. Investigative drug studies: participation in the evaluation of any drug within 90 days prior to first drug administration, confirmed by a negative Volunteers Inclusion Period (VIP)-check (with the VIP check to be completed before randomization)

15. Renal failure or renal dysfunction (i.e., estimated glomerular filtration rate [eGFR] <90 mL/min) as assessed by using the estimated measure with the Modification of Diet in Renal Disease (MDRD) equation

16. History or presence of relevant liver diseases or hepatic dysfunction. Subjects with gall bladder removal

17. Use of any investigational medicinal product within 60 days prior to first levothyroxine administration

18. Administration of medications that prolong the QT interval within 4 weeks prior to trial initiation

19. Use of any prescription or non-prescription medication within 2 weeks prior to dosing or 5 half-lives, whichever is longer, before the trial drug administration including multivitamins, nutritional supplements and herbal products (e.g., St John's wort) and during the PK sampling period

20. Subjects taking medications known to affect thyroid hormone metabolism, e.g., oral contraceptives, hormonal implants, parenteral hormones, anabolic steroids, androgens, and so on

21. High fiber consumption within 24 hours before dosing in each period

22. Special diet of the subject

23. Intake of grapefruit, orange, cranberry or juices of these 3 fruits, from 48 hours prior to drug administration until collection of last PK sample in each period

24. Excessive consumption of xanthine-containing food or beverages (>5 cups of coffee a day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to drug administration until collection of last PK sample in each period

25. Subject has received a tattoo within 2 months previous to screening or plans to receive one during the trial

26. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for FU visits, and improbability of completing the trial

27. Subject is the Principal Investigator or any sub-investigator, research assistant, pharmacist, trial coordinator, other staff or relative thereof directly involved in the conduct of the trial

28. Inability to communicate or cooperate with the Investigator (e.g., language problem, illiterates, poor mental status) or to comply with the requirements of the entire trial, including dietary restrictions

29. Vulnerable subjects (e.g., persons kept in detention)

30. Legal incapacity or limited legal capacity

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects were free to discontinue from the trial at any time without giving their reasons.

A subject was to be withdrawn from the trial in the event of any of the following:

- Withdrawal of the subject's consent.
- Development of unacceptable toxicities

A subject may have been withdrawn in the event of any of the following:

- Protocol violations, including non-compliance, lost to follow-up.
- Inter-current illness or significant worsening of inter-current illness.
- Administrative reasons.

If a subject failed to attend scheduled trial assessments, the Investigator had to determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, the investigations scheduled for the last visit (FU Visit) were performed. In any case, the appropriate ClinBase™ section was completed.

The subject was to be withdrawn from the IMP in the event of any of the following:

- Clinically significant cardiac arrhythmias related to the IMP intake, e.g. atrial fibrillation or confirmed significant tachycardia >120 bpm
- QTc >500 ms or increase of 60 ms compared to baseline
- Occurrence of a serious adverse event (SAE) related to IMP
- Occurrence of an exclusion criterion which was clinically relevant and affected the subject's safety, if discontinuation was considered necessary by the Investigator and/or sponsor
- Occurrence of AEs, if discontinuation of trial drug was desired or considered necessary by the Investigator and/or the subject

- Occurrence of pregnancy
- Use of a non-permitted concomitant drug, as defined in Section 9.4.7.2, where the predefined consequence was withdrawal from the IMP
- Non-compliance.

9.4 Treatments

The term "Investigational Medicinal Product (IMP)" refers to the investigational drug undergoing trial.

9.4.1 Treatments Administered

Levothyroxine (Test Product)

The composition is provided in Section 9.4.2.1.

A 600 µg levothyroxine dose was chosen as this is the minimal dose resulting in robust PK parameters (confirmed in previous Merck KGaA trials). Six BA/BE trials have been conducted with identical total levothyroxine doses of 600 µg administered in all trial periods. In 3 of those 436-99-263, 436-99-264, and 436-99-277), different formulations or strengths were compared, also with an oral solution. No safety concerns were raised in the above cited trials. Based on the data available to date, the conduct of this trial is regarded as justifiable at the planned dose.

Administration

Single doses of levothyroxine (600 µg) were administered with 240 mL water in the morning of Day 1 of each treatment period following at least a 10 hour overnight fast. Subjects remained fasting for 4 hours following IMP administration, with water allowed one hour after IMP administration.

9.4.2 Identity of the Investigational Products

9.4.2.1 Levothyroxine (Test)

Three formulations of levothyroxine were supplied as white tablets containing 50, 100 or 200 µg levothyroxine sodium. These formulations contained as excipients mannitol, maize starch, gelatine, croscarmellose, anhydrous citric acid and magnesium stearate.

	50 µg Levothyroxine	100 µg Levothyroxine	200 µg Levothyroxine
Batch numbers:			
Packaging number:			
Lot number:			

Data Source: Appendix 16.1.6

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects received their subject identification number as soon as they had signed their informed consent. Subjects who met all inclusion criteria and none of the exclusion criteria were randomized to one of the 6 sequences after recheck of eligibility on Day -1 in each treatment period.

The Investigator or delegate allocated a randomization number according to the randomization scheme (see Appendix 16.1.7) to each subject in sequential order before first dosing of IMP (see also Section 9.7.1.1).

9.4.3.1 Criteria for Randomization of Treatment with the Investigational Medicinal Product

After eligibility was confirmed and relevant in/exclusion criteria had been rechecked on Day -1, subjects were randomized to receive the IMP on Day 1 of each treatment period.

Randomization was done according to a randomization list produced by the Contract Research Organization (CRO) and approved by the Sponsor.

For inclusion in the treatment period, the following criteria had to be fulfilled before each administration of the IMP:

- Subjects underwent checks for pregnancy (female subjects) and alcohol/drugs of abuse during Screening. On Day -1 prior to dosing in each treatment period, subjects were again checked for pregnancy (female subjects) and for alcohol/drugs of abuse.

9.4.4 Selection of Doses in the Trial

In each treatment period, one single dose of 600 µg of levothyroxine (three dose strengths) was administered.

For selection of doses in the trial, see Section 9.4.1.

9.4.5 Selection and Timing of Dose for Each Subject

The administration of the IMP was performed in a fasted state on the morning of Day 1 of each treatment period. Subjects remained in the fasted state for 4 hours after IMP administration, with water allowed 1 hour following IMP administration. No breakfast was served.

9.4.6 Blinding

Not applicable, because this was an open-label trial.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Permitted Medicines

Occasional use of paracetamol was permitted within the screening period. The Investigator may have allowed the subject to take paracetamol in case of pain during the trial, but the dose was not to exceed 1000 mg/day. The amount of paracetamol administered must have been recorded in ClinBase™.

9.4.7.2 Non-Permitted Medicines

NOTE: The administration of a non-permitted concomitant medications during the trial (e.g., because of AEs), was to result in discontinuation of the subject from the trial.

Administration of any investigational product or use of any investigational device within 60 days prior to first administration of IMP and during the entire clinical trial was not permitted.

The use of any medications that prolonged the QT interval was not permitted within 4 weeks prior to trial initiation. The use of any prescription or non-prescription medication (with paracetamol being the only exemption), including multivitamins, nutritional supplements and herbal products (e.g., St John's wort) was not permitted within 2 weeks prior to dosing or 5 half-lives, whichever was longer, before the first IMP administration, during the washout period and during the PK sampling period.

9.4.7.3 Other Trial Considerations

General food and water restrictions are provided in Section 9.4.1.

Before and throughout the PK profiling days (until Day 3) the following additional restrictions were to be met:

- No alcohol, caffeine- and xanthine-containing food and beverages (e.g., coffee, black or green tea, chocolate or chocolate containing food or beverages) 48 hours before first IMP administration until Day 4
- No intake of recreational drugs at least 72 hours before first application of IMP until final examination
- No exhausting physical activities (body building, sports) during the hospitalization period at least 12 hours before IMP administration until Day 4
- No sun bathes, solarium, or sauna at least 12 hours before IMP administration until Day 4

Any unplanned diagnostic, therapeutic, or surgical procedure performed during the trial period was to be recorded in the concomitant procedure section in ClinBase™, including the date, indication, and description of the procedure(s) and outcome.

9.4.8 Treatment Compliance

All IMPs were administered orally by the Investigator or designee. The IMP administration was recorded in ClinBase™. Treatment compliance may also have been controlled by PK data.

9.4.9 Special Precautions

The trial was performed in a clinical unit with direct access to a hospital emergency unit. Equipment and other agents (epinephrine, prednisolone equivalents, etc.) were available at the EPCU in case of severe allergic reactions.

Women of child-bearing potential must have used acceptable methods (failure rate <1%) of birth control at least 4 weeks prior to Screening until the end of the trial. Women should have been informed of the potential risks associated with becoming pregnant while enrolled. Accepted forms of contraception were non-hormonal contraception (e.g., condoms or occlusive cap [diaphragm or cervical/vault cap] with spermicide, non-hormonal intra-uterine device with a Pearl index of less than 1%, previous sterilization of the subject or her partner or being sexually inactive).

Female subjects who had been postmenopausal for more than two years or surgically sterile or had undergone hysterectomy may have been enrolled. Female subjects must have had a negative serum pregnancy test (β-human chorionic gonadotropin) at Screening and on Day -1 in each period.

Subjects were required to comply with all trial restrictions. Any deviations from these restrictions were to be considered protocol deviations and were to be recorded in ClinBase™.

Standardization of diet

General food and water restrictions are provided in Section 9.4.1.

Subjects were instructed not to consume alcohol, caffeine or xanthine-containing products (chocolate, tea, coffee, cola, energy drinks, etc.) from 48 hours prior IMP administration until last PK sample collection in each period.

Standardization of physical activity

While resident in the clinical unit, the subjects were confined to bed during the first 1 hour after IMP administration. Thereafter, they could leave the bed, however restricting their activity to a minimum. During the time of the trial until the last PK sample, when the subjects were outside the clinical unit, they were to avoid excessive physical exercises.

Smoking restrictions

Subjects had to be non-smokers (at least 3 months) to participate in this trial.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

No efficacy parameters were assessed in this trial.

A schedule of assessments and evaluations is presented in Table 9.1. For PK blood sampling times, see Section 9.5.4. Pharmacokinetic measurements, variables and evaluation are described in Section 9.5.5.

Table 9.1 Schedule of Assessments

	Screening	Period 1					Washout	Period 2					Washout	Period 3					FU
Day	-21 to -1	-1	1	2	3	4	35 to 38 days after IMP	-1	1	2	3	4	35 to 38 days after IMP	-1	1	2	3	4	14 to 18 days after last IMP
Informed consent	X																		
Confinement[a]		X	X	X				X	X	X				X	X	X			
Ambulatory Visit[b]	X			X	X	X				X	X	X				X	X	X	X
Inclusion/Exclusion Criteria Check/Re-check	X	X						X						X					
Demographics Including Body Weight and Height	X																		
Medical History and History of Medication	X																		
Physical Examination[c]	X	X						X						X					X
Drugs and Alcohol Screening[d]	X	X						X						X					
Vital Signs (BP, pulse, temperature)[e]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X
12-Lead ECG[f]	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X
Safety Laboratory[g]	X	X						X						X					X
Pregnancy Test (serum)	X	X						X						X					
Randomization			X																
IMP Administration			X						X						X				
PK Blood Sampling for levothyroxine[h]			X	X	X	X			X	X	X	X			X	X	X	X	
Assessment of AEs and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand-out of diary cards				X						X						X			
Collection of diary cards								X						X					X

AE: adverse event; BP: blood pressure; CRO: Contract Research Organization; FU: follow-up; IMP: Investigational Medicinal Product, PK: pharmacokinetics, ECG: electrocardiogram

Footnotes:

a. From at least 12 hours before each IMP administration until the morning of Day 2 after each IMP administration.

b. Ambulatory visit: Subjects were discharged in the morning of Day 2 but had to come back in the evening of Day 2 and on Day 3 and 4 for PK blood sampling and vital signs and ECG assessments at 48 and 72 hours postdose.

c. Physical examination: According to the CRO standards.

d. Drug, alcohol abuse. Other time points at the discretion of the Investigator.

e. Vital signs (BP, pulse rate, body temperature) were measured after 10 minutes in supine position at the following time points: baseline (within 60 minutes before dosing), 2, 3, 6, 12, 24, 48 and 72 hours postdose in each period.

f. 12-lead ECG was recorded after 10 minutes in supine position at the following time points: Baseline (within 60 minutes before dosing), 2, 6, 12, 24, 48 and 72 hours postdose in each period.

g. Safety laboratory assessments included hematology, clinical chemistry (including total T4 and T3) and urinalysis. Serology was assessed at Screening only. Free T4, free T3 and TSH were assessed at Screening and Follow-up only.

h. PK assessments of levothyroxine at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours postdose.

9.5.1.1 Safety Observations and Measurements

9.5.1.1.1 Adverse Events

Adverse Event Definition

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure was considered as the AE rather than the procedure itself. In case of a fatality, the cause of death was considered as the AE, and the death was considered as its OUTCOME.

The Investigator was required to grade the severity/intensity of each AE.

Investigators assessed the severity/intensity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild: The subject was aware of the event or symptom, but the event or symptom was easily tolerated.

Moderate: The subject experienced sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject was unable to carry out usual activities.

Investigators also systematically assessed the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP included, but might not have been limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not suspected to be reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation was to be available.

Related: Suspected to be reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) were not to be reported as AEs unless they were associated with clinical signs and symptoms, led to treatment discontinuation or were considered by the Investigator as otherwise medically important. If an abnormality fulfilled these criteria, the identified medical condition (e.g., anemia, increased ALT) was to be reported as the AE rather than the abnormal value itself.

Serious Adverse Event

An SAE was any untoward medical occurrence that at any dose:

- Resulted in death.
- Was life-threatening.

NOTE: The term "life-threatening" in this definition referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event that hypothetically might cause death if it were more severe.

- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect.
- Was otherwise considered as medically important.

Important medical events that did not result in death, were life-threatening, or required hospitalization could have been considered as SAEs when, based upon appropriate medical judgment, they might have jeopardized the subject or might have required medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency, or drug abuse.

In this clinical trial, any late spontaneous abortion, fetal death in utero, ectopic pregnancy, chronic fetal distress, still birth, neonatal death or prematurity related complication more than is typical for prematurity should be considered serious under this criterion.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP was also considered a serious adverse reaction and all such cases were to be reported in an expedited manner as described in Section 9.5.1.1.4.

Events that Did Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate therapy application) were not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) were to be documented and reported as SAEs.

Events Not to Have Been Considered as AEs/SAEs

Medical conditions present at the initial trial visit that did not worsen in severity or frequency during the trial were defined as Baseline Medical Conditions, and were not to be considered AEs.

9.5.1.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject was queried on changes in his or her condition. During the reporting period of the trial any unfavorable changes in the subject's condition were recorded as AEs, whether reported by the subject or observed by the Investigator.

During the ambulatory phase of the trial the subject was asked to record details of AEs and concomitant medication in subject diary cards. The Investigator performed a medical review of the diary cards, asked the subjects for further details or clarifications, if necessary, and recorded the AEs in the appropriate section of ClinBase™.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period defined in Section 9.5.1.1.3 were reported on an ongoing basis in the appropriate section of ClinBase™. Among these AEs, all SAEs were to be additionally documented and reported using an AE Safety Report Form (Clinical Trial) as described in Section 9.5.1.1.4. A sample Case Report Form (CRF) is presented in Appendix 16.1.2.

It was important that each AE reported included a description of the event, its duration (onset and resolution dates [times to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its relationship with the trial treatment (IMP), any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP) and its outcome. In addition, serious cases were to be identified and the appropriate seriousness criteria documented.

9.5.1.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance began when the subject was included in the trial (date of first signature of informed consent) and continued through the trial's post treatment FU period, defined as the last trial visit, which was to occur at least 14 to 18 days after last treatment.

9.5.1.1.4 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator was to immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the SAE check desk by telephone, by fax or by e-mail.

When an event (or follow-up information) was reported by telephone, a written report was to be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines were the same for any new information on a previously reported SAE (= follow-up).

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the AE Safety Report Form (Clinical Trials).

All written reports were to be transmitted using the AE Safety Report Form (Clinical Trials), which was to be completed and signed by the Investigator following specific completion instructions.

The AE section of ClinBase™ must be completed and a copy of the information transmitted with the Adverse Event Safety Report Form (Clinical Trials). Other relevant section from ClinBase™ may also have been provided (e.g., medical history, concomitant drugs).

The Investigator was to respond to any request for follow-up information (e.g., additional information, outcome, and final evaluation, specific records where needed) or to any question the Sponsor might have had on the AE within the same timelines as described for initial reports. This was necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up were usually to be made by the responsible monitor, although in exceptional circumstances the Global Drug Safety department could have contacted the Investigator directly to obtain clarification or to discuss a particularly critical event.

9.5.1.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor sent appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator was to comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/ (Institutional Review Board) IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor informed the Investigator of "findings that could have adversely affected the safety of subjects, impacted the conduct of the trial, or altered

the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor was to inform the Investigator of AEs that were both serious and unexpected and were considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The investigator was to place copies of safety reports in the Investigator Site File (ISF). National regulations with regard to safety report notifications to Investigators were to be taken into account.

When specifically required by regulations and guidelines, the Sponsor was to provide appropriate safety reports directly to the concerned lead IEC/IRB and was to maintain records of these notifications. When direct reporting by the Sponsor was not clearly defined by national or site-specific regulations, the Investigator was responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the ISF.

This trial was conducted in Germany and was covered by the European Directive 2001/20/EC. It was the Sponsor's responsibility to report SAEs/SUSARs/Safety Issues to Health Authorities and IEC/IRB, in accordance with that Directive and with the related Detailed Guidance.

9.5.1.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurred during the course of a clinical trial and was considered to be possibly related to the IMP was to be monitored and followed up by the Investigator until stabilization or until the outcome was known, unless the subject was documented as "lost to follow-up." Reasonable attempts to obtain this information were to be made and documented. It was also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures were performed. The Sponsor actively followed-up and collected information on any AE that occurred during the course of a clinical trial, however while this activity continued for any serious AEs until stabilization or until the outcome was known, it was discontinued at the time of database lock for non-serious AEs.

9.5.1.1.7 Pregnancy and In-Utero Drug Exposure

Only pregnancies considered by the Investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) were considered as AEs. However, all pregnancies with an estimated conception date during the period defined in Section 9.5.1.1.3 must be recorded by convention in the AE page/section of the ClinBase™. The same rule applied to pregnancies in female subjects and in female partners of male subjects. The Investigator must notify the sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must have been transmitted according to the same process as described for SAE reporting in Section 9.5.1.1.4.

Investigators were to actively follow up, document and report on the outcome of all these pregnancies, even if the subjects were withdrawn from the trial.

The Investigator was to notify the Sponsor of these outcomes using the initial Pregnancy Report Form and completing the outcome section (in case of abnormal outcome, the AE Safety Report

Form [Clinical Trials] when the subject sustained an event and the Parent-Child/Fetus AE Report Form when the child/fetus sustained an event).

Any abnormal outcome was to be reported in an expedited manner as described in Section 9.5.1.1.4 while normal outcomes were to be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject was to be discontinued from trial medication immediately. The Sponsor was to be notified without delay and the subject was to be followed-up as mentioned above.

9.5.1.1.8 Laboratory Assessments

The safety laboratory parameters (hematology, clinical chemistry, serology, urinalysis, drugs of abuse) were performed in accordance with the clinical unit's standard operating procedures (SOPs). For details regarding the assessment schedule, please refer to assessment schedule in Table 9.1.

Analyses of safety laboratory parameters were performed at Synlab Pharma Institute, Berlin, Germany, according to their SOPs.

Detailed description of the procedures and methods were given in a separate laboratory manual. Documentation of inter-laboratory standardization methods and quality assurance procedures are presented in Appendix 16.1.10.

It was essential that the Sponsor was provided with a list of laboratory normal ranges before shipment of trial drug. Any changes in laboratory normal ranges during the trial were additionally forwarded to the Sponsor.

The total volume of blood withdrawn was approximately 478.5 mL.

Pregnancy Testing

Serum pregnancy tests were performed at Screening and Day -1 of each treatment period. Refer to Section 9.5.1.1.7, "Pregnancy and In-Utero Drug Exposure" for details of the procedure for reporting pregnancies to the Sponsor in case of positive pregnancy test results.

For serum pregnancy test, blood (2.7 mL) was collected into a propylene serum gel tube (Monovette 05.1557.001, Sarstedt) to determine beta-human chorionic gonadotropin (β-hCG) in serum using a test kit from DPC Biermann GmbH, Bad Nauheim, Germany, at Synlab Pharma Institute, Berlin, Germany.

9.5.1.1.9 Vital Signs, Physical Examinations, and Other Assessments

9.5.1.1.9.1 Vital Signs and Physical Examination

Vital signs including BP, pulse, and oral body temperature were performed according to the trial schedule in Table 9.1. Supine systolic and diastolic BP was measured on the same arm after the

subject had been in supine position for at least 10 minutes. Systolic/diastolic BP and pulse were measured using an oscillometric BP monitor (Dinamap® Pro Care, manufactured by General Electric Medical Systems [GEMS]). Pulse was recorded simultaneously with the BP measurements by the same monitor.

Oral body temperature was measured using a digital thermometer. Oral body temperature was taken together with measurements of BP and pulse.

Physical examination (including general appearance, skin, head, neck (including thyroid), ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system) was done according to the clinical unit's standard procedures. Body weight was recorded at Screening.

9.5.1.1.9.2 Other Assessments

For details regarding other assessments, please refer to assessment schedule in Table 9.1.

Electrocardiogram
The 12-lead ECGs were recorded after the subjects had rested for at least 10 minutes in supine position. A full standard 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) for about 5 seconds (at least four adjacent beats, calibration: 25 mm/sec 10 mm/mV) and HR corrected QT interval using Fridericia and Bazett formula was calculated. In addition, a rhythm recording from lead II for 60 seconds (calibration: 10 mm/sec 12.5 mm/mV) was recorded.

ECGs could have been repeated for quality reasons and the repeat used for analysis. Additional ECGs might have been collected by the Investigator for safety reasons. Clinically relevant abnormal findings were to be reported as AEs.

9.5.2 Appropriateness of Measurements

All PK and safety assessments performed as part of this trial were standard measures for this type of trial.

9.5.3 Primary Efficacy Variables

Not applicable.

9.5.4 Drug Concentration Measurements

Samples for PK (total T3 and T4, respectively) were collected according to the time points presented in Table 9.1. Actual date and time of blood sampling for PK was recorded in ClinBase™.

The determination of T3 and T4 was performed by using a Liquid Chromatography Tandem Mass Spectrometry method according to Good Laboratory Practices principles, which was fully validated according to the Guidelines for Industry applicable to Bioanalytical Methods.

Analysis methods are defined in a bioanalytical protocol, and respective results are reported in a bioanalytical report (see Appendix 16.1.12).

Detailed description of the labels, procedures, methods, and shipments was provided in a separate laboratory manual.

9.5.5 Pharmacokinetic Variables and Pharmacokinetic Evaluation

The PK parameters for total T3 and T4 were calculated by PAREXEL International using the validated software tool Phoenix WinNonlin™ (Version 6.3), and were evaluated using non-compartmental standard methods.

PK parameters included:

AUC_{0-72} Area under the plasma concentration time curve (AUC) from time zero to 72 hours (total T3 and T4).

C_{max} Maximum plasma concentration (total T3 and T4).

$AUC_{0-72,adj}$ AUC from time zero to 72 hours postdose, adjusted for baseline (total T4 only).

$C_{max,adj}$ C_{max}, adjusted for baseline (total T4 only).

AUC_{0-48} AUC from zero to 48 hours postdose (total T3 and T4)

t_{max} Time point at which C_{max} occurred (total T3 and T4)

$AUC_{extra,adj}$ $C_{72,adj}/\lambda_z$ where $C_{72,adj}$ is calculated adjusted concentration at the time point 72 hours (total T4 only).

$AUC_{0-\infty,adj}$ $AUC_{0-72,adj} + AUC_{extra,adj}$ (total T4 only)

$t_{½}$ Apparent terminal half-life, calculated by $\ln 2/\lambda_z$ (total T4 only)

λ_z Apparent terminal elimination rate constant: Estimated at terminal phase by linear regression (calculated using baseline-adjusted concentration data) (total T4 only)

V_z/F Apparent volume of distribution during baseline-adjusted terminal phase, calculated by: $Dose/(AUC_{0-\infty,adj}*\lambda_z)$ (total T4 only)

CL/F Apparent total body clearance of drug from plasma, calculated by: $Dose/AUC_{0-\infty,adj}$ (total T4 only)

The calculation of the AUC was performed using the mixed log-linear trapezoidal method. The actual time of blood sampling was used for PK evaluation.

There was no imputation of missing data. The baseline for PK refers to the mean of the three predose samples.

For determination of PK parameters the following rules were applied to concentration values:

- Concentrations below the lower limit of quantification (LLOQ) were presented as BLQ (i.e. below limit of quantification) in the listings.
- Concentrations that were BLQ were set to ½ LLOQ for summary statistic calculations.
- Negative concentrations following baseline-adjustment were considered missing.

The PK variables were evaluated and listed for all subjects who provided sufficient concentration time data.

9.6 Data Quality Assurance

This trial was monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The site Monitor performed visits to the EPCU at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, were permitted to inspect all trial-related documents and other materials at the EPCU, including the ISF, the completed CRF, the IMP(s) and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure and the handling of the data, including the final clinical trial report, was subject to independent Quality Assurance activities. Audits were conducted to ensure the validity and integrity of the trial data.

The following audits were performed:

- Study Conduct, Date of Audit: 09 Jan 2014
- Investigator Site File, Date of Audit: 17 Jan 2014
- Case Report Form, Date of Audit: 19 Feb 2014
- Signed Informed Consent Forms, Date of Audit: 19 Feb 2014

For copies of the audit certificates, refer to Appendix 16.1.8. For details on data collection, management, and validation, refer to Section 10.1 of the clinical trial protocol (Appendix 16.1.1).

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

This section provides an outline of the planned data summarization and statistical methodology. Details on the statistical analysis were presented in the statistical analysis plan (SAP) prior to database lock (for the SAP, refer to Appendix 16.1.9).

9.7.1 Statistical and Analytical Plans

9.7.1.1 Randomization

A total of 42 subjects were to be randomized to one of 6 treatment sequences, such that 7 subjects were assigned to each treatment sequence (see also Section 9.1 and Section 9.4.3). Male and female subjects were included. Every effort was made to aim gender balance (minimum proportion of 30% for each gender). Stratification by gender was not intended. The randomization list was prepared by the CRO. As specified in Section 9.4.6, this trial was conducted open-label and no blinding was performed.

9.7.1.2 Endpoints

9.7.1.2.1 Primary Endpoints

The primary variables were AUC_{0-72} and C_{max} (Set 1) and $AUC_{0-72,adj}$ and $C_{max,adj}$ (Set 2) of total T4 in plasma.

9.7.1.2.2 Secondary Endpoints

All other PK endpoints were considered secondary and were analyzed descriptively. These included $AUC_{0-\infty,adj}$, $AUC_{extra,adj}$, AUC_{0-48}, $AUC_{0-48,adj}$, t_{max}, $t_{½}$, λ_z, CL/F, and V_z/F for total T4. Secondary endpoints for total T3 included C_{max}, AUC_{0-48}, AUC_{0-72}, and t_{max}.

9.7.1.2.3 Safety Endpoints

Safety parameters as assessed by standard laboratory hematology and biochemical parameters, treatment-emergent AEs (TEAEs), vital signs (body temperature, systolic and diastolic BP, and pulse rate), and ECG parameters.

9.7.1.2.4 Further Endpoints of Interest

Not applicable.

9.7.1.3 Analysis Sets and Subgroup

The PK analysis set

The PK population included all randomized subjects who had been treated according to protocol and fulfilled the following criteria:

- Absence of relevant protocol violations with respect to factors likely to affect the comparability of PK results.
- Adequate IMP compliance
- Availability of all four primary PK variables for total T4 (AUC_{0-72}, C_{max}, $AUC_{0-72,adj.}$, and $C_{max,adj}$) for all treatment periods.

If subjects received concomitant medication for the treatment of AE(s), their inclusion in the PK population was to be discussed. If subjects received any prohibited concomitant medications, they were to be excluded from the PK population.

The PK population was the primary analysis population for this trial.

Relevant protocol violations in the sense of this definition were identified before data base lock. The decisions were taken between Sponsor and the CRO in a data review meeting that was held before data base lock.

The safety analysis set

The safety analysis set consisted of all randomized subjects who received at least one dose of IMP. The safety analysis set was used for the presentation of all baseline, demographic, safety, and tolerability data.

A by-subject listing of analysis set assignment is presented in Appendix 16.2.3.

9.7.1.4 Description of Statistical Analyses

9.7.1.4.1 General Considerations

Pharmacokinetic analyses were derived using Phoenix WinNonlin (Version 6.3). Core WinNonlin output is presented in Appendix 16.1.9.3. All other statistical analyses were performed using SAS® (Statistical Analysis System, SAS Institute, Cary NC, USA, Windows® Version 9.2). Statistical model output is presented in Appendix 16.1.9.2. If not stated otherwise, the level of statistical significance is alpha=0.05. Details on the statistical analysis were presented in the SAP prior to database lock.

The statistical analysis was not started until all data were corrected and checked for plausibility and all necessary coding and assessments were completed.

Medical history and AE terms were coded with Medical Dictionary for Regulatory Activities (MedDRA), version 17.0 and concomitant medication was coded with World Health Organization - Drug Dictionary (WHO-DD; Version date September 2013). Versions of dictionaries used for coding were defined in the Data Management Plan (DMP).

All data recorded during the trial were presented in individual data listings. All data were evaluated as observed; no imputation method for missing values was used. Summary statistics were provided for all endpoints.

9.7.1.4.2 Analysis of Primary Endpoint

The primary variables, AUC_{0-72} and C_{max} (Set 1) and $AUC_{0-72,adj}$ and $C_{max,adj}$ (Set 2) of total T4 in plasma were log-transformed and estimated according to non-compartmental standard methods. A generalized linear model was applied to each set of primary endpoints including effects for treatment, period, sequence and subject within sequence. Differences Test minus Reference was estimated, and based on the residual (within-subject) variation 95% confidence intervals (CI) for the differences were calculated. Back transformation resulted in Test/Reference ratios and corresponding 95% CIs.

According to the defined BE limits [0.80 to 1.25], for each set of primary endpoints null and alternative hypotheses were:

- H_0: $\mu_T / \mu_R \leq 0.8$ or $1.25 \leq \mu_T / \mu_R$;

  for at least one of primary endpoints AUC_{0-72} or C_{max} in at least one of 3 possible Test/Reference comparisons.

- H1: $0.8 < \mu_T / \mu_R < 1.25$;

  for AUC_{0-72} and C_{max} in all 3 Test/Reference comparisons.

μ_T and μ_R are the means under Test and Reference treatment, respectively.

Comparison 1

Test treatment: 600 µg levothyroxine as 6 tablets of 100 µg (Treatment B)

Reference treatment: 600 µg levothyroxine as 12 tablets of 50 µg (Treatment A)

Comparison 2

Test treatment: 600 µg levothyroxine as 3 tablets of 200 µg (Treatment C)

Reference treatment: 600 µg levothyroxine as 12 tablets of 50 µg (Treatment A)

Comparison 3

Test treatment: 600 µg levothyroxine as 3 tablets of 200 µg (Treatment C)

Reference treatment: 600 µg levothyroxine as 6 tablets of 100 µg (Treatment B)

Dose-form-proportionality was confirmed, if the 95% CI for the ratios of GM for both AUC_{0-72} and C_{max} of total T4 in plasma, were included in the interval 0.8 to 1.25 in all three pairwise comparisons.

The same approach was applied to set 2, i.e. $AUC_{0-72,adj}$ and $C_{max,adj}$.

The PK parameters were presented in a descriptive way per treatment (number [N], mean, standard deviation [SD], standard error of the mean [SEM], arithmetic and geometric coefficient of variation percentage (CV%), median, minimum (min) and maximum (max) values, geometric means, and 95% CI of geometric means). Graphs were produced as appropriate.

9.7.1.4.3 Analysis of Secondary Endpoints

Secondary PK parameters (for T3 and T4) are listed and summarized as described for primary PK parameters.

For t_{max} only n, median, minimum, and maximum were presented.

There was no formal statistical comparison of the secondary PK endpoints. Summary statistics are provided for all secondary endpoints. In addition, treatment ratios and CIs (95% for T4 and 90% for T3) are presented. Boxplots are presented only for the following parameters:

Total T3: AUC_{0-48} and C_{max}

Total T4: AUC_{0-72}, $AUC_{0-72,adj}$, C_{max}, $C_{max,adj}$, and $AUC_{0-48,adj}$

The geometric mean ratio (Test/Reference) was obtained using a general linear model as described for the primary endpoints.

9.7.1.4.4 Safety Analyses

In general, for the evaluation of safety parameters, the numerical values were summarized descriptively (N, arithmetic mean, median, SD, standard error of mean, minimum and maximum values). Categorical variables were presented in frequency tables by the number of observations and percentages.

All AE counts and subjects with AEs were summarized for each treatment by system organ class (SOC) and preferred term (PT). In addition, AEs were tabulated and listed per group and analyzed by severity and relationship to trial drug. Subjects who prematurely withdrew from the trial or from treatment were displayed in a by-subject listing and summarized by primary withdrawal reason for each treatment group.

9.7.1.4.5 Analysis of Further Endpoints

Demographic parameters (such as age, height, weight) and other baseline characteristics were summarized by means of tabulated descriptive statistics for all subjects by sequence group and overall.

Individual and mean concentration versus time plots was prepared for total T4 and total T3.

9.7.1.5 Interim Analysis

No formal statistical interim analysis was performed.

9.7.2 Determination of Sample Size

The sample size for this trial was based on intra-individual variability in T4 PK parameters from previous trials (Table 9.2).

Table 9.2 Intra-individual Variability of Pharmacokinetic Data

Trial	Ratio AUC	Ratio C_{max}	CV% AUC	CV% C_{max}
436-99-263	0.99	0.98	11.54	13.45
436-99-264	0.97	0.94	15.37	15.15
436-99-277	1.14	1.04	15.31	13.85

CV%: coefficient of variation percentage

These results were in agreement with data published in a summary by the FDA most recently, giving 15.5% as an upper bound for the coefficient of variation percentage (CV%) of AUC of levothyroxine, and 18.6% as an upper bound for the CV% of Cmax. If we apply the upper bounds of these CV% together with common BE criteria for AUC and Cmax [0.80 – 1.25], and if we furthermore allow the true treatment ratio Test/Reference to vary within 0.95 and 1.05, 32 evaluable subjects would provide at least 80% overall power to show BE for all 3 pairwise comparisons. For a compensation of possible drop-outs 10 subjects should be included in addition, corresponding to a drop-out rate of around 20%. In total, 42 subjects should be included in the trial (7 subjects per treatment sequence). Since dosage form proportionality was tested for two sets of parameters, the usual one-sided alpha of 0.05 is adjusted to 0.025, corresponding to a confidence level of 95%.

9.8 Changes in the Conduct of the Trial or Planned Analyses

9.8.1 Changes in the Conduct of the Trial

Before start of the trial, one amendment (refer to Appendix 16.1.1.2), dated 09 Oct 2013, became necessary.

The purpose of the amendment was:

- To note a change in the medical responsible person
- To correct discrepancies regarding the primary endpoints
- The addition of details regarding the calculation of PK parameters
- To add additional withdrawal criteria
- To note a change in the drug screening method for tricyclic antidepressants
- To note a change in the method of T3 and T4 analyses
- To clarify the gender distribution method, i.e., randomization will not be stratified by gender
- The volume of blood collection was updated

The reason for the Amendment was the requirements of the IEC (additional withdrawal criteria) and corrective actions considered necessary by the clinical trial team.

In addition, a total of 22 file notes (see Appendix 16.1.1.5) were created:

- File Note #1: Documented that the test used during the trial for screening of amphetamines also covered methamphetamine, ecstacy, and other methamphetamine derivatives.
- File Note #2 was no longer required with the submission of the protocol amendment.
- File Note #3: Documented the reason for the recall of the Randomization List, Final 1.0, randomized 14 Jun 2013.
- File Note #4: ECGs for this trial was assessed by the Investigator or designee per PAREXEL SOP. However, deviating from the standard normal ranges provided in this SOP, the HR was evaluated according to Inclusion Criterion #4.
- File Note #5: Clarified that PK analysis was performed using plasma, instead of serum as stated in the protocol.
- File Note #6: Clarified that the eligibility of randomized subjects after completion of Period 1 was verified using withdrawal criteria rather than inclusion/exclusion criteria review. Furthermore, it was clarified that with reference to ECG withdrawal criteria QTcF value was used, rather than QTc as stated in the protocol.
- File Note #7: Documented that three subjects (Subject) appeared to have suspension period below 90 days in ClinResults; however, it was confirmed that a suspension period of greater than 90 days existed for all three subjects.

- File Note #8: Documented that the PK samples drawn from Subject at 30 min postdose on Day 1 of Period 3 was taken with a delay of 30, 27, 22, and 19 minutes, respectively.

- File Note #9: Documented that Subject 1055 was dosed on 19 Feb 2014 although the subject took prohibited concomitant medication (xylometazoline hydrochloride [0.1%]) on 15 Feb 2014. This was considered a minor violation since it was not considered as a PK or a safety issue.

- File Note #10: Clarified that in line with Exclusion Criterion #17, but contrary to Exclusion Criterion 14, the participation in the trial was set to 60 days.

- File Note #11: Clarified the transcribing process for AEs documented in subject diaries. Changes may be made by the Investigator with regards to severity/intensity, start and stop dates, and also the number of AEs. Furthermore, orally reported AEs, not documented in the diary, were also entered into the trial database.

- File Note #12: Documented the reason why Subject eening failure) signed a second Informed Consent Form.

- File Note #13: Documented that an Investigator performed assessments during the trial without having signed the Master Signature Log (i.e., the authorization of the staff member was not formally completed). However, since these types of responsibilities are also included in job description for Investigators the Investigator was in fact authorized to perform these duties.

- File Note #14: Documented that Subject d a washout period of 39 days between Period 2 and Period 3; the protocol allows a range of 35 to 38 days only.

- File Note #15: Documented that Subject s dosed on 26 Feb 2014 although the subject took prohibited concomitant medication (sodium chloride nasal spray and Pulmotin®) on 24 Feb 2014. This was considered a minor violation since it was not considered as a PK or a safety issue.

- File Note #16: Documented that Subject signed the Data Privacy Statement on 06 Dec 2013, although he entered 07 Dec 2013 as the date of signature.

- File Note #17: Clarified the reason for having two sets of Batch I queries and for sharing Batch II queries with the EPCU without having received responses for Batch I queries.

- File Note #18: Documented that Subject number s not assigned to any subject during screening.

- File Note #19: Documented that through a mutual agreement between Merck KGaA and PAREXEL International the DMP and Data validation Specifications (DVS) was not

reviewed or approved by Merck's Data Management team but was only provided for their information.

- File Note #20: Documented that the investigator did not complete the field for time of signature on the informed consent document (ICD) due to human error.
- File Note #21: Clarified the process employed for AE capturing in terms of the Source Data Capturing System (ClinBase™). Also see Appendix 16.1.2.2 for a statement on electronic data capturing procedure.
- File Note #22: Documented that no fields were created in ClinBase™ to record failed Inclusion and Exclusion criteria.

9.8.2 Changes in the Planned Analyses

In the SAP, no changes to the planned analyses in the Clinical Trial Protocol were documented.

10 Trial Subjects

In this report, the subject number is used to identify the subjects.

10.1 Disposition of Subjects

Subject discontinuations and treatment terminations are provided in Appendix 16.2, Listing 16.2.1.1 and Listing 16.2.1.2, respectively. Screening and informed consent data and screening failures are listed in Appendix 16.2, Listing 16.2.1.3 and Listing 16.2.1.5, respectively.

The disposition of subjects is summarized in Table 10.1.

Table 10.1 Subject Disposition

Subjects	Sequence 1 N = 7	Sequence 2 N = 7	Sequence 3 N = 7	Sequence 4 N = 7	Sequence 5 N = 7	Sequence 6 N = 7	Overall N = 42
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screened	-	-	-	-	-	-	103
Randomized	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	42 (100.0%)
Subjects Treated	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	42 (100.0%)
Completed	7 (100.0%)	5 (71.4%)	7 (100.0%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	37 (88.1%)
Withdrawn	0	2 (28.6%)	0	1 (14.3%)	1 (14.3%)	1 (14.3%)	5 (11.9%)
Adverse event	0	1 (14.3%)	0	1 (14.3%)	0	0	2 (4.8%)
Protocol non-compliance	0	1 (14.3%)	0	1 (14.3%)	0	0	1 (2.4%)
Death	0	0	0	0	0	0	0
Subject withdrew at own request	0	0	0	0	1 (14.3%)	1 (14.3%)	2 (4.8%)
Safety population	7 (100.0%)	5 (71.4%)	7 (100.0%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	37 (88.1%)
PK population	0	2 (28.6%)	0	1 (14.3%)	1 (14.3%)	1 (14.3%)	5 (11.9%)

N = number of subjects for each treatment arm; n = number of subjects affected; PK = pharmacokinetics

Sequence 1: (A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg

Sequence 2: (B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg

Sequence 3: (C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg

Sequence 4: (A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg

Sequence 5: (B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg

Sequence 6: (C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg

Source: Appendix 16.2, Listing 16.2.1.1, Listing 16.2.4.1, and Listing 16.2.5.1; Section 15.3, Table 15.1.1

Overall, 103 subjects were screened for inclusion in this trial (main reasons for screening failures included entry criteria violations for eGFR [<90 mL/min], total T4 [outside inclusion range], and body weight [outside inclusion range]). Of these, 42 subjects were randomized to treatment sequence. A total of 37 subjects completed the trial.

- Five (5) subjects were discontinued from the trial prematurely:
    - Subject equence: BCA) – Treatment C (3 tablets of 200 µg) (withdrawn due to positive drug screen [opiates] at predose)
    - Subject (Sequence: ACB) – Treatment A (12 tablets of 50 µg) (withdrawn due to SAE)
    - Subject equence: BCA) – Treatment B (6 tablets of 100 µg) (withdrawn due to AE)
    - Subject Sequence: BAC) – Treatment B (6 tablets of 100 µg) (subject withdrew consent)
    - Subject Sequence: CBA) – Treatment C (3 tablets of 200 µg) (subject withdrew consent)

10.2 Protocol Deviations

Listings of protocol deviations and time window deviations are provided in Appendix 16.2, Listing 16.2.2.1 and Listing 16.2.2.2, respectively.

There were no major protocol deviations reported during the trial.

Minor protocol deviations comprised predominantly assessments performed out of time window allowance, including eligibility review, washout (prolonged), dosing, trial follow-up, diary card review, centrifugation procedure, PK blood sampling, ECG, and vital sign assessment.

Other clinically relevant protocol deviations considered not to have unduly affected the results of the trial (i.e., minor deviations) included:

- Subject had HR measurements of >90 beats per minute (bpm) on Day -1 during eligibility check that did not comply with Inclusion Criterion #4, however a within acceptable range measurement (82 bpm) was reported at Day 1 (predose).

- Subject had BP measurements of <90 mmHg on Day -1 during eligibility check that did not comply with Inclusion Criterion #4, however a within acceptable range measurement (92 mmHg) was reported at Day 1 (predose).

- Subject sed prohibited concomitant medication (xylometazoline hydrochloride [0.1%] nasal spray) approximately 3 days prior to IMP administration (See Appendix 16.1.1, File Note #9).

- Subject [redacted] ed prohibited concomitant medications (sodium chloride and Pulmotin® nasal spray) approximately 2 days prior to IMP administration (See Appendix 16.1.1, File Note #15).

- Subject [redacted] ad BP measurements of >140 mmHg on Day -1 during eligibility check that did not comply with Inclusion Criterion #4, however a within acceptable range measurement (133 mmHg) was reported at Day 1 (predose).

10.3 Previous and Concomitant Medication and Procedures

Individual listings of previous and concomitant medication and of concomitant procedures are provided in Appendix 16.2, Listing 16.2.4.3 and Listing 16.2.4.4, respectively.

Previous medication

No previous medications were reported.

Concomitant medication

A total of 10 subjects were administered 13 concomitant medications for the treatment of AEs during the trial (Appendix 16.2, Listing 16.2.4.3).

Eight (8) of the 10 subjects who were administered concomitant medication during the trial took anilides (paracetamol) for headache (Subjects [redacted] lower abdominal pain (Subject [redacted] r common cold symptoms (Subjec [redacted] Subject [redacted] vas administered heparin and vitamin K antagonists for the treatment of an SAE of deep vein thrombosis (see Section 12.3.2); the subject was subsequently withdrawn from the trial.

Two (2) subjects took 3 prohibited concomitant medications (considered minor deviations); Subject [redacted] took xylometazoline hydrochloride (0.1%) nasal spray, and Subject [redacted] took sodium chloride and Pulmotin® nasal spray, both for common cold symptoms (Appendix 16.2, Listing 16.2.4.3). The concomitant medications were considered to have no undue effect on the results of the trial.

11 Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The safety population included all randomized subjects who received at least 1 dose of the trial medication and who had follow-up safety assessments, i.e., the data of 42 subjects were analyzed, 7 subjects in each sequence.

The PK population included all subjects who completed the trial according to the definition provided in Section 9.7.1.3, i.e., the data of 37 subjects were analyzed. Five (5) subjects (Subject [redacted]) were excluded from the PK population (see Section 10.1 for details).

11.2 Demographic and Other Baseline Characteristics

Demographic data are summarized descriptively, see Section 15.1, Table 15.1.2 and is presented in-text in Table 11.1. Individual listing of demographics is available in Appendix 16.2, Listing 16.2.4.1. A subject listing of medical and surgical history is available in Appendix 16.2, Listing 16.2.4.2. Subject alcohol and caffeine consumption, as well as the smoking status of the subjects are listed individually in Appendix 16.2, Listing 16.2.4.5.

Other baseline characteristics are available in Appendix 16.2, Listing 16.2.8.4 (pregnancy status), Listing 16.2.8.5 (serum virology), and Listing 16.2.8.6 (urine test for alcohol and drugs of abuse).

Table 11.1 Subject Demographics by Sequence (Safety Population)

Subjects	Statistic		Sequence 1 N = 7	Sequence 2 N = 7	Sequence 3 N = 7	Sequence 4 N = 7	Sequence 5 N = 7	Sequence 6 N = 7	Overall N = 42
Age (years)	n		7	7	7	7	7	7	42
	Mean		31.1	38.0	38.9	32.6	33.0	35.9	34.9
	SD		7.20	10.66	11.23	9.55	10.17	12.55	10.13
Gender	Male	n (%)	3 (42.9)	3 (42.9)	3 (42.9)	3 (42.9)	3 (42.9)	4 (57.1)	19 (45.2)
	Female	n (%)	4 (57.1)	4 (57.1)	4 (57.1)	4 (57.1)	4 (57.1)	3 (42.9)	23 (54.8)
Height (cm)	n		7	7	7	7	7	7	42
	Mean		172.0	170.9	176.9	174.1	171.9	174.1	173.3
	SD		6.03	7.93	10.16	9.69	5.24	7.17	7.68
Weight (kg)	n		7	7	7	7	7	7	42
	Mean		70.23	69.79	71.27	66.06	65.37	71.94	69.11
	SD		9.790	7.523	11.686	8.760	7.780	11.383	9.369
BMI (kg/m^2)	n		7	7	7	7	7	7	42
	Mean		23.67	23.90	22.67	21.69	22.10	23.64	22.95
	SD		2.469	2.026	1.884	1.068	1.865	2.700	2.119

N = number of subjects for each treatment arm; n = number of subjects affected; PK = pharmacokinetics
Sequence 1: (A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg
Sequence 2: (B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg
Sequence 3: (C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg
Sequence 4: (A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg
Sequence 5: (B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg
Sequence 6: (C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg
Source: Section 15.1, Table 15.1.2

All (100%) healthy female and male subjects included in the trial were considered Caucasian and of not-Hispanic ethnicity (Section 15.1, Table 15.1.2). For all randomized subjects, the mean age (±SD) was 34.9±10.13 years, the mean (±SD) height was 173.3±7.68 cm, the mean weight (±SD) was 69.11±9.369 kg, and the mean (±SD) BMI was 22.95±2.119 kg/m^2; similar distribution was observed within treatment sequences (Table 11.1).

In total, 33 of the 42 enrolled subjects in this trial had at least one previous or ongoing medical or surgical event in their history. The previous findings included events of abnormal labour and subsequent caesarian section, acne, adenoidectomy, adnexal torsion and subsequent oophorectomy, appendicitis and appendicectomy (in four subjects), arthroscopy, chondropathy, dysmenorrhea, deep vein thrombosis, eczema, fractures (in three subjects) (including facial bones, foot, upper limb [elbow] with subsequent corrective operation), gastric ulcer, completely cured hepatitis (not specified) infection, hysterectomy, immune tolerance induction (in two subjects), inguinal hernia and surgical repair (in three subjects), intervertebral disc protrusion, laceration, laser therapy, mammoplasty, meniscus injury and meniscus removal (occurring twice in one subject), microgenia and jaw operation, nasal septum deviation and nasal septum operation (in three subjects), nasal operation, nasopharyngitis, osteoma and ostectomy, pneumonia, premature separation of placenta and subsequent uterine dilation and curettage, seasonal allergy, schlerotherapy, sterilization (in four subjects), tinea versicolour, tonsillitis and tonsillectomy (in seven subjects), vasectomy, and varicose vein (in two subjects) and varicose vein operation. The ongoing findings included events of allergies (animals [in two subjects], cats, nickel [in four subjects], dust, seasonal [in 11 subjects]), osteoma, sensitivity to perfumes, developmental hip dysplasia, dysphemia, uterine leiomyoma, and dermatitis atopic (Appendix 16.2, Listing 16.2.4.2).

Of the 42 enrolled subjects, all (100%) subjects reported occasional consumption of alcoholic beverages, 27 (64.3%) subjects commonly consumed stimulating (caffeine-containing) beverages, and 17 (40.5%) subjects had past history of smoking (Appendix 16.2, Listing 16.2.4.5).

No subjects returned positive results during assessment for pregnancy (females) or serology testing (Appendix 16.2, Listing 16.2.8.4 and Listing 16.2.8.5, respectively). One subject (Subject 1017) returned a positive drugs of abuse screening result (opiates) at predose and was subsequently withdrawn from the trial (Appendix 16.2, Listing 16.2.8.6).

11.3 Measurement of Treatment Compliance

To ensure compliance, the IMPs were administered by the Principal Investigator or designee at the EPCU.

11.4 Efficacy Results and Tabulations of Individual Subject Data

No efficacy assessments were performed within this trial.

11.4.1 Analysis of Efficacy

Not applicable.

11.4.2 Statistical and Analytical Issues

Details of the statistical methods are outlined in the SAP (Appendix 16.1.9). The statistical methodology is outlined in Section 9.7 of this clinical study report and changes in the planned analyses are provided in Section 9.8. Statistical and analytical issues related to the PK analysis are described in Section 11.5.2.

11.4.3 Tabulation of Individual Response Data

Not applicable.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

Not applicable. An analysis of PK is provided in Section 11.5.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By-Subject Displays

Not applicable.

11.4.7 Efficacy Conclusions

Not applicable.

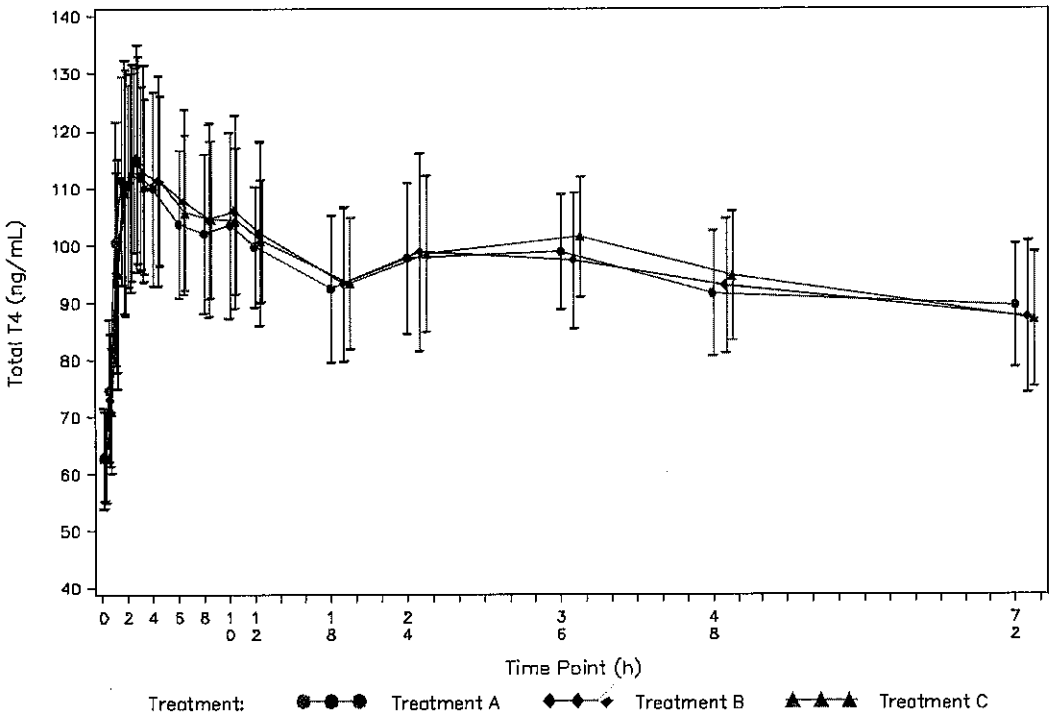
11.5 Pharmacokinetic Evaluation

11.5.1 Presentation and Evaluation of Plasma Concentrations

Individual concentrations of total T4 and total T3 in plasma per subject and treatment are presented in Appendix 16.2, Listing 16.2.5.2 and Listing 16.2.5.3. The individual plasma total T4 concentration-time profiles simultaneously for all treatments on a linear and a semi-logarithmic scale are displayed in Section 15.4, Figure 15.4.2.9 and Figure 15.4.2.10, respectively. The individual plasma total T3 concentration-time profiles simultaneously for all treatments on a linear and a l semi-logarithmic scale are displayed in Section 15.4, Figure 15.4.2.11 and Figure 15.4.2.12, respectively. Individual and summary statistics for plasma concentrations by treatment are presented in Section 15.4, Table 15.4.1.1.1 for total T4 and Table 15.4.1.1.3 for total T3.

Figure 11.1 and Figure 11.2 display the arithmetic mean plasma total T4 concentration-time profiles simultaneously for all treatments on a linear and a semi-logarithmic scale. Figure 11.3 and Figure 11.4 display the arithmetic mean plasma total T3 concentration-time profiles simultaneously for all treatments on a linear and a semi-logarithmic scale. Spaghetti plots of all subjects by treatment are presented on linear and semi-logarithmic scales are displayed in Section 15.4, Figure 15.4.2.5 and Figure 15.4.2.6 for total T4 and Figure 15.4.2.7 and Figure 15.4.2.8 for total T3, respectively.

Figure 11.1 **Arithmetic Mean (± Standard Deviation) Plasma Total T4 versus Nominal Time on Linear Scale following 600 µg Levothyroxine (PK Population)**

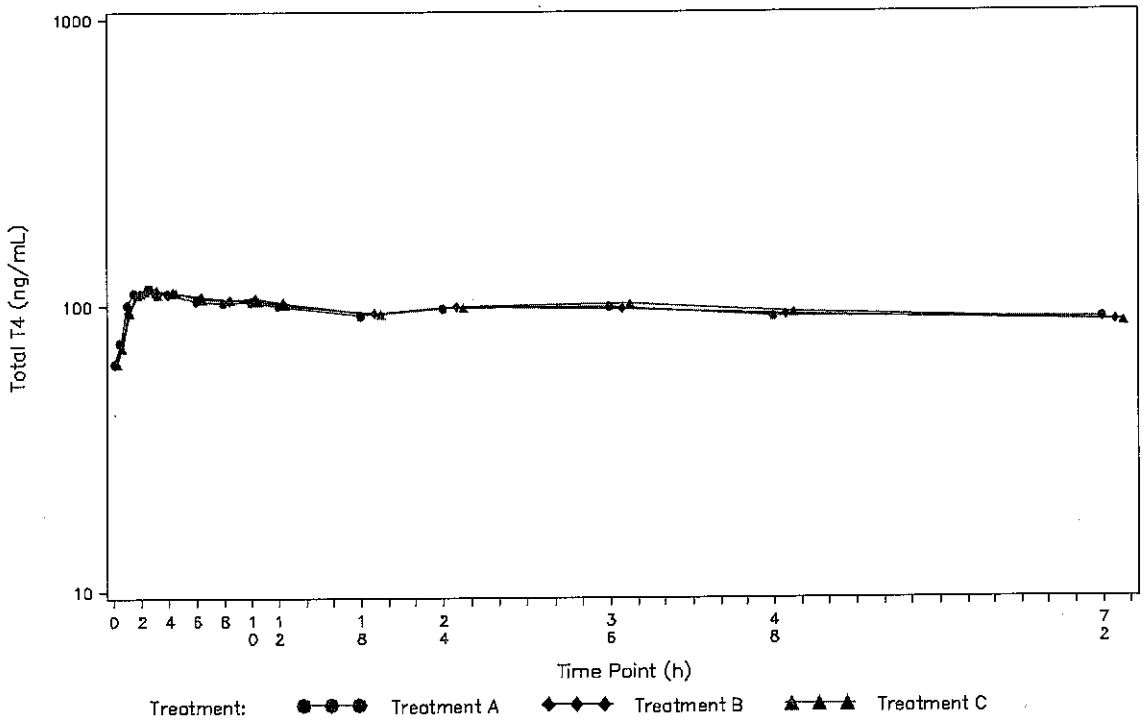


Subjects were excluded from the PK Population.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine.

Source: Section 15.4, Figure 15.4.2.1

Figure 11.2 **Arithmetic Mean Plasma Total T4 versus Nominal Time on Semi-logarithmic Scale following 600 µg Levothyroxine (PK Population)**

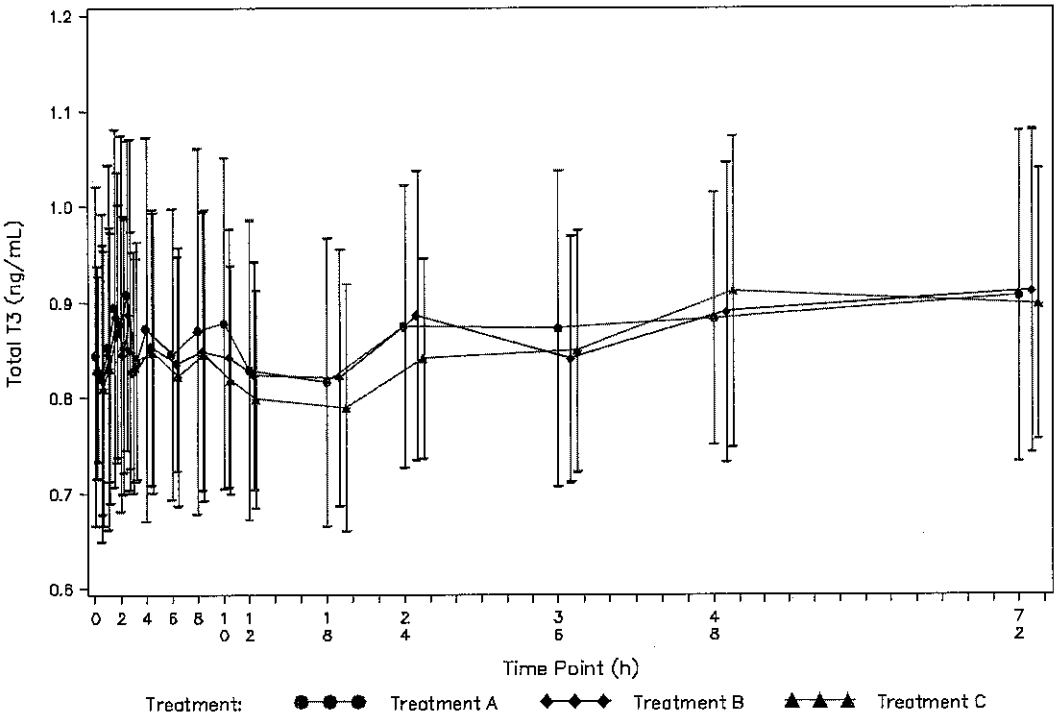


Subjects were excluded from the PK Population.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine.

Source: Section 15.4, Figure 15.4.2.2

Figure 11.3 **Arithmetic Mean (± Standard Deviation) Plasma Total T3 versus Nominal Time on Linear Scale following 600 µg Levothyroxine (PK Population)**

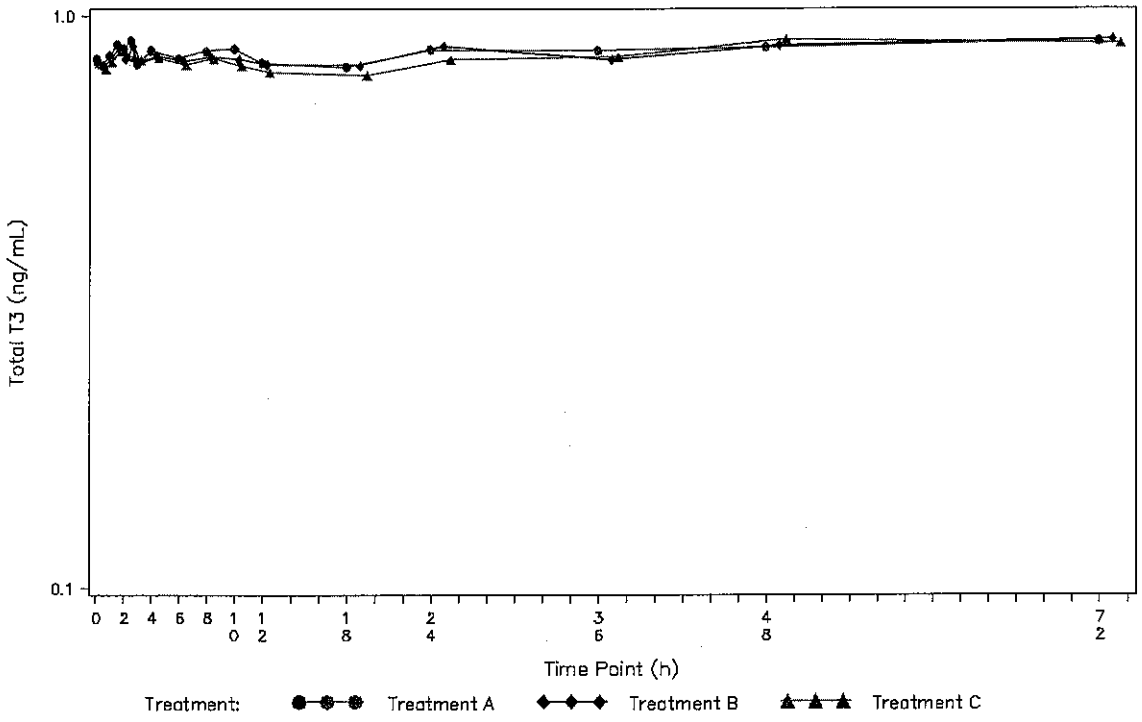


Subjects were excluded from the PK Population.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine.

Source: Section 15.4, Figure 15.4.2.3

Figure 11.4 **Arithmetic Mean Plasma Total T3 versus Nominal Time on Semi-logarithmic Scale following 600 µg Levothyroxine (PK Population)**



Subjects were excluded from the PK Population.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine.

Source: Section 15.4, Figure 15.4.2.4

11.5.2 Statistical Analysis

The statistical analysis was performed according the specifications in Section 16.1 of the SAP (refer to Appendix 16.1.9). The core WinNonlin output is presented in Appendix 16.1.9.3. Individual PK parameters are presented in Appendix 16.2, Listing 16.2.5.4 for total T4 and Listing 16.2.5.5 for total T3. Individual and summary statistics for total T4 PK parameters are presented in Section 15.4, Table 15.4.1.1.2. Individual and summary statistics for total T3 PK parameters are presented in Section 15.4, Table 15.4.1.1.4.

Statistical analysis of primary PK parameters

The results of the statistical analysis for PK parameter comparisons for total T4 of AUC_{0-72}, $AUC_{0-72,adj}$, C_{max}, and $C_{max,adj}$ using analysis of variance (ANOVA) are summarized in Section 15.4, Table 15.4.3.1. Box plots of total T4 $C_{max,adj}$ and $AUC_{0-72,adj}$ by treatment are presented in Section 15.4, Figure 15.4.3.1.2 and for C_{max} and AUC_{0-72} in Figure 15.4.3.1.1. Box

plots of total T3 C_{max} and $AUC_{0-48,}$ and $AUC_{0-48,adj}$ by treatment are presented in Section 15.4, Figure 15.4.3.1.4 and Figure 15.4.3.2.3, respectively.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 6 x 100 µg tablets and levothyroxine 12 x 50 µg tablets were 99.3% and 103.8%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25 (Table 11.2). The PK parameters for total T4 are summarized in Table 11.3.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 12 x 50 µg tablets were 104.1% and 103.2%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 6 x 100 µg tablets were 104.8% and 99.4%, respectively, and the corresponding 95% CI were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 6 x 100 µg tablets and levothyroxine 12 x 50 µg tablets were 100.1% and 101.8%, respectively, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 12 x 50 µg tablets were both 101.7%, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 6 x 100 µg tablets were 101.5% and 99.9%, respectively, and the corresponding 95% CIs were within the predefined BE margin of 0.8 to 1.25.

Table 11.2 Summary of ANOVA of Primary Pharmacokinetic Parameters for T4 (Pharmacokinetic Population)

Parameter	Treatment	N	Geo-LSMean	Ratio (Treatments) (%)	95% CI of Ratio	Intra-CV (%)
AUC_{0-72} (hr*ng/mL)	B	37	6780.981	100.1	97.6 - 102.7	5.4
	A	37	6772.424			
	C	37	6884.607	101.7	99.1 - 104.2	5.4
	A	37	6772.424			
	C	37	6884.607	101.5	99.0 - 104.1	5.4
	B	37	6780.981			
C_{max} (ng/mL)	B	37	125.1199	101.8	98.4 - 105.3	7.3
	A	37	122.9188			
	C	37	125.0102	101.7	98.3 - 105.2	7.3
	A	37	122.9188			
	C	37	125.0102	99.9	96.6 - 103.3	7.3
	B	37	125.1199			
$AUC_{0-72,adj}$ (hr*ng/mL)	B	37	2222.979	99.3	91.8 - 107.5	17.1
	A	37	2237.745			
	C	37	2329.393	104.1	96.2 - 112.6	17.1
	A	37	2237.745			
	C	37	2329.393	104.8	96.8 - 113.4	17.1
	B	37	2222.979			
$C_{max,adj}$ (ng/mL)	B	37	62.1190	103.8	96.7 - 111.5	15.5
	A	37	59.8409			
	C	37	61.7588	103.2	96.1 - 110.8	15.5
	A	37	59.8409			
	C	37	61.7588	99.4	92.6 - 106.8	15.5
	B	37	62.1190			

CI: Confidence Interval; CV%: Coefficient of Variation Percentage; Geo-LSMean: Geometric Least Square Mean;
N: Number of subjects included in the analysis. T4: Tetraiodothyronine;
Subjects were excluded from the PK Population.
Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;
Source: Section 15.4, Table 15.4.3.1.

Table 11.3 Summary Statistics of Primary Total T4 Pharmacokinetic Parameters (Pharmacokinetic Population)

	Statistic	$AUC_{0-72,adj}$ * (hr*ng/mL)	$C_{max,adj}$ (ng/mL)	AUC_{0-72} * (hr*ng/mL)	C_{max} (ng/mL)
Treatment A	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2312.18 (525.549)	61.5394 (13.24115)	6828.58 (674.946)	124.267 (15.2342)
	Geo Mean (95% CI)	2249.63 (2073.95;2440.19)	60.0991 (55.7575;64.7787)	6796.27 (6576.12;7023.78)	123.343 (118.321;128.577)
	Geo CV (CV%)	24.8 (22.7)	22.8 (21.5)	9.9 (9.9)	12.5 (12.3)
	SEM	86.400	2.17683	110.960	2.5045
	Median	2363.56	62.3370	6863.29	124.900
	Min; Max	1265.0; 3531.2	32.547; 90.860	5718.7; 8157.7	94.58; 150.40
Treatment B	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2333.14 (649.583)	63.6903 (14.41836)	6846.87 (838.557)	126.381 (17.7666)
	Geo Mean (95% CI)	2237.16 (2021.46;2475.88)	62.1576 (57.7031;66.9560)	6797.17 (6525.39;7080.26)	125.208 (119.599;131.081)
	Geo CV (CV%)	31.1 (27.8)	22.6 (22.6)	12.3 (12.2)	13.8 (14.1)
	SEM	106.791	2.37036	137.858	2.9208
	Median	2324.91	60.1670	6602.39	125.700
	Min; Max	1056.8; 3796.0	44.287; 99.350	5601.4; 8455.1	101.20; 161.50
Treatment C	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2386.83 (518.752)	62.8319 (12.25621)	6937.85 (704.070)	126.041 (15.1427)
	Geo Mean (95% CI)	2334.75 (2175.34;2505.85)	61.7272 (57.9543;65.7457)	6903.36 (6674.44;7140.13)	125.159 (120.246;130.273)
	Geo CV (CV%)	21.5 (21.7)	19.1 (19.5)	10.1 (10.1)	12.1 (12.0)
	SEM	85.282	2.01491	115.748	2.4895
	Median	2335.06	60.9600	6941.44	126.200
	Min; Max	1528.9; 3954.6	45.293; 87.290	5657.4; 8289.1	102.60; 152.50

CI: Confidence Interval; CV%: Coefficient of Variation Percentage; GeoCV: Geometric Coefficient of Variation; GeoMean: Geometric Mean; Max: Maximum Value; Min: Minimum Value; n: The number of subjects with specific parameter calculable; SD: Standard Deviation; SEM: Standard Error of the Mean; T4: Tetraiodothyronine

*: $AUC_{(0-tlast)}$ was used in many instances (See Table 15.4.1.1.2). Normalization to exactly 72 hours was not possible because of invalid Lambda_z.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;

Source: Section 15.4, Table 15.4.1.1.2

Statistical analysis of secondary PK parameters

The results of the statistical analysis for secondary PK parameter comparisons for total T3 of AUC_{0-48} and C_{max} using ANOVA are summarized in Section 15.4, Table 15.4.3.2. The results for the secondary PK parameters for total T3 are summarized in Table 11.4.

The geometric LS mean ratios for total T3 AUC_{0-72} and C_{max} following administration of levothyroxine 6 x 100 µg tablets and levothyroxine 12 x 50 µg tablets were 100.0% and 98.4%, respectively.

The geometric LS mean ratios for total T3 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 12 x 50 µg tablets were 99.3% and 99.4%, respectively.

The geometric LS mean ratios for total T3 AUC_{0-72} and C_{max} following administration of levothyroxine 3 x 200 µg tablets and levothyroxine 6 x 100 µg tablets were 99.4% and 101.0%, respectively.

The PK parameters for total T4 and T3 are summarized in Table 11.5 and Table 11.6, respectively. Parameter values for $t_{½}$, λ_z, $AUC_{extra,adj}$, $AUC_{0-\infty,adj}$, V_z/F, and CL/F were presented for individuals in Appendix 16.2, Listing 16.2.5.4 (T4 only), but excluded from summary statistics. These parameters could not be reliably estimated as the analytes were endogenous and presented no clear elimination phase. The λ_z did not meet standard acceptability criteria and therefore all dependent parameters were also not considered reliable.

Table 11.4 Summary of ANOVA of Secondary Pharmacokinetic Parameters for T3 (Pharmacokinetic Population)

Analyte	Parameter	Treatment	N	Geo-LSMean	Ratio (Treatments) (%)	90% CI of Ratio	Intra-CV (%)
T3	AUC_{0-48} (hr*ng/mL)	B	37	40.2952	99.5	96.7 – 102.2	7.1
		A	37	40.5169			
	C_{max} (ng/mL)	B	37	1.0269	98.4	94.7 – 102.3	10.0
		A	37	1.0434			
	AUC_{0-48} (hr*ng/mL)	C	37	39.8096	98.3	95.6 – 101.0	7.1
		A	37	40.5169			
	C_{max} (ng/mL)	C	37	1.0373	99.4	95.7 – 103.3	10.0
		A	37	1.0434			
	AUC_{0-48} (hr*ng/mL)	C	37	39.8096	98.8	96.1 – 101.6	7.1
		B	37	40.2952			
	C_{max} (ng/mL)	C	37	1.0373	101.0	97.2 – 105.0	10.0
		B	37	1.0269			

CI: Confidence Interval; CV%: Coefficient of Variation Percentage; Geo-LSMean: Geometric Least Square Mean; T3: Triiodothyronine.

N: Number of subjects included in the analysis.

Subject[redacted] were excluded from the PK Population.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;

Source: Section 15.4, Table 15.4.3.2

Table 11.5 Summary Statistics of Secondary Total T4 Pharmacokinetic Parameters (Pharmacokinetic Population)

Treatment	Statistic	AUC_{0-48} (hr*ng/mL)	$AUC_{0-48,adj}$ (hr*ng/mL)	t_{max} (hr)
A	n (missing)	37 (0)	37 (0)	37 (0)
	Mean (SD)	4684.78 (455.288)	1673.84 (354.508)	
	Geo Mean (95% CI)	4663.35 (4514.83;4816.75)	1635.22 (1517.67;1761.87)	
	Geo CV (CV%)	9.7 (9.7)	22.7 (21.2)	
	SEM	74.849	58.281	
	Median	4685.97	1719.50	2.500
	Min; Max	3938.0; 5585.3	933.3; 2527.4	1.00; 36.52
B	n (missing)	37 (0)	37 (0)	37 (0)
	Mean (SD)	4707.87 (574.186)	1698.72 (448.630)	
	Geo Mean (95% CI)	4674.01 (4488.05;4867.68)	1637.71 (1490.82;1799.07)	
	Geo CV (CV%)	12.2 (12.2)	28.8 (26.4)	
	SEM	94.396	73.754	
	Median	4635.06	1663.78	2.500
	Min; Max	3855.4; 5757.6	825.6; 2899.2	1.00; 24.08
C	n (missing)	37 (0)	37 (0)	37 (0)
	Mean (SD)	4777.62 (475.749)	1743.61 (353.811)	
	Geo Mean (95% CI)	4754.88 (4600.77;4914.15)	1710.43 (1601.36;1826.93)	
	Geo CV (CV%)	9.9 (10.0)	20.0 (20.3)	
	SEM	78.213	58.166	
	Median	4743.73	1701.00	2.517
	Min; Max	4024.0; 5791.0	1150.9; 2720.4	1.00; 35.45

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; GeoCV = Geometric Coefficient of Variation; GeoMean = Geometric Mean; Max = Maximum Value; Min = Minimum Value; n = The number of subjects with specific parameter calculable; SD = Standard Deviation; SEM = Standard Error of the Mean; T4 = thyroxine;

Parameter values for $t_{½}$, λ_z, $AUC_{extra,adj}$, $AUC_{0-\infty,adj}$, V_z/F, and CL/F were presented for individuals but excluded from summary statistics.

*: $AUC_{(0-tlast)}$ was used in many instances (See Section 15.4, Table 15.4.1.1.2). Normalization to exactly 72 hours was not possible because of invalid λz.

Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;

Source: Section 15.4, Table 15.4.1.1.2

Table 11.6 Summary Statistics of Total T3 Pharmacokinetic Parameters (Pharmacokinetic Population)

	Statistic	AUC_{0-48} (hr*ng/mL)	AUC_{0-72} * (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (hr)
A	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	40.936 (5.6091)	62.030 (8.1808)	1.0650 (0.22190)	
	Geo Mean (95% CI)	40.571 (38.780;42.444)	61.528 (58.953;64.215)	1.0453 (0.9809;1.1140)	
	Geo CV (CV%)	13.6 (13.7)	12.9 (13.2)	19.3 (20.8)	
	SEM	0.9221	1.3449	0.03648	
	Median	39.975	60.531	0.9920	8.017
	Min; Max	29.57; 54.05	45.81; 87.89	0.698; 1.750	0.00; 72.90
B	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	40.613 (4.8717)	61.953 (7.9329)	1.0391 (0.16066)	
	Geo Mean (95% CI)	40.328 (38.734;41.987)	61.466 (58.910;64.133)	1.0270 (0.9753;1.0815)	
	GeoCV (CV%)	12.1 (12.0)	12.8 (12.8)	15.6 (15.5)	
	SEM	0.8009	1.3042	0.02641	
	Median	41.012	62.501	1.0400	18.033
	Min; Max	30.95; 52.59	45.85; 80.91	0.730; 1.500	0.00; 72.87
C	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	40.050 (4.2284)	61.420 (6.7321)	1.0490 (0.15952)	
	Geo Mean (95% CI)	39.844 (38.516;41.218)	61.075 (58.942;63.285)	1.0381 (0.9894;1.0891)	
	GeoCV (CV%)	10.2 (10.6)	10.7 (11.0)	14.5 (15.2)	
	SEM	0.6951	1.1068	0.02623	
	Median	39.021	59.919	1.0000	2.500
	Min; Max	34.31; 50.86	50.54; 75.66	0.857; 1.460	0.00; 72.17

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; GeoCV = Geometric Coefficient of Variation; GeoMean = Geometric Mean; Max = Maximum Value; Min = Minimum Value; n = The number of subjects with specific parameter calculable; SD = Standard Deviation; SEM = Standard Error of the Mean; T3 = Triiodothyronine.

*: $AUC_{(0\text{-}tlast)}$ was used for numerous subjects (see Section 15.4, Table 15.4.1.1.4). Normalization to exactly 72 hours was not possible because of invalid λz.

Test: levothyroxine new formulation.
Reference: levothyroxine old formulation.

Source: Section 15.4, Table 15.4.1.1.4

11.5.3 Pharmacokinetic Conclusions

The primary objective of the trial was to demonstrate dosage form proportionality of three dosage forms of the new formulation in healthy subjects by estimating the relative BA and by pairwise BE testing.

The three dosage forms (50 µg, 100 µg, and 200 µg tablets) of the new levothyroxine formulation administered as 600 µg single doses were determined to be dose proportional as the relative BA for total T4 AUC_{0-72} and C_{max} with and without baseline adjustment ranged from 99.3% to 104.8%, and all 95% CIs for the pairwise comparisons for BE were within the predefined margin of 0.8 to 1.25.

12 Safety Evaluation

12.1 Extent of Exposure

Exposure to IMPs is provided per subject in Appendix 16.2, Listing 16.2.5.1.

A total of 37 subjects received all three dosage forms of new formulation levothyroxine as planned per protocol, resulting in a total 1800 µg levothyroxine dose exposure.

Five (5) subjects discontinued the trial before receiving their complete assigned sequence (Appendix 16.2, Listing 16.2.1.2):

- Subject [redacted] Sequence: BCA) – Completed Treatment B and was withdrawn due to positive drug screen [opiates] at predose Treatment C (200 µg)
- Subject [redacted] Sequence: ACB) – Completed Treatment A (50 µg) before subject was withdrawn due to SAE (deep vein thrombosis)
- Subject [redacted] Sequence: BCA) – Completed Treatment B (100 µg) before subject was withdrawn due to AE (vomiting)
- Subject [redacted] equence: BAC) – Completed Treatment B (100 µg) before subject withdrew consent
- Subject [redacted] Sequence: CBA) – Completed Treatment C (200 µg) before subject withdrew consent

12.2 Adverse Events

All AEs and TEAEs are listed individually in Appendix 16.2, Listing 16.2.7.1 and Listing 16.2.7.2, respectively.

Summaries of TEAEs are provided in Section 15.3, Table 15.3.1.1 (Summary of TEAEs by SOC and PT), Table 15.3.1.2 (Summary of TEAEs by Intensity), Table 15.3.1.3 (Summary of TEAEs by Causality), Table 15.3.1.4 (Summary of TEAEs Leading to Discontinuation), Table 15.3.2.1 (SAEs with Outcome of Death), Table 15.3.2.2 (Other SAEs), and Table 15.3.2.3 (SAEs Leading to Discontinuation).

The term TEAE is defined as AEs starting or worsening after the first intake of the IMP.

All AEs were coded according to MedDRA Version 17.

12.2.1 Brief Summary of Adverse Events

There were no deaths reported during the trial. Two (2) subjects were withdrawn from the trial; Subject as withdrawn due to an SAE of moderate deep vein thrombosis and Subject was withdrawn due to an AE of mild vomiting (see Section 12.3.2 for further details).

Overall, the incidence of TEAEs was similar for all three dosage forms of the new formulation levothyroxine. In total, 27 (64.3%) subjects reported 85 TEAEs; 11 (28.9%) subjects reported 27 TEAEs during 12 tablets of 50 µg treatment, 16 (40.0%) subjects reported 27 TEAEs during 6 tablets of 100 µg treatment, and 13 (33.3%) subjects reported 31 TEAEs during 3 tablets of 200 µg treatment. Slightly more than one third (37.6%) of all reported TEAEs (32 of 85 TEAEs) were considered related to IMP by the Investigator: Five (13.2%) subjects reported 9 IMP-related TEAEs during 12 tablets of 50 µg treatment, 6 (15.0%) subjects reported 10 IMP-related TEAEs during 6 tablets of 100 µg treatment, and 7 (17.9%) subjects reported 13 IMP-related TEAEs during 3 tablets of 200 µg treatment. Among these IMP-related TEAEs, only headache and dizziness were reported across all three treatments. The remaining IMP-related TEAEs included abdominal pain, diarrhea, nausea, vomiting, and fatigue, reported during 12 tablets of 50 µg treatment, diplopia, vomiting, asthenia, and fatigue reported during 6 tablets of 100 µg treatment, and palpitations, abdominal pain (lower), nausea, sleep disorder, and hot flush reported during 3 tablets of 200 µg treatment.

Headache was the most commonly reported TEAE (22 of 85 TEAEs) (reported by >12% of subjects during 6 tablets of 100 µg treatment and 3 tablets of 200 µg treatment, respectively). In addition, nausea (10 of 85 TEAEs) was reported by >12% subjects during 3 tablets of 200 µg treatment. All TEAEs except one were considered mild or moderate in intensity; Subject (6 tablets of 100 µg treatment) had a severe TEAE of vomiting considered unrelated to IMP.

The majority of TEAEs were resolved by the end of the trial; only Subject (dizziness), Subject (headache), Subject (nausea), Subject headache), and Subject (nasopharyngitis) had an outcome of "unknown". Furthermore, Subject (deep vein thrombosis) was ongoing (unresolved due to ongoing chronic anticoagulant therapy) at the trial follow-up visit (see Section 12.3.2 for further details).

12.2.2 Display of Adverse Events

Table 12.1 Summary of Treatment-Emergent Adverse Events by Treatment (Safety Population)

	Treatment A (N = 38)	Treatment B (N = 40)	Treatment C (N = 39)	Overall (N = 42)
No. of TEAEs	**E**	**E**	**E**	**E**
Any TEAEs	27	27	31	85
Serious TEAEs	1	0	0	1
TEAEs Resulting in Discontinuation	0	1	0	1
TEAEs Of Severe Intensity	0	1	0	0
IMP-related TEAEs	9	10	13	32
No. of Subjects Experiencing TEAEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAEs	11 (28.9%)	16 (40.0%)	13 (33.3%)	27 (64.3%)
Serious TEAEs	1 (2.6%)	0	0	1 (2.4%)
TEAEs Resulting in Discontinuation	0	1 (2.5%)	0	1 (2.4%)
TEAEs Of Severe Intensity	0	1 (2.5%)	0	1 (2.4%)
IMP-related TEAEs	5 (13.2%)	6 (15.0%)	7 (17.9%)	16 (38.1%)

N = number of subjects, E = number of AEs; TEAE = treatment-emergent adverse events

Treatment A: 12 tablets of 50 µg

Treatment B: 6 tablets of 100 µg

Treatment C: 3 tablets of 200 µg

Source: Appendix 16.2, Listing 16.2.7.2 and Section 15.1, Table 15.3.1.1, Table 15.3.1.2, and Table 15.3.1.3

Table 12.2 Summary of Treatment-Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Treatment A (N = 38)			Treatment B (N = 40)			Treatment C (N = 39)			Overall (N = 42)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	11	(28.9)	27	16	(40.0)	27	13	(33.3)	31	27	(64.3)	85
Cardiac Disorders	2	(5.3)	2	-	-	-	1	(2.6)	1	2	(4.8)	3
Palpitations	2	(5.3)	2	-	-	-	1	(2.6)	1	2	(4.8)	3
Eye Disorders	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Diplopia	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Gastrointestinal Disorders	3	(7.9)	7	2	(5.0)	4	6	(15.4)	10	11	(26.2)	21
Abdominal Discomfort	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Abdominal Pain	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Abdominal Pain Lower	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Diarrhoea	2	(5.3)	2	1	(2.5)	1	-	-	-	3	(7.1)	3
Nausea	2	(5.3)	2	1	(2.5)	1	5	(12.8)	7	8	(19.0)	10
Vomiting	2	(5.3)	2	2	(5.0)	2	1	(2.6)	1	5	(11.9)	5
General Disorders And Administration Site Conditions	3	(7.9)	4	2	(5.0)	3	1	(2.6)	1	6	(14.3)	8
Asthenia	1	(2.6)	1	1	(2.5)	1	-	-	-	2	(4.8)	2
Catheter Site Phlebitis	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Fatigue	1	(2.6)	1	1	(2.5)	1	-	-	-	2	(4.8)	2
Hunger	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Non-Cardiac Chest Pain	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Pyrexia	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Infections And Infestations	3	(7.9)	4	4	(10.0)	4	1	(2.6)	1	7	(16.7)	9
Nasopharyngitis	2	(5.3)	3	4	(10.0)	4	1	(2.6)	1	6	(14.3)	8
Otitis Media	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Injury, Poisoning And Procedural Complications	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Muscle Rupture	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1

Levothyroxine **Dosage Form Proportionality of Levothyroxine New Formulations (50 µg, 100 µg, and 200 µg Tablets) in Fasted State**

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System Organ Class Preferred Term	Treatment A (N = 38)			Treatment B (N = 40)			Treatment C (N = 39)			Overall (N = 42)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Musculoskeletal And Connective Tissue Disorders	2	(5.3)	2	1	(2.5)	1	-	-	-	3	(7.1)	3
Back Pain	1	(2.6)	1	1	(2.5)	1	-	-	-	2	(4.8)	2
Pain In Extremity	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Nervous System Disorders	5	(13.2)	6	8	(20.0)	12	6	(15.4)	13	14	(33.3)	31
Dizziness	4	(10.5)	4	1	(2.5)	1	2	(5.1)	4	5	(11.9)	9
Headache	2	(5.3)	2	8	(20.0)	11	5	(12.8)	9	12	(28.6)	22
Psychiatric Disorders	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Sleep Disorder	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Respiratory, Thoracic And Mediastinal Disorders	1	(2.6)	1	1	(2.5)	1	1	(2.6)	1	3	(7.1)	3
Nasal Congestion	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Oropharyngeal Pain	1	(2.6)	1	1	(2.5)	1	-	-	-	2	(4.8)	2
Skin And Subcutaneous Tissue Disorders	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Dermatitis Atopic	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Vascular Disorders	1	(2.6)	1	-	-	-	2	(5.1)	2	3	(7.1)	3
Deep Vein Thrombosis	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Hot Flush	-	-	-	-	-	-	2	(5.1)	2	2	(4.8)	2

N = number of subjects dosed, n = number of subject with at least one AE; E = number of AEs; Subject % = (n/N)*100; TEAE = treatment-emergent adverse events

Treatment A: 12 tablets of 50 µg
Treatment B: 6 tablets of 100 µg
Treatment C: 3 tablets of 200 µg

Source: Section 15.1, Table 15.3.1.1

Table 12.3 Summary of Treatment-Related Treatment-Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Treatment A (N = 38)			Treatment B (N = 40)			Treatment C (N = 39)			Overall (N = 42)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one treatment-related TEAE	5	(13.2)	9	6	(15.0)	10	7	(17.9)	13	16	(38.1)	32
Cardiac Disorders	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Palpitations	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Eye Disorders	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Diplopia	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Gastrointestinal Disorders	2	(5.3)	5	1	(2.5)	1	4	(10.3)	4	7	(16.7)	10
Abdominal Pain	1	(2.6)	1	-	-	-	-	-	-	1	(2.4)	1
Abdominal Pain Lower	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Diarrhoea	2	(5.3)	2	-	-	-	-	-	-	2	(4.8)	2
Nausea	1	(2.6)	1	-	-	-	3	(7.7)	3	4	(9.5)	4
Vomiting	1	(2.6)	1	-	-	-	-	-	-	2	(4.8)	2
General Disorders And Administration Site Conditions	1	(2.6)	1	1	(2.5)	2	-	-	-	2	(4.8)	3
Asthenia	-	-	-	1	(2.5)	1	-	-	-	1	(2.4)	1
Fatigue	1	(2.6)	1	1	(2.5)	1	-	-	-	2	(4.8)	2
Nervous System Disorders	2	(5.3)	3	4	(10.0)	6	2	(5.1)	5	7	(16.7)	14
Dizziness	2	(5.3)	2	1	(2.5)	1	2	(5.1)	4	4	(9.5)	7
Headache	1	(2.6)	1	4	(10.0)	5	1	(2.6)	1	6	(14.3)	7
Psychiatric Disorders	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1
Sleep Disorder	-	-	-	-	-	-	1	(2.6)	1	1	(2.4)	1

Levothyroxine **Dosage Form Proportionality of Levothyroxine New Formulations (50 µg, 100 µg, and 200 µg Tablets) in Fasted State**

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System Organ Class Preferred Term	Treatment A (N = 38)			Treatment B (N = 40)			Treatment C (N = 39)			Overall (N = 42)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Vascular Disorders	-	-	-	-	-	-	2	(5.1)	2	2	(4.8)	2
Hot Flush	-	-	-	-	-	-	2	(5.1)	2	2	(4.8)	2

N = number of subjects dosed, n = number of subject with at least one AE; E = number of AEs; Subject % = (n/N)*100; TEAE = treatment-emergent adverse events

Treatment A: 12 tablets of 50 µg
Treatment B: 6 tablets of 100 µg
Treatment C: 3 tablets of 200 µg
Source: Section 15.1, Table 15.3.1.3

12.2.3 Analysis of Adverse Events

Overall, the incidence of TEAEs was similar for all three dosage forms of the new formulation levothyroxine. In total, 27 (64.3%) subjects reported 85 TEAEs; 11 (28.9%) subjects reported 27 TEAEs during 12 tablets of 50 µg treatment, 16 (40.0%) subjects reported 27 TEAEs during 6 tablets of 100 µg treatment, and 13 (33.3%) subjects reported 31 TEAEs during 3 tablets of 200 µg treatment (see Table 12.2).

Headache was the most commonly reported TEAE (22 of 85 TEAEs) (reported by >12% of subjects during 6 tablets of 100 µg treatment and 3 tablets of 200 µg treatment, respectively). In addition, nausea (10 of 85 TEAEs) was reported by >12% subjects during 3 tablets of 200 µg treatment (see Table 12.2).

All TEAEs except one were considered mild to moderate in intensity; Subject 6 tablets of 100 µg treatment) had a severe TEAE of vomiting considered unrelated to IMP (Section 15.3, Table 15.3.1.2).

Slightly more than one third (37.6%) of all reported TEAEs (32 of 85 TEAEs) were considered related to IMP by the Investigator: Five (13.2%) subjects reported 9 IMP-related TEAEs during 12 tablets of 50 µg treatment, 6 (15.0%) subjects reported 10 IMP-related TEAEs during 6 tablets of 100 µg treatment, and 7 (17.9%) subjects reported 13 IMP-related TEAEs during 3 tablets of 200 µg treatment (see Table 12.3).

There were no deaths reported during the trial. Two (2) subjects were withdrawn from the trial; Subject as withdrawn due to an SAE of moderate deep vein thrombosis and Subject was withdrawn due to an AE of mild vomiting (see Section 12.3.2 for further details).

12.2.4 Listing of Adverse Events by Subject

Listing of all individual AEs and TEAEs are presented in Appendix 16.2, Listing 16.2.7.1 and Listing 16.2.7.2, respectively.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the trial.

12.3.1.2 Other Serious Adverse Events

One SAE (Subject] moderate deep vein thrombosis) was reported during the trial (see Section 12.3.2 for further details). This event also led to withdrawal of the subject.

12.3.1.3 Other Significant Adverse Events

Two (2) subjects were withdrawn from the trial: Subject ... vas withdrawn due to an SAE of moderate deep vein thrombosis and Subject ... as withdrawn due to an AE of mild vomiting (see Section 12.3.2 for further details)

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

The CRFs for Subject e presented in Appendix 16.3.1.

12.3.2.1 Narrative of SAE Withdrawal: Subject ...

Subject Number:	
Age (years):	36
Gender:	Female
Race / Ethnicity	White / Not Hispanic or Latino
Weight (kg):	65.9
Height (cm):	175
BMI (kg/m^2):	21.5
Reason for Discontinuation:	SAE withdrawal

Subject a 36-year-old female, was randomized to Sequence 4 (ACB) and received Treatment A (12 tablets of 50 µg) on 16 Dec 2013 at 8:18. The subject had clinically relevant medical history of varicose veins (2010/2011), varicose vein operation (Jul 2011), and deep vein thrombosis (left leg) (from Dec 2012 to Jun 2013).

On 17 Dec 2013 (at 10:00), at discharge from the EPCU, the subject presented to the emergency room with a TEAE of pain in extremity (described as similar to pain experienced in Dec 2012). The event was considered moderate in intensity by the Investigator. During this time, at 9:30, the subjects also experienced a TEAE of mild dizziness, considered related to the IMP which lasted for 30 minutes prior to resolution. Twelve (12) hours after the report of pain in extremity (at 22:00) D-dimer returned positive results and clinical imaging indicated deep vein thrombosis. At 23:00 the subject was administered 0.5 mL Innohep® subcutaneously (s.c.) and follow-up clinical imaging performed on 18 Dec 2013 confirmed a diagnosis of deep vein thrombosis. The Investigator considered the TEAE of deep vein thrombosis an SAE (Seriousness criteria: required hospitalization) and the event of moderate in intensity. The subject mentioned retrospectively that transient pain in the left leg had been present for approximately 2 weeks preceding this event. The subject was withdrawn from the trial on 18 Dec 2013.

On 20 Dec 2013, the subject experienced non-cardiac chest pain assessed as mild in intensity by the Investigator. No concomitant therapy was administered as treatment.

The subject was discharged from hospital on 24 Dec 2013, with chronic prescribed 3 mg Falithrom® to be taken daily.

All reported TEAEs were considered unrelated to IMP. The TEAEs of non-cardiac chest pain and pain in extremity resolved without concomitant treatment on 27 Dec 2013 and 29 Dec 2013, respectively. The SAE of deep vein thrombosis remains unresolved due to chronic anticoagulant therapy.

Follow-up performed on 15 Mar 2014, showed the subject in stable condition, with no further reported symptoms.

12.3.2.2 Narrative of AE Withdrawal: Subject

Subject Number:	
Age (years):	42
Gender:	Female
Race / Ethnicity	White / Not Hispanic or Latino
Weight (kg):	64.5
Height (cm):	162
BMI (kg/m^2):	24.6
Reason for Discontinuation:	AE withdrawal

Subject a 42-year-old female, was randomized to Sequence 2 (BCA) and received Treatment B (6 tablets of 100 µg) on 16 Dec 2013 at 8:24. The subject had unremarkable medical history of pneumonia (in 1975), seasonal allergy (from 1985), osteoma (from 1985 to 1990), ostectomy (in 1990), allergy to nickel (from 1986), osteoma (from 1996), and nasopharyngitis (in Nov 2013).

On 16 Dec 2013 (at 8:27 [3 minutes after IMP administration]), the subject experienced vomiting. The TEAE of vomiting was considered mild in intensity and related to IMP by the Investigator. The event resolved without concomitant treatment on the same day (at 8:28).

The subject was withdrawn from the trial on 16 Dec 2013.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Individual abnormal values are listed in Section 15.3, Table 15.3.4.1.

Individual laboratory data are provided in Appendix 16.2, Listing 16.2.8.1 (Hematology), Listing 16.2.8.2 (Chemistry), Listing 16.2.8.3 (Urinalysis), and Listing 16.2.8.4 (Pregnancy Testing).

12.4.2 Evaluation of Each Laboratory Parameter

Summaries of hematology and chemistry data including change from baseline are available in Section 15.3, Table 15.3.5.1.1 and Table 15.3.5.1.2, respectively.

12.4.2.1 Laboratory Values over Time

During the trial, laboratory values were measured at screening, before IMP administration in Period 1 (Day -1), Period 2 (Day -1), Period 3 (Day -1), and at the follow-up examination.

Mean and median values of any parameter of hematology, clinical chemistry, and urinalysis investigated did not show any noteworthy difference between time points, or any noteworthy change from baseline (screening) at the follow-up assessment.

12.4.2.2 Individual Subject Changes

There were no notable changes from baseline (screening) in any of the laboratory parameters in any subject at any time point of the assessments. This can be concluded from inspection of individual laboratory values as well as of the frequency of changes from normal to abnormal. All abnormal individual laboratory values were considered not clinically significant.

12.4.2.3 Individual Clinically Significant Abnormalities

None of the abnormal laboratory parameters were considered by the Investigator to be clinically significant. Thus, none of the laboratory abnormalities were documented as a TEAE.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

12.5.1 Vital Signs

A summary of vital sign data by treatment, trial day and time point including change from baseline (screening) to follow-up is provided in Section 15.3, Table 15.3.6.1.1. Individual vital sign data are presented in Appendix 16.2, Listing 16.2.9.1.

During the trial, vital signs were measured at screening, and during Period 1, Period 2, and Period 3 at 24 hours predose (Day -1), 50 min predose (Day 1), at 2, 3, 6, 12, 24, 48, and 72 hours postdose, and at the follow-up examination.

There were no notable differences in mean or median values of the parameters systolic and diastolic BP, pulse, and oral body temperature, between time points, or any noteworthy change from baseline (screening) to the follow-up assessment. All abnormal individual vital sign assessments were considered not clinically significant. Thus, none of the vital sign parameters values was documented as a TEAE.

There was also no relevant change in the subjects' mean or median weight from screening to follow-up.

12.5.2 Physical Findings

For all randomized subjects, physical examination was performed at screening, Day -1 (Period 1, Period 2, and Period 3), and at follow-up, as documented in Appendix 16.2, Listing 16.2.9.3. No abnormal physical examination was reported. Any significantly abnormal findings were to be documented as AEs.

12.5.3 Other Observations Related to Safety

12.5.3.1 Electrocardiogram Parameters

A summary of 12-lead ECG evaluations by treatment, trial day and time point, is provided in Section 15.3, Table 15.3.6.2.1. Individual ECG results are provided in Appendix 16.2, Listing 16.2.9.2.

During the trial, ECG was measured at screening, and during Period 1, Period 2, and Period 3 at 24 hours predose (Day -1), 50 min predose (Day 1), and at 2, 6, 12, 24, 48, and 72 hours postdose, and at the follow-up examination.

Mean and median values of HR, RR, PR, QRS, QT, QT corrected with Bazzett method (QTcB), and QTcF interval did not show any relevant differences between the different time points of assessment or notable changes from baseline to follow-up. All abnormal individual ECG assessments were considered not clinically significant. Any significantly abnormal ECG findings were to be documented as a TEAE.

12.6 Safety Conclusions

Overall, treatment with all three dosage forms (50 µg, 100 µg and 200 µg) at a total dose of 600 µg of the new formulation levothyroxine as investigated in this trial can be considered as safe and well tolerated. The safety and tolerability of the three dosage forms were similar between treatment periods.

The incidence of TEAEs was similar for all three dosage forms of the new formulation levothyroxine. In total, 27 (64.3%) subjects reported 85 TEAEs; 11 (28.9%) subjects reported 27 TEAEs during 12 tablets of 50 µg treatment, 16 (40.0%) subjects reporting 27 TEAEs during 6 tablets of 100 µg treatment, and 13 (33.3%) subjects reporting 31 TEAEs during 3 tablets of 200 µg treatment. Slightly more than one third (37.6%) of all reported TEAEs (32 of 85 TEAEs) were considered related to IMP by the Investigator: Five (13.2%) subjects reported 9 IMP-related TEAEs during 12 tablets of 50 µg treatment, 6 (15.0%) subjects reported 10 IMP-related TEAEs during 6 tablets of 100 µg treatment, and 7 (17.9%) subjects reported 13 IMP-related TEAEs during 3 tablets of 200 µg treatment. Headache was the most commonly reported TEAE (22 of 85 TEAEs) (reported by >12% of subjects during 6 tablets of 100 µg treatment and 3 tablets of 200 µg treatment, respectively). In addition, nausea (10 of 85 TEAEs) was reported by >12% subjects during 3 tablets of 200 µg treatment. All TEAEs except one were considered mild or moderate in intensity; Subject ablets of 100 µg treatment) had a severe TEAE of vomiting considered unrelated to IMP.

There were no deaths reported during the trial. In total, 2 subjects (Subject and Subject were withdrawn from the trial for safety reasons. Subject 12 tablets of 50 µg treatment) was withdrawn from the trial due to an SAE of moderate deep vein thrombosis, considered unrelated to IMP. Subject 6 tablets of 100 µg) was withdrawn from the trial due to an AE of mild vomiting, considered related to IMP.

Compared with predose values none of the safety laboratory, vital sign or ECG parameters showed any clinically relevant changes after treatment.

13 Discussion and Overall Conclusions

The primary objective of the trial was to demonstrate dosage form proportionality of three dosage forms of the new formulation in healthy subjects by estimating the relative BA and by pairwise BE testing.

The three dosage forms (50 µg, 100 µg, and 200 µg tablets) of the new levothyroxine formulation administered as 600 µg single doses were determined to be dose proportional as the relative BA for total T4 AUC_{0-72} and C_{max} with and without baseline adjustment ranged from 99.3% to 104.8%, and the 95% CIs for the pairwise comparisons for BE were within the predefined margin of 0.8 to 1.25.

Overall, treatment with all three dosage forms (50 µg, 100 µg and 200 µg) at a total dose of 600 µg of the new formulation levothyroxine as investigated in this trial can be considered as safe and well tolerated.

14 Reference List

There are no publications referenced in this CSR.

15 Tables, Figures, and Graphs Referred to but Not Included in the Text ...

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15.1 Demographic and Baseline Data

Table 15.1.1 Summary of Subject Disposition

Table 15.1.2 Demographic Data (Safety Population)