Clinical Trial Report

Protocol Identification No.:	EMR 200125-001
Title:	An open-label, single-dose, randomized, two-period, two-sequence crossover, single-center trial to assess bioequivalence of 600 µg levothyroxine new formulation versus old formulation administered orally as 3 white tablets of 200 µg in healthy volunteers
Short Title:	Bioequivalence trial of new levothyroxine formulation versus old formulation
Development Phase:	Phase I
Investigational Product:	Levothyroxine (600 µg [3 tablets of 200 µg] single dose of new formulation)
Treatment Duration:	One (1) single administration separated by a wash-out period of at least 35 to maximal 38 days
Indication:	Not applicable
Trial Design:	Phase I, open-label, randomized, two-period, two-sequence crossover, single-center trial
Trial Initiation Date:	18 Nov 2013 (first subject screened)
Trial Completion Date:	15 Jul 2014 (last subject last visit)
Principal Investigator:	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 **Bioequivalence trial of new levothyroxine formulation versus old formulation**

EMR 200125-001

Sponsor Contacts:

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Date of Report: 12 Dec 2014, Version 1.0

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

1 Approval Page

Clinical Trial Report: EMR 200125-001

An open-label, single-dose, randomized, two-period, two-sequence crossover, single-center trial to assess bioequivalence of 600 µg levothyroxine new formulation versus old formulation administered orally as 3 white tablets of 200 µg in healthy volunteers

Signatures may be found in Appendix 16.1.5.

Medical Responsible

Merck KGaA
Frankfurter Strasse 250
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Principal Investigator

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Trial Biostatistician

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

2 Synopsis

Title of Trial:

An open-label, single-dose, randomized, two-period, two-sequence crossover, single-center trial to assess bioequivalence of 600 µg levothyroxine new formulation versus old formulation administered orally as 3 white tablets of 200 µg in healthy volunteers

Trial Number:

EMR 200125-001

Principal Investigator:

Dr. med.

Trial Center:

Early Phase Clinical Unit (EPCU) – Berlin
PAREXEL International GmbH
Spandauer Damm 130, Haus 18
14050 Berlin, Germany

Publication (reference):

None

Trial Period (years):

18 Nov 2013 (first subject screened) to 15 Jul 2014 (last subject last visit)

Phase of Development:

Phase I

Objectives:

- The primary objective of the trial was to demonstrate bioequivalence (BE) of the new formulation (Test) versus the old formulation of levothyroxine (Reference) in healthy volunteers by estimating the relative bioavailability (BA) and by BE testing.
- 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, two-period, two-sequence crossover, single-center trial to assess the BE of 600 µg of levothyroxine new formulation versus old formulation given

as single dose of 3 tablets of 200 µg in healthy subjects. There was a washout period of at least 35 to maximal 38 days between dosing with the two formulations. 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 2 trial periods, respectively.

Subjects was to remain in the unit until the morning of Day 2, but needed to come back to the EPCU for regular ambulatory visits (including blood sample collections) 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 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: 216 subjects

Screened: 762 subjects

Randomized: 216 subjects (Sequence 1: 108 subjects; Sequence 2: 108 subjects)

Completed: 204 subjects (Sequence 1: 103 subjects; Sequence 2: 101 subjects)

Withdrawals: 12 subjects (Sequence 1: 5 subjects; Sequence 2: 7 subjects)

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 females and 55 to 95 kg for males 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.

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

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

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

The Test IMP was a 600 µg administration of new formulation levothyroxine, provided in 3 tablets of 200 µg.

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

New formulation (Test)

Batch number:
Packaging number:
Lot number: nal batch number)

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
- FU Visit 14 to 18 days after last IMP administration in Period 2

Total duration per subject: approximately 6 months (up to 77 days, including Screening and FU visit).

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

Marketed formulation of levothyroxine sodium tablets, oral administration of a single dose of 600 µg (3 tablets of 200 µg) with 240 mL water in fasted state in the morning of Day 1 (either in Period 1 or 2).

Old formulation (Reference)

Batch number
Packaging number:
Lot number: rnal batch number)

Criteria for Evaluation:

Efficacy:

Not applicable

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Pharmacokinetics:

Primary pharmacokinetic (PK) endpoints:

- Baseline-adjusted area under the concentration-time curve (AUC) from time zero to 72 hours postdose ($AUC_{0-72,adj}$) and baseline-adjusted observed maximum concentration ($C_{max,adj}$) of total (endogenous plus drug related) T4 after dosing with the Test and Reference formulation of 600 µg levothyroxine given as 3 tablets of 200 µg.

Secondary PK endpoints:

- For total T4: Baseline-adjusted AUC from time zero to infinity ($AUC_{0-\infty,adj}$), baseline-adjusted extrapolated part of the AUC from time zero to infinity ($AUC_{extra,adj}$), AUC from time zero to 48 hours postdose (AUC_{0-48}), AUC from time zero to 72 hours postdose (AUC_{0-72}), observed maximum concentration (C_{max}), time to reach C_{max} (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 apparent volume of distribution (Vz/f).

- Total (endogenous plus drug related) 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 (PD):

Not applicable.

Statistical Methods:

Pharmacokinetics:

The primary variables, $AUC_{0-72,adj}$ and $C_{max,adj}$ of total T4 were log-transformed before analysis. A generalized linear model was for treatment, period, sequence and subject within sequence. Differences, Test minus Reference, were estimated on the log scale, and based on the residual (within-subject) variation the 90% confidence intervals (CIs) for the differences were calculated. Back transformation resulted in Test/Reference ratios and corresponding 90% CIs for the GeoMean ratios. Bioequivalence testing was performed sequentially starting with the first set of BE limits. Alpha-adjustment was not needed.

The region-specific defined lower and upper BE bounds were:

- Food and Drug Administration (FDA) / United States of America (USA) (first set):

  $AUC_{0-72,adj}$: [0.80 – 1.25]

  $C_{max,adj}$: [0.80 – 1.25]

- Bundesinstitut für Arzneimittel und Medizinprodukte, Germany (second set)

  $AUC_{0-72,adj}$: [0.90 – 1.11]

  $C_{max,adj}$: [0.80 – 1.25]

- Agence Nationale de Sécurité du Médicament et des Produits de Santé, France (third set)

  $AUC_{0-72,adj}$: [0.90 – 1.11]

  $C_{max,adj}$: [0.90 – 1.11]

Primary PK parameters (for total T4) are listed by subject and summarized for each treatment. In addition, boxplots are presented by treatment. Secondary PK parameters (for total T3 and total T4) are presented 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. Unless otherwise stated, summary statistics were provided for all secondary endpoints. In addition, treatment ratios and 90% CIs, as well as boxplots were presented for the following parameters;

Total T3: AUC_{0-72} and C_{max}

Total T4: AUC_{0-72} and C_{max}

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

Safety

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

Summary and Conclusions:

Subject Disposition:

Overall, 762 subjects were screened for inclusion in this trial. The majority of screening failures were due to unmet eligibility criteria. Of these, 216 subjects were randomized to treatment sequence (108 subjects per sequence). A total of 204 (94.4%) subjects completed the trial.

- Twelve (12) subjects were discontinued from the trial prematurely:
    - Subject (Reference/Test) – Withdrawn due to AE (moderate sinus tachycardia, considered unrelated to IMP) (during Reference [old formulation] treatment)
    - Subject (Reference/Test) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen) (during Reference [old formulation] treatment)
    - Subject (Reference/Test) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (Neo-Angin®) (during Reference [old formulation] treatment)
    - Subject (Reference/Test) – Withdrawal by subject due to AEs found to be personally intolerable (during Reference [old formulation] treatment)
    - Subject (Reference/Test) – Withdrawn due to AEs (mild dizziness, mild nausea, and moderate diarrhea, all considered unrelated to IMP) (during Reference [old formulation] treatment)
    - Subject (Test/Reference) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen) (during Test [new formulation] treatment)
    - Subject (Test/Reference) – Withdrawal by subject due to AEs found to be personally intolerable (during Test [new formulation] treatment)
    - Subject (Reference/Test) – Withdrawn due to protocol non-compliance; positive urine drug screen (during Reference [old formulation] treatment)
    - Subject (Test/Reference) – Withdrawn due to AE (severe elevated creatinine phosphokinase [CPK], considered unrelated to IMP) (during Test [new formulation] treatment)
    - Subject (Test/Reference) – Protocol non-compliance; erroneously included in the trial (during Test [new formulation] treatment)
    - Subject (Test/Reference) – Withdrawn due to SAE (moderate otitis media, considered unrelated to IMP) (during Test [new formulation] treatment)
    - Subject (Reference/Test) – Withdrawal by subject; private reason (during Reference [old formulation] treatment)

There were 2 major protocol violations reported during the trial:

- Subject was included in the trial without volunteers inclusion period (VIP) check
- Subject was included even though exclusion criterion (the subject had previously reported use of L-thyroxin in 2006) was met.

Demographics and Baseline Characteristics:

Of the 216 healthy male and female subjects included in this trial 128 (59.3%) were male and 88 (40.7%) were female. The majority of subjects (99.1%) were considered "White", with 2 (0.9%) subjects categorized as "Black or African American". All subjects were considered to be of "Not Hispanic or Latino" ethnicity. For all randomized subjects, the mean age (±standard deviation [±SD]) was 34.5±9.32 years, the mean (±SD) height was 174.5±8.11 cm, the mean weight (±SD) was 71.64±9.464 kg, and the mean (±SD) BMI was 23.47±2.156 kg/m^2; similar distribution was observed between all treatment sequences.

Pharmacokinetic Results:

The geometric LS mean ratios (Test/Reference) for total T4 $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ following administration of levothyroxine new formulation and levothyroxine old formulation were 99.3 and 101.7, respectively. Since the corresponding 90% CIs were within the predefined "strongest condition (third set)" BE margin of 0.90 to 1.11 for $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$, as set by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France, all three bioequivalence tests were successful.

The median t_{max} values for the two products were comparable.

Summary of ANOVA of Primary Pharmacokinetic Parameters for Baseline-Adjusted Total T4 (Pharmacokinetic Population)

Parameter	Treatment	N	Geo-LSMean	Ratio (Test/Ref) (%)	90% CI of Ratio	Intra-CV (%)
$AUC_{0\text{-}72,adj}$ (hr*ng/mL)	Test	204	1852.079	99.3	95.6 - 103.2	23.7
	Reference	204	1864.359			
$C_{max,adj}$ (ng/mL)	Test	204	53.5473	101.7	98.8 - 104.6	17.7
	Reference	204	52.6736			

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; Geo-LSMean = Geometric Least Square Mean; N = Number of subjects included in the analysis.

Subjects ere excluded from the PK Population.

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

Secondary Endpoints

The geometric LS mean ratios (Test/Reference) for total T3 $AUC_{0\text{-}72}$ and C_{max} following administration of levothyroxine new formulation and levothyroxine old formulation were 99.7 and 99.9, respectively.

The geometric LS mean ratios (Test/Reference) for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine new formulation and levothyroxine old formulation were 99.7 and 100.6, respectively.

The total T3 median t_{max} values for the two products were comparable.

Summary of ANOVA of Secondary Pharmacokinetic Parameters for Total T4 and Total T3 (Pharmacokinetic Population)

Analyte	Parameter	Treatment	N	Geo-LSMean	Ratio (Test/Ref) (%)	90% CI of Ratio	Intra-CV (%)
T3	AUC_{0-72} (hr*ng/mL)	Test	204	57.1222	99.7	98.8 - 100.6	5.5
		Reference	204	57.2855			
	C_{max} (ng/mL)	Test	204	0.9711	99.9	98.5 - 101.3	8.6
		Reference	204	0.9718			
T4	AUC_{0-72} (hr*ng/mL)	Test	204	6169.484	99.7	98.8 - 100.6	5.5
		Reference	204	6190.588			
	C_{max} (ng/mL)	Test	204	113.0876	100.6	99.2 - 102.0	8.5
		Reference	204	112.4192			

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; Geo-LSMean = Geometric Least Square Mean; PK = pharmacokinetic; T3 = triiodothyronine T4 = thyroxine

N = Number of subjects included in the analysis.

Subjects ere excluded from the PK Population.

Test: levothyroxine new formulation.

Reference: levothyroxine old formulation.

Safety Results:

Overall, treatment with both new and old formulations at a total dose of 600 µg levothyroxine as investigated in this trial can be considered as safe and well tolerated. The safety and tolerability were comparable between treatment periods.

Overall, the number of subjects experiencing at least one TEAE was similar for both the new and the old formulations of levothyroxine (30.1 % of subjects [Test] compared with 28.9% of subjects [Reference], with 118 events [Test] compared with 165 events [Reference]). Of the 283 reported TEAEs, just over half (154 [54.4%]) were considered related to IMP (67 events [Test] compared with 87 events [Reference]).

The most commonly reported TEAEs were within the SOC "Nervous System Disorders", with the most commonly reported TEAE being headache (24 [11.5%] subjects with 35 events [Test] compared with 26 [12.3%] subjects with 44 events [Reference]). A similar trend was observed for drug-related TEAEs, with headache the most frequently reported drug-related event (16 [7.7%] subjects with 22 events [Test] compared with 16 [7.6%] subjects with 26 events [Reference]).

There were no deaths reported during the trial. Two (2) subjects reported SAEs during the trial; Subject had severe radius fracture considered unrelated to IMP, also leading to withdrawal from the trial, and Subject had moderate otitis media considered unrelated to IMP. In addition, 4 subjects were withdrawn from the trial due to AE(s); Subject (moderate sinus

tachycardia considered unrelated to IMP), Subject (mild dizziness, moderate diarrhoea, and mild nausea; all considered unrelated to IMP), Subject (moderate depressed mood considered related to IMP), and Subject (severe increased blood CPK considered unrelated to IMP).

All TEAEs were resolved by the end of the trial. However, subjects who had a change in severity had outcomes indicated as "unknown", per Study Data Tabulation Model (SDTM) method. The following subject had AE resolution indicated as "unknown" for AEs that worsened in severity: Subjects (nasopharyngitis), (headache), (headache), (headache), (headache), (headache). Subjects who had "unknown" AE resolution for AEs that improved in severity included: Subject (nasopharyngitis), (headache, dizziness), and (musculoskeletal discomfort).

None of the safety laboratory, vital sign or ECG parameters showed any relevant mean or median changes after treatment and none of the individual values were clinically significant.

Conclusions:

The new formulation of levothyroxine (Test) was determined to be bioequivalent to the old formulation of levothyroxine (Reference), in healthy subjects, as the geometric LS mean ratios (Test/Reference) for total T4 $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ were 99.3 and 101.7, respectively. Since the corresponding 90% CIs were within the predefined "strongest condition (third set)" BE margin of 0.90 to 1.11 for $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$, as set by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France, all three bioequivalence tests were successful.

Overall, treatment with both formulations (new and old formulation) at a total dose of 600 µg levothyroxine as investigated in this trial can be considered as safe and well tolerated.

Date of Report/Version No.: 12 Dec 2014, Version 1.0

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4 List of Abbreviations and Definition of Terms

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	AUC from time zero to infinity
$AUC_{0-\infty,adj}$	Baseline-adjusted AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to the last quantifiable concentration
AUC_{0-48}	AUC from time zero to 48 hours
AUC_{0-72}	AUC from time zero to 72 hours
$AUC_{0-72,adj}$	Baseline-adjusted AUC from time zero to 72 hours
$AUC_{extra,adj}$	Baseline-adjusted extrapolated part of the AUC from time zero to infinity
β-hCG	Beta-human chorionic gonadotropin
BA	Bioavailability
BE	Bioequivalence
BLQ	Below limit of quantification
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
$C_{max,adj}$	Baseline-adjusted maximum observed concentration in plasma
CPK	Creatinine phosphokinase
CRO	Contract research organization
CV	Coefficient of variation

DMP	Data Management Plan
DVS	Data Validation Specification
ECG	Electrocardiogram
EPCU	Early Phase Clinical Unit
EU	European Union
FDA	Food and Drug Administration
FU	Follow-up
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	Geometric mean
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator Site File
LLOQ	Lower limit of quantification
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
NTF	Note to file
PK	Pharmacokinetics
PR	Time from the onset of the P wave to the start of the QRS complex

PT	Preferred term
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
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia formula
RR	ECG interval, the time between successive R wave peaks
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SEM	Standard error of the mean
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent terminal half-life
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach the maximum concentration
TSH	Thyroid stimulating hormone
USA	United States of America
VIP	Volunteers Inclusion Period
Vz/f	Apparent volume of distribution
WHO	World Health Organization
WHO-DD	World Health Organization - Drug Dictionary
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) and local regulatory authority.

A complete list of IECs/IRBs, the contact details for the local regulatory authority, names and committee chairs can be found in Appendix 16.1.3.1 and Appendix 16.1.3.2.

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 person designated by the investigator might have given the information, if permitted by local regulations). 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 (ICF) 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 have been retrieved at any time for monitoring, auditing and inspection purposes. An original of the signed and dated information and ICF was provided to the subject prior to participation.

For a copy of the sample ICF, refer to Appendix 16.1.3.3.

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	
[2]Trial Director	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. PAREXEL International GmbH Spandauer Damm 130, Haus 18 14050 Berlin, Germany

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

Sub-Investigator	Early Phase Clinical Unit Berlin PAREXEL International GmbH Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: E-Mail:
[3]Medical Responsible	Dr. med Early Phase Scientific Affairs Berlin PAREXEL International GmbH Klinikum Westend, Haus 17 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: + E-Mail:
Data Management	Early Phase Clinical Data Services PAREXEL International GmbH Klinikum Westend, Haus 17 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: E-Mail :
Pharmacokinetic (PK) Scientist	Early Phase Clinical Pharmacokinetic/Pharmacodynamic – Baltimore United States of America Phone: E-Mail

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

Statistical Processing	Early Phase Biostatistics and Programming - Bloemfontein South Africa Phone: E-Mail:
Project Manager	Early Phase Clinical Unit - Berlin PAREXEL International GmbH Klinikum Westend, Haus 17 Spandauer Damm 130 14050 Berlin, Germany Phone: Fax: E-Mail :
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	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)	on behalf of Monitoring Systems Wolfgang Feth GmbH Möckernstrasse 112 D-10963 Berlin, Germany
Responsible Pharmacist	Hubertus-Apotheke am Salzufer Salzufer 13/14 10587 Berlin, Germany Phone: Fax: E-Mail:
Laboratory	Technical Head of Laboratory Synlab Pharma Institute (formerly Synlab Clinical Trial GmbH) Turmstr. 21 (Haus M) 10559 Berlin, Germany

The study administrative structure is presented in Appendix 16.1.4. For signatures of the principal investigator, the trial director (acting as medical responsible) and the trial biostatistician, refer to Appendix 16.1.5.

7 Introduction

7.1 Background Information

Levothyroxine was first registered in 1972 and is sold worldwide for the treatment of hypothyroidism. Merck KGaA has marketing authorizations worldwide (registered in over 100 countries and 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.

The new formulation shall meet potency specifications of 95.0 to 105.0% at release and over the envisaged shelf-life of at least 18 months at the storage condition of 25°C to comply with the changing potency requirements for levothyroxine tablets.

The qualitative and quantitative composition of excipients was changed in the reformulated levothyroxine tablets. The formulation, manufacturing process, in-process-controls, specifications and container closure system of the finished product are intended to be identical across all strengths, except for the levothyroxine sodium and the adapted filler amount.

The bioequivalence study has been conducted with the highest strength of the new formulation which will be registered worldwide i.e. 200 µg.

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 females 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.

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, cephalgia, muscular weakness and cramps, flushing, fever, vomiting, disorders of menstruation, pseudotumor cerebri, tremor, restlessness, insomnia, hyperhidrosis, weight loss, and diarrhea. In case of hypersensitivity levothyroxine allergic reactions particularly of the skin and the respiratory tract may occur. Cases of angioedema have been reported.

8 Trial Objectives

Primary

- The objective of the trial was to demonstrate bioequivalence (BE) of the new formulation (Test) versus the old formulation of levothyroxine (Reference) in healthy subjects by estimating the relative bioavailability (BA) and by BE testing.

Secondary

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

9 Investigational Plan

9.1 Overall Trial Design and Plan: Description

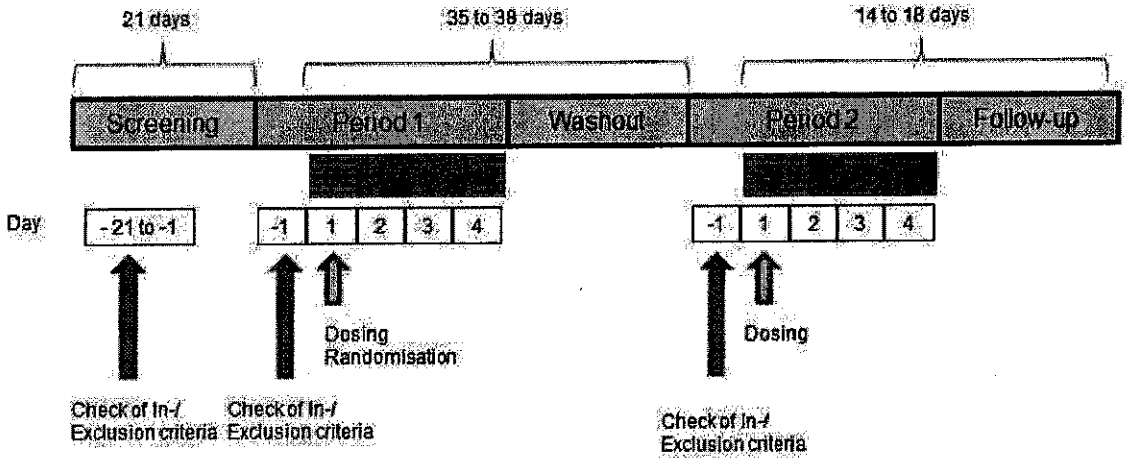
This is a Phase I, open-label, randomized, two-period, two-sequence crossover, single-center trial. Primary and secondary endpoints are described in Section 9.7.1.2. The treatments studied are described in Section 9.4.1. The trial protocol, including any amendment(s) is presented in Appendix 16.1.1. A sample Case Report Form (CRF) is presented in Appendix 16.1.2.

The trial was to be conducted in 2 periods. Assuming a drop-out rate of 20%, two-hundred sixteen (216) subjects (108 subjects per sequence) were enrolled in the trial. The replacement of drop-outs was 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. For details regarding the replacement of subjects, refer to Section 9.3.3.

In each period blood sampling for PK was performed at -0.5, -0.25 and 0 hours predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours postdose. The mean of the 3 predose samples was used to adjust for the baseline thyroxine (T4) level.

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 FU Visit was approximately 11 weeks (up to 77 days).

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 reconfirmed prior to IMP administration in Period 2. 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 to 18 days after administration of IMP in Treatment Period 2.

9.2 Discussion of Trial Design

The trial design was in line with the United States Food and Drug Administration (FDA) Guidance for Industry (CDER 2000) for levothyroxine sodium tablets. 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 in accordance with the Committee for Medicinal Products for Human use (CHMP) European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence 2010. Baseline correction is required by the European Union (EU) Guideline but not by the FDA Guideline, and for the primary endpoint baseline correction was agreed, while uncorrected values were calculated as secondary endpoints.

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 assessed on 22 June 2014), a dose of 600 µg was the appropriate dose that ensures proper serum concentrations to allow full characterization of the PK profile of levothyroxine with minimum 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, and 3 others assessed BE between 300 µg levothyroxine tablets (Genpharm, Canada) with 2 different reference products from the United States of America (USA).

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 females and 55 to 95 kg for males 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 [min] in supine position):

    - systolic blood pressure (SBP): 90 to 140 mmHg
    - diastolic blood pressure (DBP): 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 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], QT interval corrected for heart rate using Fridericia method [QTcF] had to be within normal range, no conduction abnormalities, etc.)

6. Non-smoker for at least 3 months

7. Total and free 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. 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

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

16. Administration of any investigational product or use of any investigational device within 60 days prior to first levothyroxine administration, confirmed by a negative Volunteers Inclusion Period (VIP)-check (with the VIP check to have been completed before randomization)

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

18. Use of any prescription or nonprescription medication within 2 weeks prior to dosing or 5 half-lives, whichever was 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

19. Subjects taking medications known to affect thyroid hormone metabolism, e.g., oral contraceptives, hormonal implants, parenteral hormones, anabolic steroids, androgens, etc.

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

21. Special diet of the subject

22. 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

23. 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

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

25. 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

26. Subject was 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

27. 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

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

29. 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, as well as to any comparator drug or placebo (as applicable).

Levothyroxine was administered as levothyroxine sodium. Both formulations (Test and Reference) were supplied as white tablets containing 200 µg levothyroxine sodium.

9.4.1 Treatments Administered

The composition is provided in Section 0.

New formulation (Test Product)

A single dose of 600 µg levothyroxine sodium was administered as 3 tablets of 200 µg levothyroxine sodium with 240 mL water in the morning of Day 1 (in either Period 1 or 2) after an overnight fast of at least 10 hours. Subjects remained fasted for 4 hours after dosing, with water only allowed after the first hour of IMP intake.

Old formulation (Reference Product)

A single dose of 600 µg levothyroxine sodium was administered as 3 tablets of 200 µg levothyroxine sodium with 240 mL water in the morning of Day 1 (in either Period 1 or 2) after an overnight fast of at least 10 hours. Subjects remained fasted for 4 hours after dosing, with water only allowed after the first hour of IMP intake.

9.4.2 Identity of the Investigational Products

New Formulation (Test Product)

The new formulation (Test) contains as excipients mannitol, maize starch, gelatine, croscarmellose sodium, anhydrous citric acid and magnesium stearate.

Batch number:
Packaging number
Lot number: (external batch number)

Old Formulation (Reference Product)

The old formulation (Reference) contains as excipients maize starch, croscarmellose sodium, gelatine, lactose monohydrate and magnesium stearate.

Batch numbe
Packaging num
Lot number (external batch number)

Details on identity of IMP (shipping, packaging, and batch information) are presented in Appendix 16.1.6.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects were randomly assigned to 1 of 2 different treatment sequences (see Section 9.1). Further details on the randomization procedure are provided in Appendix 16.1.7.

The investigator or delegate allocated a randomization number 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

The eligibility of the subjects' criteria as denoted in the lists of inclusion (Section 9.3.1) and exclusion criteria (Section 9.3.2) were checked during Screening and confirmed on Day -1 in Period 1. On Day -1 of the second period the criteria for the removal of subjects from therapy or assessment were checked (Section 9.3.3). Randomization and initiation of treatment was only allowed if all of the inclusion and none of the exclusion criteria applied.

9.4.4 Selection of Doses in the Trial

The dose was in line with the Guidance for Industry FDA CDER 2000, 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 assessed on 22 June 2014), a 600 µg dose is the appropriate dose that ensures proper plasma levels 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 (6) bioavailability/BE trials conducted with identical total levothyroxine doses of 600 µg administered in all trial periods were provided. In 3 of those trials (436-99-263, 436-99-264 and 436-99-277), different formulations or strengths were compared, also with an oral solution, and 3 others assessed BE between 300 µg levothyroxine tablets (Genpharm, Canada) with 2 different USA reference products.

No safety concerns were raised in the above cited trials. Based on the data available to date, the conduct of the trial was regarded as justifiable at the planned dose.

9.4.5 Selection and Timing of Dose for Each Subject

Following a 10 hour overnight fast, the administration of the IMP was performed on the morning of Day 1 of each treatment period. Subjects remained in the fasted state for 4 hours after IMP administration, with water only allowed up to 1 hour before and after the first hour following IMP administration. No breakfast was served on Day 1. Subjects were served standardized meals according to the schedule during inpatient period.

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 medication 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 nonprescription 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

Subjects fasted for at least 10 hours before dosing and remained fasting until 4 hours after dosing with water only allowed up to one hour before and after the first hour of IMP intake. No breakfast was provided on Day 1. All other meals were provided at the usual mealtimes of the trial center.

Before and throughout the PK profiling days (until Day 4) 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™.

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.

Females 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. Females 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 post-menopausal 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 nonsmokers (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					FU
Day	-21 to -1	-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			
Ambulatory Visit[b]	X			X	X	X				X	X	X	X
Inclusion/Exclusion Criteria Check/Re-check	X	X						X					
Demographics Including Body Weight and Height	X												
Medical History and History of Medication	X												
Physical Examination[c]	X	X						X					X
Drugs and Alcohol Screening[d]	X	X						X					
Vital Signs (blood pressure, pulse, temperature)[e]	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
Safety Laboratory[g]	X	X						X					X
Pregnancy Test (serum)	X	X						X					
Randomization			X										
IMP Administration			X						X				
PK Blood Sampling for levothyroxine[h]			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

AE = adverse event; CRO = Contract research organization; FU = follow-up; IMP = Investigational Medicinal Product, PK = pharmacokinetics, ECG = electrocardiogram; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

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. The use of drugs, alcohol abuse, and tricyclic antidepressant use was assessed at screening, and at any other time point at the discretion of the investigator.

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

f. 12-lead ECG was recorded after 10 minute in supine position at the following time points: Baseline (within 60 minute 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 T4 and T3 in plasma 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

The safety profile of the IMP was assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests and 12-lead ECGs.

Comprehensive assessment of any apparent toxicity experienced by the subject was performed throughout the course of the trial, from the time of the subject's signature of informed consent. The EPCU personnel reported any AE, whether observed by the investigator or reported by the subject.

9.5.1.1.1 Adverse Event

An 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 alanine aminotransferase [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 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.

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 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 would 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) or the clinical trial protocol.

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). Documentation on inter-laboratory standardization methods and quality assurance procedures are presented in Appendix 16.1.10. 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.

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 drawn was approximately 325.8 mL.

Hematology

Hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count and platelet count.

Clinical chemistry (serum)

Total T4, total T3, aspartate aminotransferase (AST), ALT, γ-Glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, creatinine phosphokinase, bilirubin (total), amylase, lipase, protein (total), potassium, sodium, chloride, calcium, creatinine, urea and glucose were determined at each safety laboratory. Free T4, free T3 and TSH were assessed at Screening and Follow-up only.

Some additional parameters were routinely done by the laboratory in case of abnormal findings such as manual differential blood count, direct/indirect bilirubin and creatinine phosphokinase myocard/brain type.

Urinalysis

pH, nitrite, protein, glucose, ketone bodies, urobilinogen, bilirubin, red blood cell count, white blood cell count. On positive findings or on demand of the investigator a subsidiary microscopic examination of the sediment was performed.

Alcohol and Drug Tests

Spot urine was assessed for alcohol and recreational drugs. It covered the following drugs or metabolites in urine: methadone, benzodiazepines, cocaine, amphetamine (including derivatives as e.g. methamphetamine and ecstasy), tetrahydrocannabinol, opiates, barbiturates and tricyclic antidepressants.

Additional urine drug test during the course of the trial was at the discretion of the investigator.

Pregnancy Test

Blood samples were collected from all females and used for assessment of beta-human chorionic gonadotropin (β-hCG). Additional pregnancy tests during the course of the trial were at the discretion of the investigator.

Serology

Serology for Human Immunodeficiency Virus 1/2 antibodies, Hepatitis B surface antigen and Hepatitis C Virus antibodies were assessed.

Glomerular filtration rate (at Screening only)

The eGFR was calculated at Screening using the Modification of Diet in Renal Disease equation (for creatinine in µmol/L):

$eGFR = 30849 * \text{serum creatinine}^{-1.154} * \text{age}^{-0.203} * [1.212 \text{ if black}] * [0.742 \text{ if female}]$

9.5.1.1.9 Vital Signs, Physical Examinations, and Other Assessments

Vital Signs

Vital signs including blood pressure (BP), pulse, and oral body temperature were performed according to the trial schedule in Table 9.1. Blood pressure and pulse rate were measured after at least 10 minute in a supine position. Body temperature was measured orally. Further vital sign measurements during the course of the trial were at the discretion of the investigator.

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

Physical Examination

Physical examination was performed according to the assessment schedule in Table 9.1. 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.

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 minute in supine position. A full standard 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) for about 5 seconds (at least 4 adjacent beats, calibration: 25 mm/sec 10 mm/mV) and heart rate 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.

Electrocardiograms 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 total T3 and T4 in plasma was performed by using a Liquid Chromatography Tandem Mass Spectrometry method according to Good Laboratory Practices (GLP) principles, which was fully validated according to the Guidelines for Industry applicable to Bioanalytical Methods.

Analysis methods are described in a bioanalytical protocol, and respective results are reported in a bioanalytical report (see Appendix 16.1.13).

Further details on the collection, processing, labeling and shipping of these samples were detailed in the trial Manual of Operations (MOP)/laboratory manual.

9.5.5 Pharmacokinetic Variables and Pharmacokinetic Evaluation

The PK parameters for T3 and T4 were calculated by PAREXEL International using the validated software tool Phoenix WinNonlin™ (Version 6.3), and were evaluated using noncompartmental 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)

Vz/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 mean of the 3 predose samples was used to adjust for the baseline T4 level.

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

- Concentrations below the lower limit of quantification (LLOQ) were presented as below limit of quantification (BLQ) 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 case report forms, 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: 28 Jan 2014
- Investigator Site File, Date of Audit: 29 Jan 2014
- Case Report Forms, Date of Audit: 04 to 27 Mar 2014
- Signed Informed Consent Forms, Date of Audit: 04 Mar 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). A CRF is presented in Appendix 16.1.2.

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 [redacted] were to be randomized to one of two treatment sequences, such that 108 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 contract research organization (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 $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ of total T4 after dosing with the Test and Reference formulation of 600 µg levothyroxine given as 3 tablets of 200 µg, adjusted for baseline (predose level).

9.7.1.2.2 Secondary Endpoints

All other PK endpoints (total T4 [$AUC_{0\text{-}\infty,adj}$, $AUC_{extra,adj}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-}72}$, C_{max}, t_{max}, $t_{½}$, λ_Z, CL/f and Vz/f] and total T3 [C_{max}, $AUC_{0\text{-}48}$, $AUC_{0\text{-}72}$ and t_{max}]) were considered secondary and were analyzed descriptively.

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 following sets of populations were used for the analysis:

Safety Population

The safety population included all subjects who received at least 1 dose of planned trial treatment. Subjects were analyzed according to the actual treatment they received.

Pharmacokinetic Population

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 primary PK variables ($AUC_{0-72,adj}$ and $C_{max,adj}$) for both 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 1 dose of IMP. The safety analysis set was used for the presentation of all baseline, demographic, safety, and tolerability data.

9.7.1.4 Description of Statistical Analyses

9.7.1.4.1 General Considerations

Pharmacokinetic analyses were performed using Phoenix WinNonlin (Version 6.3). All other statistical analyses were performed using SAS® (Statistical Analysis System, SAS Institute, Cary NC, USA, Windows® Version 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 16.1 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.

The mean of the 3 predose samples was used to adjust for the baseline T4 level. If the baseline measurement (derived mean or single measurement) was higher than the first postdose T4 concentration, the baseline-adjusted PK parameters were not calculated for the specific treatment period.

For the estimation of λz, and consequently $t_{1/2}$, baseline-adjusted concentrations were used. The mean of 3 predose measurements was subtracted from each concentration at each time point.

Predose concentrations that were below the limit of quantitation (BLQ) were set to ½ lower limit of quantification (LLOQ) in the calculation of the mean baseline concentration. Below the limit of quantification values were set to ½ LLOQ in the estimation of AUC_{0-t} and C_{max}. If all concentrations were BLQ for a given subject, then all PK parameters were considered as missing for that subject and the subject was excluded from the PK population. Negative values for baseline-adjusted concentrations difference were considered as missing values in the estimation of terminal elimination parameters.

9.7.1.4.2 Analysis of Primary Endpoint

The primary variables, $AUC_{0-72,adj}$ and $C_{max,adj}$ of total T4 were log-transformed before analysis. A generalized linear model was for treatment, period, sequence and subject within sequence. Differences, Test minus Reference, were estimated on the log scale, and based on the residual (within-subject) variation the 90% confidence intervals (CI) for the differences were calculated. Back transformation resulted in Test/Reference ratios and corresponding 90% CIs for the GeoMean ratios. Bioequivalence testing was performed sequentially starting with the first set of BE limits. Alpha-adjustment was not needed.

In this trial, null and alternative hypotheses were:

- H_0: $\mu_T / \mu_R \leq 0.80$ or $1.25 \leq \mu_T / \mu_R$ for $AUC_{0-72,adj}$ or $C_{max,adj}$ or both
- H_1: $0.80 < \mu_T / \mu_R < 1.25$ for $AUC_{0-72,adj}$ or $C_{max,adj}$

μ_T and μ_R being the geometric mean (GM) under Test and Reference treatment, respectively.

BE was confirmed, if the 90% CI for the ratios of GM for both, $AUC_{0-72,adj}$ or $C_{max,adj}$ of total T4 in plasma, were included in the region-specific BE acceptance interval.

The region-specific lower and upper BE bounds were:

- FDA / USA (first set):

  $AUC_{0-72,adj}$: [0.80 – 1.25]

$C_{max,adj}$: [0.80 – 1.25]

- Bundesinstitut für Arzneimittel und Medizinprodukte, Germany (second set)

  $AUC_{0-72,adj}$: [0.90 – 1.11]

  $C_{max,adj}$: [0.80 – 1.25]

- Agence Nationale de Sécurité du Médicament et des Produits de Santé, France (third set)

  $AUC_{0-72,adj}$: [0.90 – 1.11]

  $C_{max,adj}$: [0.90 – 1.11]

Primary PK parameters (for total T4) are listed by subject and summarized for each treatment. In addition, boxplots are presented by treatment.

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. Unless otherwise stated, summary statistics were provided for all secondary endpoints. In addition, treatment ratios and 90% CIs, as well as boxplots were presented for the following parameters;

Total T3: AUC_{0-72} and C_{max}

Total T4: AUC_{0-72} and C_{max}

The GM ratios (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, standard deviation (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. The current version of the MedDRA coding system was used to classify the AEs. Concomitant medication was coded according to World Health Organization (WHO) Drug Reference List and Anatomical Therapeutic Chemical Classification System, the current version. Medical history was coded according to the current

version of MedDRA. 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 were 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 (CV) of AUC of levothyroxine, and 18.6% as an upper bound for the CV of C_{max}. If the upper bounds of these CVs together with applicable BE criteria [0.90 to 1.11] for AUC and C_{max} are applied, (third set below), and if furthermore the true treatment ratio Test/Reference is allowed to vary within 0.95 and 1.05, 172 evaluable subjects would provide at least 83% overall power to show bioequivalence. For a compensation of possible drop-outs 44 subjects should have been included in addition, corresponding to a drop-out rate of around 20%. In total, 216 subjects should have been included in the trial (108 subjects per treatment sequence). BE testing was performed sequentially starting with the first set of BE limits (See Section 9.7.1.4.2). Alpha-adjustment was not needed.

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), dated 09 Oct 2013, became necessary.

The purpose for the amendment was:

- To note a change in the Investigator's signature page
- To include a VIP in Inclusion Criterion #16, and subsequently to add the abbreviation to the abbreviation list
- To add additional withdrawal criteria
- To add the use of diary cards
- To change the drug screening method used for tricyclic antidepressants (subsequently the blood volume required during the trial decreased)
- To change the method used for the analysis of T3 and T4
- To clarify the gender distribution
- To clarify the description of subject identification and data privacy

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 21 notes to file (NTF) (see Appendix 16.1.1.5) were created:

- NTF #1: Clarified that the test used during the trial for screening of amphetamines also covered methamphetamine, ecstacy, and other methamphetamine derivatives.
- NTF #2: Cancelled – no longer required with the submission of the clinical trial amendment.
- NTF #3: ECGs for this trial were assessed according to PAREXEL SOP. However, deviating from the standard normal ranges provided per SOP, the heart rate was evaluated according to specifications provided in Inclusion Criterion #4.
- NTF #4: The PK analysis was performed in plasma, and not in serum as stated in the clinical trial protocol
- NTF #5: The eligibility of subjects after completion of Period 1 was verified on the basis of withdrawal criteria and not the review of inclusion / exclusion criteria. Note: those criteria considered of clinical significance should be reviewed. The withdrawal criteria relevant to QTc do not specify the correction method and agreement was reached to use QTcF.
- NTF #6: The fasting status was not documented in ClinBase™ prior to safety blood sample draws for Subjects

- NTF #7: Subject took concomitant medication (ibuprofen) within 2 weeks prior to dosing and was erroneously entered into the trial regardless. Since the concomitant medication has a short half-life of ≤3.5 hours and is not a CYP2C9 substrate and not an inhibitor of CYP P450 no impact on subject safety was expected.

- NTF #8: Subject was included in the trial without the required VIP check.

- NTF #9: According to the clinical trial protocol male subjects were randomized randomization number 101 and upwards, and female subjects from last randomization number downwards. Erroneously however, three female subjects (Subjects re randomized in upwards order.

- NTF #10: Administrative issue.

- NTF #11: Subjects were enrolled in the trial even though heart rate < 45 bpm at Admission (Day -1).

- NTF #12: Subject is erroneously included in the trial with medical history of L-thyroxine treated hypothyroidism (in 2006). The subject received IMP in Period 1, but was withdrawn from the trial and did not receive IMP in Period 2.

- NTF #13: Two sets of batch I queries were created, and batch II queries were sent to the EPCU without responses having been received on the batch I queries.

- NTF #14: Subjects had assessments performed outside of the window allowance agreement to enable them to leave the EPCU early for work-related reasons.

- NTF #15: Documented that mutual agreement was reached between Merck KGaA and PAREXEL International that 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.

- NTF #16: Administrative issue

- NTF #17: Subject missed Period 2, Day 3 visit due to illness. All other visits were completed successfully and this subject was not a drop-out / discontinuation.

- NTF #18: Administrative issue

- NTF #19: Documented that the Follow-up visit was performed one day earlier (i.e. 13 days after last IMP administration) than allowed per protocol for a number of subjects.

- NTF #20: Documented the procedure for capturing AE terms in the Source Data Capturing System Clinbase™. Also see Appendix 16.1.2.2 for a statement on electronic data capturing procedure.

- NTF #21: Subject were excluded from the trial due to weight requirement not being met. Further demographic data collection was not completed.
- NTF #22: Does not exist (See NTF #25)
- NTF #23: Subject missing end date for knee operation. The investigator confirmed that the event resolved in 1989.
- NTF #24: Documented that no fields were created in ClinBase™ to record failed Inclusion and Exclusion criteria.
- NTF #25: Was issued to document a break in NTF numbering at NTF #22.

9.8.2 Changes in the Planned Analyses

All analysis described in the SAP were per the analyses planned in the clinical trial protocol.

10 Trial Subjects

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

10.1 Disposition of Subjects

Subject terminations 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 inclusion and exclusion criteria fulfillment are listed in Appendix 16.2, Listing 16.2.1.3 and Listing 16.2.1.4, respectively. Screening failures are listed in Appendix 16.2, Listing 16.2.1.5.

The disposition of subjects is summarized in Table 10.1.

Table 10.1 Subject Disposition

Subjects	Sequence 1 N = 108	Sequence 2 N = 108	Overall N = 216
	n (%)	n (%)	n (%)
Screened	-	-	762
Randomized	108 (100.0%)	108 (100.0%)	216 (100.0%)
Subjects Treated	108 (100.0%)	108 (100.0%)	216 (100.0%)
Completed	103 (95.4%)	101 (93.5%)	204 (94.4%)
Withdrawn	5 (4.6%)	7 (6.5%)	12 (5.6%)
Adverse event	2 (1.9%)	2 (1.9%)	4 (1.9%)
Protocol non-compliance	2 (1.9%)	3 (2.8%)	5 (2.3%)
Withdrawal by subject	1 (0.9%)	2 (1.9%)	3 (1.4%)
Safety population	108 (100.0%)	108 (100.0%)	216 (100.0%)
PK population	103 (95.4%)	101 (93.5%)	204 (94.4%)

N = number of subjects dosed with at least one treatment in that treatment sequence, or the number subjects in the safety population for the total summary; n = number of subjects in the specific category; PK = pharmacokinetics

Treatment Sequence 1: Test (new formulation)/Reference (old formulation)
Treatment Sequence 2: Reference (old formulation)/Test (new formulation)

Source: Appendix 16.2, Listing 16.2.1.1, and Section 15.1, Table 15.1.1

Overall, 762 subjects were screened for inclusion in this trial. The majority of screening failures were due to unmet eligibility criteria [Appendix 16.2, Listing 16.2.1.5]. Of these, 216 subjects were randomized to treatment sequence (108 subjects per sequence). A total of 204 (94.4%) subjects completed the trial.

- Twelve (12) subjects were discontinued from the trial prematurely:
    - Subject (Sequence: Reference/Test) – Withdrawn due to AE (moderate sinus tachycardia, considered unrelated to IMP) (during Reference [old formulation] treatment)
    - Subject (Sequence: Reference/Test) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen [see Appendix 16.1.1.5, NTF #7]) (during Reference [old formulation] treatment)
    - Subject (Sequence: Reference/Test) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (during Reference [old formulation] treatment)
    - Subject (Sequence: Reference/Test) – Withdrawal by subject due to AEs found to be personally intolerable (during Reference [old formulation] treatment)
    - Subject (Sequence: Reference/Test) – Withdrawn due to AEs (mild dizziness, mild nausea, and moderate diarrhea, all considered unrelated to IMP) (during Reference [old formulation] treatment)
    - Subject (Sequence: Test/Reference) – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen) (during Test [new formulation] treatment)

- Subject (Sequence: Test/Reference) – Withdrawal by subject due to AEs found to be personally intolerable (during Test [new formulation] treatment)
- Subject (Sequence: Reference/Test) – Withdrawn due to protocol non-compliance; positive urine drug screen (during Reference [old formulation] treatment)
- Subject (Sequence: Test/Reference) – Withdrawn due to AE (severe elevated creatinine phosphokinase [CPK], considered unrelated to IMP) (during Test [new formulation] treatment)
- Subject (Sequence: Test/Reference) – Protocol non-compliance; erroneously included in the trial (during Test [new formulation] treatment) (also see NTF #12 [Appendix 16.1.1.5])
- Subject (Sequence: Test/Reference) – Withdrawn due to AE (moderate otitis media, considered unrelated to IMP) (during Test [new formulation] treatment)
- Subject (Sequence: Reference/Test) – Withdrawal by subject; private reason (during Reference [old formulation] treatment)

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 2 major protocol violations reported during the trial:

- Subject was included in the trial without VIP check (also see NTF #8, Appendix 16.1.1.5)
- Subject was included even though Exclusion Criterion #4 was met (the subject had previously reported use of L-thyroxin in 2006) (also see NTF #12, Appendix 16.1.1.5).

Minor protocol deviations comprised predominantly assessments performed out of time window allowance, including follow-up visit, other visits, diary card distribution and collection, PK blood sampling, centrifugation procedure, ECG, vital signs, and eligibility criteria review.

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

- Subject , Subject , Subject , Subject Subject , and Subject had missing trial diaries.
- Subject had missing PK sample due to absence
- Subject had insufficient PK sample volume
- Subject had abnormal ECG without control measurement (heart rate [HR] <45 bpm)

- Subject [redacted] self-administered 1500 mg paracetamol (maximum 1000 mg allowed per protocol)

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

One (1) subject reported a prior medication during the trial:

Subject [redacted]: The subject took 500 mg once daily paracetamol orally prior to randomisation during the screening period on 4 May 2014 at 19:50, approximately 1 day prior to IMP administration in the first treatment period.

Concomitant medication

A total of 26 subjects were administered 55 concomitant medications during the trial for the treatment of AEs (Appendix 16.2, Listing 16.2.4.3).

The majority (19) of the 26 subjects who were administered concomitant medication during the trial took anilides (paracetamol); for headache ([redacted] and [redacted]), dislocated distal radius fracture right side ([redacted]), neck discomfort ([redacted]), tonsillitis ([redacted]), abdominal "crampy" pains ([redacted]), or for common cold symptoms ([redacted], and [redacted]).

Other concomitant medications administered during the trial included:

- Subject [redacted]: Bepanthen® ointment for Herpes Labialis; considered not to have unduly affected the PK or safety results of the trial.
- Subject [redacted] Ibuprofen, Oxygesic®, and Targin® for dislocated distal radius fracture right side, pantoprazole as gastric ulcer prophylaxis. The subject was withdrawn from trial due to SAE of severe radius fracture.
- Subject [redacted] Unspecified herbal and traditional remedy for common cold symptoms; considered not to have unduly affected the PK or safety results of the trial as it was administered approximately 17 days after IMP administration in the final treatment period.
- Subject [redacted]: Neo-Angin® for sore throat. The subject was withdrawn from the trial due to prohibited concomitant medication.
- Subject [redacted] Voltaren® for pain in left elbow. Subject withdrew due to AEs found to be personally intolerable.

- Subject : Ibuprofen for back pain. The subject was withdrawn from the trial due to prohibited concomitant medication.
- Subject : Penicillin for tonsillitis; considered not to have unduly affected the PK or safety results of the trial as it was administered approximately 5 days after IMP administration in the final treatment period.
- Subject : Aciclovir® cream for Herpes Labialis. As this preparation was administered outside the PK sampling interval and topical in nature it was considered not to have unduly affected the PK or safety results of the trial.
- Subject : Novaminsulfon and Cymbalta® for otitis media, potassium for hypokalemia, Cefuroxim® for otitis media and tonsillitis, and Propofol® as sedative during tympanic drainage. The subject was withdrawn from the trial due to SAE of otitis media.

Medication after Final IMP Administration

A total of 2 subjects reported medications administered after final IMP administration:

Subject : 1 tablet twice daily orally Amoxicillin 1000 for cat bite. Dose administration commenced approximately 9 days following Reference therapy administration in the final treatment period.

Subject : 500 mg three times daily orally paracetamol for headache. Dose administration commenced approximately 5 days following Test therapy administration in the first treatment period.

11 Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The safety population included all randomized subjects who received at least 1 dose of IMP and who had follow-up safety assessments, i.e., the data of 216 subjects were analyzed, 108 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 204 subjects were analyzed, 103 (95.4%) subjects in Sequence 1, and 101 (93.5%) subjects in Sequence 2.

The assignment of subjects to analysis populations and treatment groups are listed in Listing 16.2.3.1.

The following subjects (N = 12) were excluded from the PK population as they did not receive both the Test (new formulation) and the Reference (old formulation) treatments:

- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject
- Subject

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 = 108	Sequence 2 N = 108	Overall N = 216
Age (years)		n	108	108	216
		Mean	35.0	34.1	34.5
		SD	9.56	9.09	9.32
Gender	Male	n (%)	64 (59.3)	64 (59.3)	128 (59.3)
	Female	n (%)	44 (40.7)	44 (40.7)	88 (40.7)
Ethnic Origin	Hispanic or Latino	n (%)	0	0	0
	Not Hispanic or Latino	n (%)	108 (100.0%)	108 (100.0%)	108 (100.0%)
Race	White/Caucasian	n (%)	108 (100.0%)	106 (98.1%)	214 (99.1%)
	Black/African American	n (%)	0	2 (1.9%)	2 (0.9%)
Height (cm)		n	108	108	216
		Mean	174.9	174.1	174.5
		SD	8.08	8.16	8.11
Weight (kg)		n	108	108	216
		Mean	71.84	71.43	71.64
		SD	9.245	9.717	9.464
BMI (kg/m2)		n	108	108	216
		Mean	23.42	23.51	23.47
		SD	1.998	2.311	2.156

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

Sequence 1: New formulation levothyroxine (Test)/Old formulation (Reference)
Sequence 2: Old formulation (Reference)/New formulation levothyroxine (Test)

Source: Section 15.1, Table 15.1.2

Of the 216 healthy male and female subjects included in the trial 128 (59.3%) were male and 88 (40.7%) were female. All 216 subjects were considered of "Non-Hipanic or Latino" ethnicity, with only 2 subjects considered of "Black or African American" race. For all randomized subjects, the mean age (±standard deviation [±SD]) was 34.5±9.32 years, the mean (±SD) height was 174.5±8.11 cm, the mean weight (±SD) was 71.64±9.464 kg, and the mean (±SD) BMI was 23.47±2.156 kg/m^2; similar distribution was observed within treatment sequences (Table 11.1).

In total, 161 of the 216 enrolled subjects in this trial had at least one previous or ongoing medical or surgical event in their history. Of these events, 50 events were considered ongoing at trial entry. The ongoing findings included seasonal allergy (19 subjects), allergy to nickel (10 subjects), house dust allergy (4 subjects), allergy to animals (2 subjects), acne (2 subjects), allergy to cats (1 subjects), and a single incidence of corneal disorder, myopia, allergy to horses, contact dermatitis, tinnitus, congenital nystagmus, scoliosis, onychomycosis, and uterine leiomyoma (Appendix 16.2, Listing 16.2.4.2).

Of the 216 enrolled subjects, all (100%) subjects reported occasional consumption of alcoholic beverages, 134 (62.0%) subjects commonly consumed stimulating (caffeine-containing) beverages, and 82 (38.0%) subjects had past history of smoking (Appendix 16.2, Listing 16.2.4.5).

No subjects returned positive results during assessment for pregnancy (females) (Appendix 16.2, Listing 16.2.8.4). One subject (Subject , returned a positive result (HCV) during serology testing at screening, however, confirmatory testing returned a negative result (Appendix 16.2, Listing 16.2.8.5). One subject (Subject eturned a positive drugs of abuse screening result (opiates) at Admission to Period 2 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 16.1.9.1). 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 9.5.5.

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.

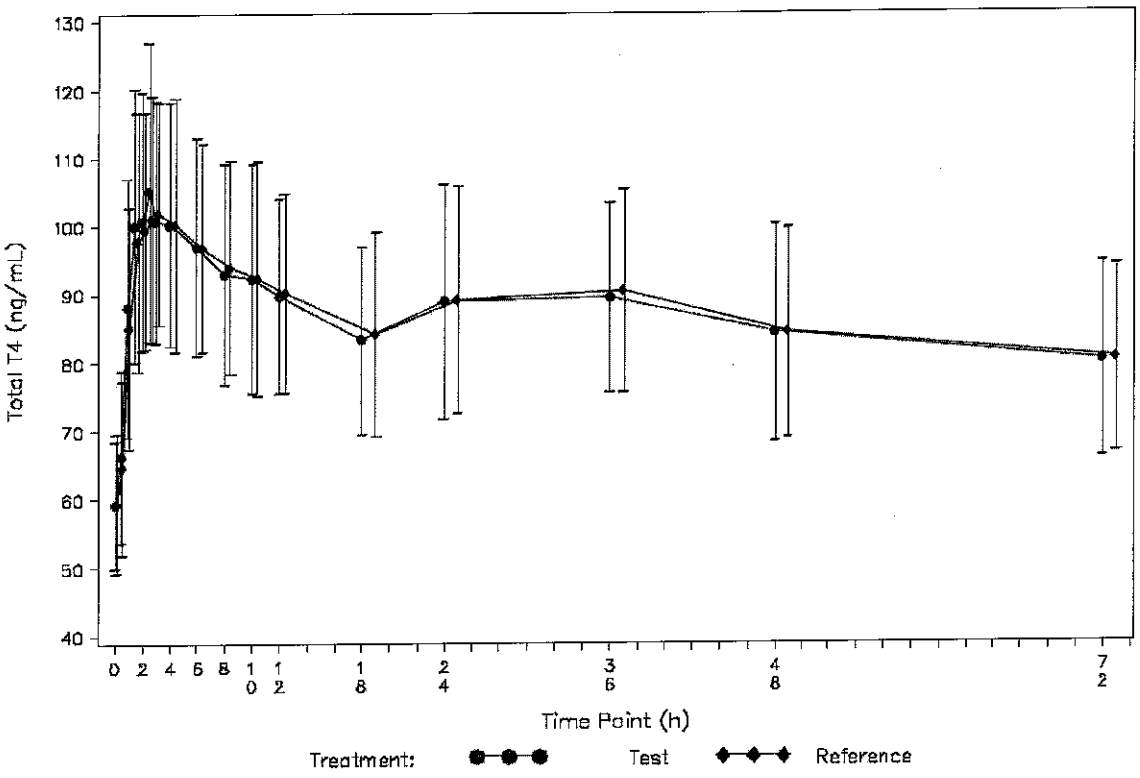
11.5 Pharmacokinetic Evaluation

11.5.1 Presentation and Evaluation of Plasma Concentrations

Individual concentrations of total (endogenous plus drug related) 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 both 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 both treatments on a linear and a 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 both 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 both treatments on a linear and a semi-logarithmic scale. Spaghetti plots of all subjects by treatment are presented on linear and semi-log 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.

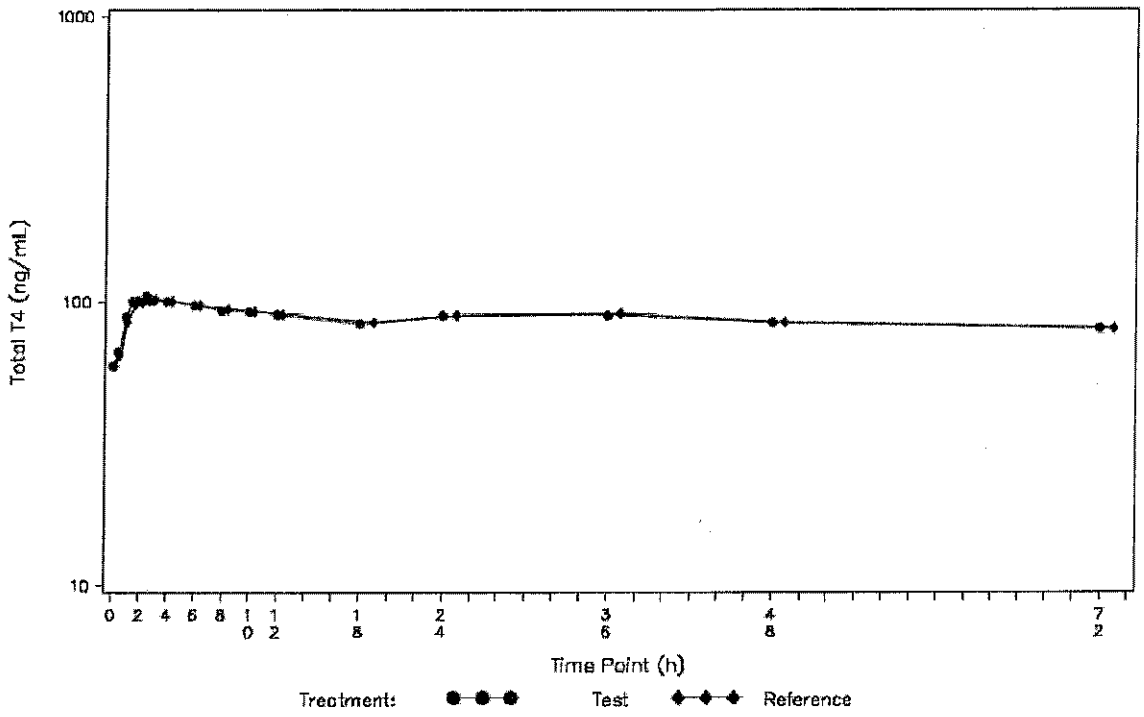
Figure 11.1 **Arithmetic Mean (± Standard Deviation) Plasma Total T4 versus Nominal Time on Linear Scale following 600 µg Levothyroxine (PK Population)**



Subjects were excluded from the PK Population.
Test: 600 µg (3*200 µg tablets) levothyroxine new formulation.
Reference: 600 µg (3*200 µg tablets) levothyroxine old formulation.

Source: Section 15.4, Figure 15.4.2.1

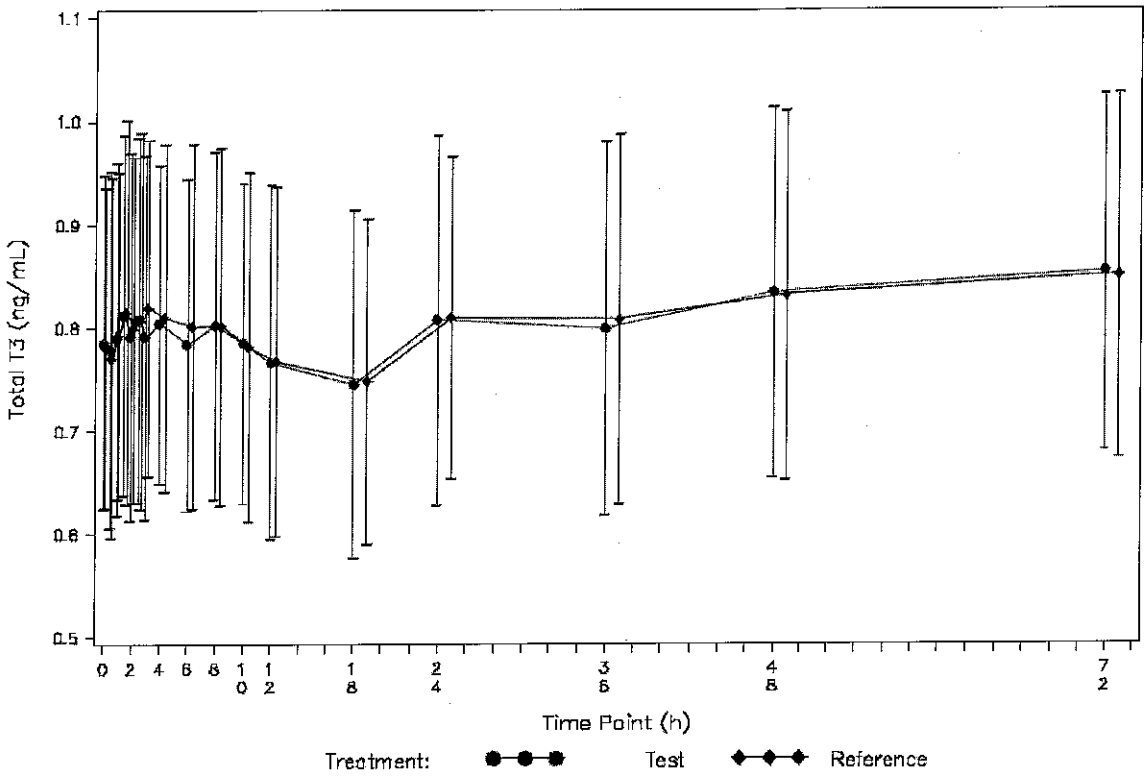
Figure 11.2 **Arithmetic Mean Plasma Total T4 versus Nominal Time on Semi-logarithmic Scale following 600 µg Levothyroxine (PK Population)**



Subjects are excluded from the PK Population.
Test: 600 µg (3*200 µg tablets) levothyroxine new formulation.
Reference: 600 µg (3*200 µg tablets) levothyroxine old formulation.

Source: Section 15.4, Figure 15.4.2.2

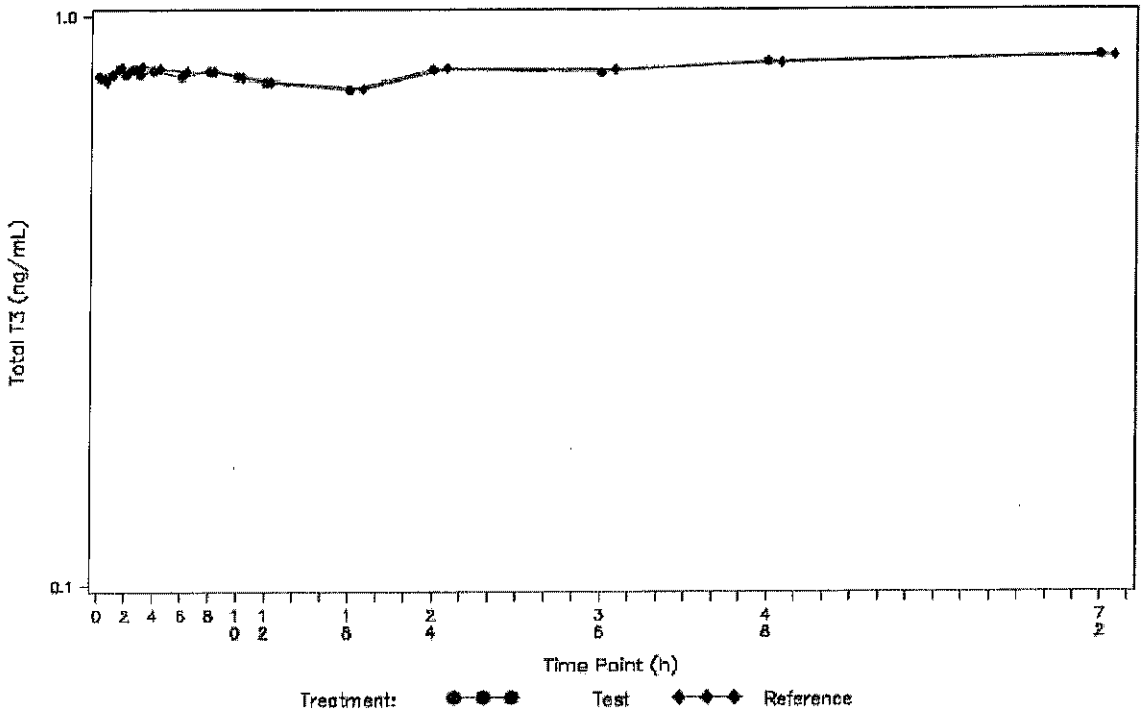
Figure 11.3 **Arithmetic Mean (± Standard Deviation) Plasma Total T3 versus Nominal Time on Linear Scale following 600 µg Levothyroxine (PK Population)**



Subjects [illegible] were excluded from the PK Population.
Test: 600 µg (3*200 µg tablets) levothyroxine new formulation.
Reference: 600 µg (3*200 µg tablets) levothyroxine old formulation.

Source: Section15.4, 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.
Test: 600 µg (3*200 µg tablets) levothyroxine new formulation.
Reference: 600 µg (3*200 µg tablets) levothyroxine old formulation.

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). 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.

NOTE: The secondary PK parameter λ_Z was non-estimable due to one or all of the following reasons:

1. The duration of time over which λz is estimated was less than twice the subsequently estimated $t_{½}$.
2. The adjusted regression coefficient (R^2adj) was less than 0.90.
3. The AUC%extrap was greater than 20%.

4. Visual inspection did not support the conclusion that the regression line is representative of the actual decline in the log concentration-time curve.

Due to non-estimation of λ_Z all parameters relating to λ_Z ($AUC_{0-\infty,adj}$, $AUC_{extra,adj}$, $t_{½}$, CL/f and Vz/f) were not estimated.

Statistical analysis of primary PK parameters

The results of the statistical analysis for primary PK parameter comparisons for total T4 of $AUC_{0-72,adj}$ 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 15.4.3.1.1 and for C_{max} and AUC_{0-72} in Figure 15.4.3.1.2. Box plots of total T3 C_{max} and AUC_{0-72} by treatment are presented in Section 15.4, Figure 15.4.3.1.3.

The geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ following administration of levothyroxine new formulation and levothyroxine old formulation were 99.3 and 101.7, respectively. Since the corresponding 90% CIs were within the predefined "strongest condition (third set)" BE margin of 0.90 to 1.11 for $AUC_{0-72,adj}$ and $C_{max,adj}$, as set by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France, all three bioequivalence tests were successful (Table 11.2). The PK parameters for total T4 are summarized in Table 11.3.

The median t_{max} values for the two products were comparable.

Table 11.2 **Summary of ANOVA of Primary Pharmacokinetic Parameters for Baseline-Adjusted T4 (Pharmacokinetic Population)**

Parameter	Treatment	N	Geo-LSMean	Ratio (Test/Ref) (%)	90% CI of Ratio	Intra-CV (%)
$AUC_{0-72,adj}$ (hr*ng/mL)	Test	204	1852.079	99.3	95.6 - 103.2	23.7
	Reference	204	1864.359			
$C_{max,adj}$ (ng/mL)	Test	204	53.5473	101.7	98.8 - 104.6	17.7
	Reference	204	52.6736			

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; Geo-LSMean= Geometric Least Square Mean; N = Number of subjects included in the analysis.

Subjects [redacted] were excluded from the PK Population.

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

Source: Section 15.4, Table 15.4.3.1

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

	Statistic	$AUC_{0-72,adj}$ * (hr*ng/mL)	$C_{max,adj}$ (ng/mL)
Test	n (missing)	204 (0)	204 (0)
	Mean (SD)	1975.81 (626.137)	55.3788 (15.93241)
	Geo Mean (95% CI)	1851.94 (1751.43;1958.22)	53.5498 (51.7064;55.4589)
	Geo CV (CV%)	42.1 (31.7)	25.8 (28.8)
	SEM	43.838	1.11549
	Median	1944.15	53.6550
	Min; Max	140.4; 3749.7	27.520; 191.233
Reference	n (missing)	204 (0)	204 (0)
	Mean (SD)	1976.87 (619.892)	54.1358 (12.72064)
	Geo Mean (95% CI)	1865.11 (1772.77;1962.25)	52.6806 (50.9997;54.4170)
	Geo CV (CV%)	38.1 (31.4)	23.8 (23.5)
	SEM	43.401	0.89062
	Median	1915.95	52.4765
	Min; Max	253.5; 3466.1	28.300; 102.830

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

* $AUC_{(0-tlast)}$ was used for Test subjec and Reference Subjects . 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 15.4.1.1.2

Statistical analysis of secondary PK parameters

The results of the statistical analysis for secondary PK parameter comparisons for total T3 of AUC_{0-72} and C_{max} and for total T4, AUC_{0-72} 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 T4 and 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 new formulation and levothyroxine old formulation were 99.7 and 99.9, respectively.

The geometric LS mean ratios for total T4 AUC_{0-72} and C_{max} following administration of levothyroxine new formulation and levothyroxine old formulation were 99.7 and 100.6, respectively.

The PK parameters for total T4 and T3 are summarized in Table 11.5 and Table 11.6, respectively. The total T3 median t_{max} values for the two products were comparable.

Table 11.4 Summary of ANOVA of Secondary Pharmacokinetic Parameters for T4 and T3 (Pharmacokinetic Population)

Analyte	Parameter	Treatment	N	Geo-LSMean	Ratio (Test/Ref) (%)	90% CI of Ratio	Intra-CV (%)
T3	AUC_{0-72} (hr*ng/mL)	Test	204	57.1222	99.7	98.8 - 100.6	5.5
		Reference	204	57.2855			
	C_{max} (ng/mL)	Test	204	0.9711	99.9	98.5 - 101.3	8.6
		Reference	204	0.9718			
T4	AUC_{0-72} (hr*ng/mL)	Test	204	6169.484	99.7	98.8 - 100.6	5.5
		Reference	204	6190.588			
	C_{max} (ng/mL)	Test	204	113.0876	100.6	99.2 - 102.0	8.5
		Reference	204	112.4192			

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; Geo-LSMean = Geometric Least Square Mean;
N = Number of subjects included in the analysis.

Subjects 1 [illegible] 7 were excluded from the PK Population.

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

Source: Section 15.4, Table 15.4.3.2

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

	Statistic	AUC_{0-72} * (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-48} (hr*ng/mL)	t_{max} (hr)
Test	n (missing)	204 (0)	204 (0)	204 (0)	204 (0)
	Mean (SD)	6241.58 (943.948)	114.633 (19.6367)	4270.49 (635.849)	
	Geo Mean (95% CI)	6169.49 (6039.61;6302.16)	113.091 (110.567;115.672)	4222.26 (4134.18;4312.22)	
	Geo CV (CV%)	15.5 (15.1)	16.5 (17.1)	15.4 (14.9)	
	SEM	66.090	1.3748	44.518	
	Median	6190.50	113.050	4267.10	2.500
	Min; Max	3839.7; 9155.7	73.78; 250.80	2495.9; 6296.7	1.00; 71.52
Reference	n (missing)	204 (0)	204 (0)	204 (0)	204 (0)
	Mean (SD)	6258.71 (922.975)	113.635 (16.6874)	4286.84 (630.777)	
	Geo Mean (95% CI)	6190.28 (6063.65;6319.55)	112.415 (110.143;114.733)	4239.73 (4152.55;4328.75)	
	Geo CV (CV%)	15.1 (14.7)	14.9 (14.7)	15.1 (14.7)	
	SEM	64.621	1.1683	44.163	
	Median	6271.72	113.300	4325.12	3.000
	Min; Max	3710.1; 8991.9	74.70; 156.50	2381.0; 6186.7	1.00; 48.98

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 λ_z were presented for individuals but excluded from summary statistics.

* $AUC_{(0\text{-last})}$ was used for Test subjec[illegible] and Reference Subjects 1[illegible], 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 15.4.1.1.2

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)
Test	n (missing)	204 (0)	204 (0)	204 (0)	204 (0)
	Mean (SD)	38.077 (7.1285)	58.130 (10.7231)	0.9891 (0.18755)	
	Geo Mean (95% CI)	37.402 (36.428;38.402)	57.137 (55.679;58.634)	0.9713 (0.9457;0.9975)	
	Geo CV (CV%)	19.3 (18.7)	18.9 (18.4)	19.5 (19.0)	
	SEM	0.4991	0.7508	0.01313	
	Median	38.140	57.591	0.9735	10.000
	Min; Max	24.48; 54.62	37.27; 84.00	0.602; 1.490	0.00; 73.50
Reference	n (missing)	204 (0)	204 (0)	204 (0)	204 (0)
	Mean (SD)	38.282 (7.0973)	58.281 (10.7196)	0.9893 (0.18680)	
	Geo Mean (95% CI)	37.616 (36.644;38.613)	57.295 (55.841;58.788)	0.9719 (0.9468;0.9976)	
	GeoCV (CV%)	19.1 (18.5)	18.8 (18.4)	19.1 (18.9)	
	SEM	0.4969	0.7505	0.01308	
	Median	38.330	58.189	0.9920	9.159
	Min; Max	23.76; 53.89	35.88; 85.45	0.627; 1.630	0.00; 72.82

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.

*: $AUC_{(0-tlast)}$ was used for numerous subjects Test and Reference (see 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 new formulation of levothyroxine (Test) was determined to be bioequivalent to the old formulation of levothyroxine (Reference), in healthy subjects, as the geometric LS mean ratios for total T4 $AUC_{0-72,adj}$ and $C_{max,adj}$ were 99.3 and 101.7, respectively. Since the corresponding 90% CIs were within the predefined "strongest condition (third set)" BE margin of 0.90 to 1.11 for $AUC_{0-72,adj}$ and $C_{max,adj}$, as set by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France, all three bioequivalence tests were successful.

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 204 subjects received both formulations of IMP as planned per protocol, resulting in a total 1200 µg levothyroxine dose exposure.

Twelve (12) subjects discontinued the trial before receiving their complete assigned sequence (Appendix 16.2, Listing 16.2.1.2).

In total, 7 subjects were exposed to 600 µg old formulation (Reference) only:

- Subject – Withdrawn due to AE (moderate sinus tachycardia, considered unrelated to IMP)
- Subject – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen [See Appendix 16.1.1.5, NTF #7])
- Subject – Withdrawn due to protocol non-compliance; prohibited concomitant medication (Neo-Angin)
- Subject – Withdrawal by subject due to AEs found to be personally intolerable
- Subject – Withdrawn due to AEs (mild dizziness, mild nausea, and moderate diarrhea, all considered unrelated to IMP)
- Subject – Withdrawn due to protocol non-compliance; positive urine drug screen
- Subject – Withdrawal by subject; private reason

In total, 5 subjects were exposed to 600 µg new formulation (Test) only:

- Subject – Withdrawn due to protocol non-compliance; prohibited concomitant medication (ibuprofen)
- Subject – Withdrawal by subject due to AEs found to be personally intolerable
- Subject – Withdrawn due to AE (severe elevated CPK, considered unrelated to IMP)
- Subject – Protocol non-compliance; erroneously included in the trial
- Subject – Withdrawn due to SAE (moderate otitis media, considered unrelated to IMP)

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 16.1.

12.2.1 Brief Summary of Adverse Events

There were no deaths reported during the trial. Two (2) subjects reported SAEs during the trial; Subject had severe radius fracture and Subject ad moderate otitis media; both events resulting in withdrawal from the trial. In addition, 4 subjects were withdrawn from the trial due to AE(s); Subject noderate sinus tachycardia), Subject (mild dizziness, moderate diarrhoea, and mild nausea), Subject moderate depressed mood), and Subject severe increased blood CPK) (see Section 15.3.3 for further details).

Overall, the number of subjects experiencing at least one TEAE was similar for both the new and the old formulations of levothyroxine (30.1 % of subjects [Test] compared with 28.9% of subjects [Reference], with 118 events [Test] compared with 165 events [Reference]). Of the 283 reported TEAEs, just over half (154 [54.4%]) were considered related to IMP (67 events [Test] compared with 87 events [Reference]).

The most commonly reported TEAEs were within the SOC "Nervous System Disorders", with the most commonly reported TEAE being headache (24 [11.5%] subjects with 35 events [Test] compared with 26 [12.3%] subjects with 44 events [Reference]). A similar trend was observed for drug-related TEAEs, with headache the most frequently reported drug-related event (16 [7.7%] subjects with 22 events [Test] compared with 16 [7.6%] subjects with 26 events [Reference]).

All TEAEs were resolved by the end of the trial. However, subjects who had a change in severity had outcomes indicated as "unknown", per Study Data Tabulation Model (SDTM) method. The following subject had AE resolution indicated as "unknown" for AEs that worsened in severity: Subjects asopharyngitis), (headache), (headache), (headache), (headache), (headache). Subjects who had "unknown" AE resolution for AEs that improved in severity included: Subject nasopharyngitis), eadache, dizziness), and (musculoskeletal discomfort).

12.2.2 Display of Adverse Events

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

	Test (N = 209)	Reference (N = 211)	Overall (N = 216)
No. of TEAEs	**E**	**E**	**E**
Any TEAEs	118	165	283
Serious TEAEs	2	0	2
TEAEs Resulting in Discontinuation	3	4	7
TEAEs Of Severe Intensity	2	0	2
IMP-related TEAEs	67	87	154
No. of Subjects Experiencing TEAEs	**n (%)**	**n (%)**	**n (%)**
Any TEAEs	63 (30.1%)	61 (28.9%)	98 (45.4%)
Serious TEAEs	2 (1.0%)	0	2 (0.9%)
TEAEs Resulting in Discontinuation	3 (1.4%)	2 (0.9%)	5 (2.3%)
TEAEs Of Severe Intensity	2 (1.0%)	0	2 (0.9%)
IMP-related TEAEs	35 (16.7%)	39 (18.5%)	61 (28.2%)

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

Test: New formulation
Reference: Old formulation

Source: Appendix 16.2, Listing 16.2.7.2 and Section 15.3, 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 Reported in ≥1% of Subjects in Any Treatment Group by Treatment, System Organ Class, and Preferred Term (Safety Population)**

System Organ Class Preferred Term	Test (N = 209)			Reference (N = 211)			Total (N = 216)		
	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	63	(30.1%)	118	61	(28.9%)	165	98	(45.4%)	283
Cardiac Disorders	2	(1.0%)	3	4	(1.9%)	5	6	(2.8%)	8
Palpitations	2	(1.0%)	3	3	(1.4%)	4	5	(2.3%)	7
Gastrointestinal Disorders	14	(6.7%)	22	14	(6.6%)	29	24	(11.1)	51
Abdominal Pain	5	(2.4%)	9	3	(1.4%)	7	7	(3.2)	16
Diarrhoea	6	(2.9%)	6	9	(4.3%)	10	13	(6.0%)	16
Nausea	3	(1.4%)	3	4	(1.9%)	5	7	(3.2%)	8
Vomiting	-	-	-	3	(1.4%)	4	3	(1.4%)	4
General Disorders and Administration Site Conditions	8	(3.8%)	8	6	(2.8%)	8	13	(6.0%)	16
Catheter Site Phlebitis	3	(1.4%)	3	1	(0.5%)	1	4	(1.9%)	4
Fatigue	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Feeling Hot	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Infections and Infestations	17	(8.1%)	19	18	(8.5%)	20	33	(15.3%)	39
Nasopharyngitis	10	(4.8%)	11	12	(5.7%)	14	22	(10.2%)	25
Rhinitis	2	(1.0%)	2	3	(1.4%)	3	5	(2.3%)	5
Tonsillitis	3	(1.4%)	3	-	-	-	3	(1.4%)	3
Musculoskeletal and Connective Tissue Disorders	3	(1.4%)	4	7	(3.3%)	16	9	(4.2%)	20
Back Pain	2	(1.0%)	2	2	(0.9%)	2	4	(1.9%)	4
Pain in extremity	-	-	-	3	(1.4%)	3	3	(1.4%)	3
Nervous System Disorders	27	(12.9%)	43	34	(16.1%)	56	54	(25.0%)	99
Dizziness	3	(1.4%)	4	7	(3.3%)	7	9	(4.2%)	11
Headache	24	(11.5%)	35	26	(12.3%)	44	45	(20.8%)	79
Somnolence	1	(0.5%)	1	3	(1.4%)	5	4	(1.9%)	6
Psychiatric Disorders	5	(2.4%)	5	2	(0.9%)	6	7	(3.2%)	11
Agitation	2	(1.0%)	2	1	(0.5%)	3	3	(1.4%)	5

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System Organ Class Preferred Term	Test (N = 209)			Reference (N = 211)			Total (N = 216)		
	n	(%)	E	n	(%)	E	n	(%)	E
Reproductive System and Breast Disorders	1	(0.5%)	1	5	(2.4%)	5	6	(2.8%)	6
Menstruation Delayed	-	-	-	3	(1.4%)	3	3	(1.4%)	3
Respiratory, Throracic, and Mediastinal Disorders	3	(1.4%)	3	8	(3.8%)	9	10	(4.6%)	12
Oropharyngeal Pain	1	(0.5%)	1	5	(2.4%)	5	6	(2.8%)	6
Vascular Disorders	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Hot Flush	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3

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

Test: New formulation
Reference: Old formulation

Source: Section 15.3, Table 15.3.1.1

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

System Organ Class Preferred Term	Test (N = 209)			Reference (N = 211)			Total (N = 216)		
	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	35	(16.7%)	67	39	(18.5%)	87	61	(28.2%)	154
Cardiac Disorders	2	(1.0%)	3	3	(1.4%)	4	5	(2.3%)	7
Palpitations	2	(1.0%)	3	3	(1.4%)	4	5	(2.3%)	7
Gastrointestinal Disorders	10	(4.8%)	15	7	(3.3%)	10	15	(6.9%)	25
Abdominal Pain	2	(1.0%)	5	2	(0.9%)	3	3	(1.4%)	8
Diarrhoea	5	(2.4%)	5	5	(2.4%)	5	8	(3.7%)	10
General Disorders and Administration Site Conditions	5	(2.4%)	5	5	(2.4%)	7	9	(4.2%)	12
Fatigue	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Feeling Hot	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Musculoskeletal and Connective Tissue Disorders	2	(1.0%)	3	5	(2.4%)	9	6	(2.8%)	12
Pain in extremity	-	-	-	3	(1.4%)	3	3	(1.4%)	3
Nervous System Disorders	19	(9.1%)	30	22	(10.4%)	36	38	(17.6%)	66
Dizziness	3	(1.4%)	4	5	(2.4%)	5	7	(3.2%)	9
Headache	16	(7.7%)	22	16	(7.6%)	26	31	(14.4%)	48
Somnolence	1	(0.5%)	1	3	(1.4%)	5	4	(1.9%)	6
Psychiatric Disorders	5	(2.4%)	5	2	(0.9%)	5	7	(3.2%)	10
Agitation	2	(1.0%)	2	1	(0.5%)	3	3	(1.4%)	5
Reproductive System and Breast Disorders	-	-	-	5	(2.4%)	5	5	(2.3%)	5
Menstruation Delayed	-	-	-	3	(1.4%)	3	3	(1.4%)	3
Respiratory, Thoracic, and Mediastinal Disorders	-	-	-	3	(1.4%)	3	3	(1.4%)	3
Skin and Subcutaneous Tissue Disorders	4	(1.9%)	4	5	(2.4%)	6	9	(4.2%)	10

System Organ Class Preferred Term	Test (N = 209)			Reference (N = 211)			Total (N = 216)		
	n	(%)	E	n	(%)	E	n	(%)	E
Vascular Disorders	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3
Hot Flush	2	(1.0%)	2	1	(0.5%)	1	3	(1.4%)	3

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

Test: New formulation
Reference: Old formulation

Source: Section 15.3, Table 15.3.1.3

Table 12.4 Summary of Drug-Related Treatment-Emergent Adverse Events by Intensity, Treatment, System Organ Class, and Preferred Term (Safety Population)

System Organ Class Preferred Term	Test (N = 209; E = 67)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	30	(14.4%)	46	13	(6.2%)	21	-	-	-
Cardiac Disorders	2	(1.0%)	3	-	-	-	-	-	-
Palpitations	2	(1.0%)	3	-	-	-	-	-	-
Gastrointestinal Disorders	10	(4.8%)	13	2	(1.0%)	2	-	-	-
Abdominal Discomfort	1	(0.5%)	1	-	-	-	-	-	-
Abdominal Pain	2	(1.0%)	3	2	(1.0%)	2	-	-	-
Abdominal Pain Lower	1	(0.5%)	1	-	-	-	-	-	-
Constipation	1	(0.5%)	1	-	-	-	-	-	-
Diarrhoea	5	(2.4%)	5	-	-	-	-	-	-
Eructation	1	(0.5%)	1	-	-	-	-	-	-
Nausea	1	(0.5%)	1	-	-	-	-	-	-
General Disorders and Administration Site Conditions	3	(1.4%)	3	2	(1.0%)	2	-	-	-
Fatigue	2	(1.0%)	2	-	-	-	-	-	-
Feeling Hot	-	-	-	2	(1.0%)	2	-	-	-
Sensation of Pressure	1	(0.5%)	1	-	-	-	-	-	-

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System Organ Class Preferred Term	Test (N = 209; E = 67)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Musculoskeletal and Connective Tissue Disorders	-	-	-	2	(1.0%)	3	-	-	-
Back Pain	-	-	-	1	(0.5%)	1	-	-	-
Musculoskeletal Pain	-	-	-	1	(0.5%)	1	-	-	-
Sensation Of Heaviness	-	-	-	1	(0.5%)	1	-	-	-
Nervous System Disorders	15	(7.2%)	19	7	(3.3%)	11	-	-	-
Disturbance In Attention	-	-	-	1	(0.5%)	1	-	-	-
Dizziness	3	(1.4%)	3	1	(0.5%)	1	-	-	-
Dysgeusia	1	(0.5%)	1	-	-	-	-	-	-
Headache	12	(5.7%)	14	6	(2.9%)	8	-	-	-
Paraesthesia	1	(0.5%)	1	-	-	-	-	-	-
Psychiatric Disorders	2	(1.0%)	2	3	(1.4%)	3	-	-	-
Agitation	1	(0.5%)	1	1	(0.5%)	1	-	-	-
Apathy	-	-	-	1	(0.5%)	1	-	-	-
Depressed Mood	-	-	-	1	(0.5%)	1	-	-	-
Libido Decreased	1	(0.5%)	1	-	-	-	-	-	-
Skin And Subcutaneous Tissue Disorders	4	(1.9%)	4	-	-	-	-	-	-
Hyperhidrosis	1	(0.5%)	1	-	-	-	-	-	-
Rash	1	(0.5%)	1	-	-	-	-	-	-
Rash Papular	1	(0.5%)	1	-	-	-	-	-	-
Swelling Face	1	(0.5%)	1	-	-	-	-	-	-
Vascular Disorders	2	(1.0%)	2	-	-	-	-	-	-
Hot Flush	2	(1.0%)	2	-	-	-	-	-	-

System Organ Class Preferred Term	Reference (N = 209; E = 87)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	37	(17.5%)	65	15	(7.1%)	22	-	-	-
Cardiac Disorders	2	(0.9%)	3	1	(0.5%)	1	-	-	-
Palpitations	2	(0.9%)	3	1	(0.5%)	1	-	-	-
Gastrointestinal Disorders	7	(3.3%)	8	2	(0.9%)	2	-	-	-
Abdominal Pain	1	(0.5%)	1	2	(0.9%)	2	-	-	-
Diarrhoea	5	(2.4%)	5	-	-	-	-	-	-
Dry Mouth	1	(0.5%)	1	-	-	-	-	-	-
Nausea	1	(0.5%)	1	-	-	-	-	-	-
General Disorders and Administration Site Conditions	3	(1.4%)	5	2	(0.9%)	2	-	-	-
Asthenia	1	(0.5%)	1	-	-	-	-	-	-
Axillary Pain	1	(0.5%)	1	-	-	-	-	-	-
Fatigue	-	-	-	1	(0.5%)	1	-	-	-
Feeling Hot	-	-	-	1	(0.5%)	1	-	-	-
Malaise	1	(0.5%)	1	-	-	-	-	-	-
Sensation of Pressure	1	(0.5%)	2	-	-	-	-	-	-
Infections and Infestations	-	-	-	1	(0.5)	1	-	-	-
Folliculitis	-	-	-	1	(0.5)	1	-	-	-
Musculoskeletal and Connective Tissue Disorders	3	(1.4%)	6	3	(1.4%)	3	-	-	-
Arthralgia	1	(0.5%)	3	1	(0.5%)	1	-	-	-
Myalgia	1	(0.5%)	1	1	(0.5%)	1	-	-	-
Pain In Extremity	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Nervous System Disorders	20	(9.5%)	27	8	(3.8%)	9	-	-	-
Dizziness	4	(1.9%)	4	1	(0.5%)	1	-	-	-
Headache	15	(7.1%)	19	7	(3.3%)	7	-	-	-
Somnolence	2	(0.9%)	4	1	(0.5%)	1	-	-	-

System Organ Class Preferred Term	Reference (N = 209; E = 87)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Psychiatric Disorders	2	(0.9%)	5	-	-	-	-	-	-
Agitation	1	(0.5%)	3	-	-	-	-	-	-
Depressed Mood	1	(0.5%)	1	-	-	-	-	-	-
Euphoric Mood	1	(0.5%)	1	-	-	-	-	-	-
Reproductive System And Breast Disorders	5	(2.4%)	5	-	-	-	-	-	-
Menstruation Delayed	3	(1.4%)	3	-	-	-	-	-	-
Menstruation Irregular	2	(0.9%)	2	-	-	-	-	-	-
Respiratory, Thoracic And Mediastinal Disorders	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Dyspnoea	-	-	-	1	(0.5%)	1	-	-	-
Epistaxis	1	(0.5%)	1	-	-	-	-	-	-
Throat Irritation	1	(0.5%)	1	-	-	-	-	-	-
Skin And Subcutaneous Tissue Disorders	3	(1.4%)	4	2	(0.9%)	2	-	-	-
Angioedema	1	(0.5%)	1	-	-	-	-	-	-
Dry Skin	2	(0.9%)	2	-	-	-	-	-	-
Hyperhidrosis	-	-	-	2	(0.9%)	2	-	-	-
Rash	1	(0.5%)	1	-	-	-	-	-	-
Vascular Disorders	-	-	-	1	(0.5%)	1	-	-	-
Hot Flush	-	-	-	1	(0.5%)	1	-	-	-

System Organ Class Preferred Term	Total (N = 209; E = 154)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Subject with at least one TEAE	56	(25.9%)	111	25	(11.6%)	43	-	-	-
Cardiac Disorders	4	(1.9%)	6	1	(0.5%)	1	-	-	-
Palpitations	4	(1.9%)	6	1	(0.5%)	1	-	-	-
Gastrointestinal Disorders	15	(6.9%)	21	3	(1.4%)	4	-	-	-
Abdominal Discomfort	1	(0.5%)	1	-	-	-	-	-	-

System Organ Class Preferred Term	Total (N = 209; E = 154)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Abdominal Pain	3	(1.4%)	4	3	(1.4%)	4	-	-	-
Abdominal Pain Lower	1	(0.5%)	1	-	-	-	-	-	-
Constipation	1	(0.5%)	1	-	-	-	-	-	-
Diarrhoea	8	(3.7%)	10	-	-	-	-	-	-
Dry Mouth	1	(0.5%)	1	-	-	-	-	-	-
Eructation	1	(0.5%)	1	-	-	-	-	-	-
Nausea	2	(0.9%)	2	-	-	-	-	-	-
General Disorders and Administration Site Conditions	5	(2.3%)	8	4	(1.9%)	4	-	-	-
Asthenia	1	(0.5%)	1	-	-	-	-	-	-
Axillary Pain	1	(0.5%)	1	-	-	-	-	-	-
Fatigue	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Feeling Hot	-	-	-	3	(1.4%)	3	-	-	-
Malaise	1	(0.5%)	1	-	-	-	-	-	-
Sensation of Pressure	1	(0.5%)	3	-	-	-	-	-	-
Infections and Infestations	-	-	-	1	(0.5%)	1	-	-	-
Folliculitis	-	-	-	1	(0.5%)	1	-	-	-
Musculoskeletal and Connective Tissue Disorders	3	(1.4%)	6	5	(2.3%)	6	-	-	-
Arthralgia	1	(0.5%)	3	1	(0.5%)	1	-	-	-
Back Pain	-	-	-	1	(0.5%)	1	-	-	-
Musculoskeletal Pain	-	-	-	1	(0.5%)	1	-	-	-
Myalgia	1	(0.5%)	1	1	(0.5%)	1	-	-	-
Pain In Extremity	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Sensation Of Heaviness	0		0	1	(0.5%)	1	-	-	-
Nervous System Disorders	33	(15.3%)	46	14	(6.5%)	20	-	-	-
Disturbance In Attention	-	-	-	1	(0.5%)	1	-	-	-
Dizziness	6	(2.8%)	7	2	(0.9%)	2	-	-	-
Dysgeusia	1	(0.5%)	1	-	-	-	-	-	-
Headache	27	(12.5%)	33	12	(5.6%)	15	-	-	-
Paraesthesia	1	(0.5%)	1	-	-	-	-	-	-

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System Organ Class Preferred Term	Total (N = 209; E = 154)								
	Mild			Moderate			Severe		
	n	(%)	E	n	(%)	E	n	(%)	E
Somnolence	2	(0.9%)	4	2	0.9%)	2	-	-	-
Psychiatric Disorders	4	(1.9%)	7	3	(1.4%)	3	-	-	-
Agitation	2	(0.9%)	4	1	(0.5%)	1	-	-	-
Apathy	-	-	-	1	(0.5%)	1	-	-	-
Depressed Mood	1	(0.5%)	1	1	(0.5%)	1	-	-	-
Euphoric Mood	1	(0.5%)	1	-	-	-	-	-	-
Libido Decreased	1	(0.5%)	1	-	-	-	-	-	-
Reproductive System And Breast Disorders	5	(2.3%)	5	-	-	-	-	-	-
Menstruation Delayed	3	(1.4%)	3	-	-	-	-	-	-
Menstruation Irregular	2	(0.9%)	2	-	-	-	-	-	-
Respiratory, Thoracic And Mediastinal Disorders	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Dyspnoea	-	-	-	1	(0.5%)	1	-	-	-
Epistaxis	1	(0.5%)	1	-	-	-	-	-	-
Throat Irritation	1	(0.5%)	1	-	-	-	-	-	-
Skin And Subcutaneous Tissue Disorders	7	(3.2%)	8	2	(0.9%)	2	-	-	-
Angioedema	1	(0.5%)	1	-	-	-	-	-	-
Dry Skin	2	(0.9%)	2	-	-	-	-	-	-
Hyperhidrosis	1	(0.5%)	1	2	(0.9%)	2	-	-	-
Rash	2	(0.9%)	2	-	-	-	-	-	-
Rash Papular	1	(0.5%)	1	-	-	-	-	-	-
Swelling Face	1	(0.5%)	1	-	-	-	-	-	-
Vascular Disorders	2	(0.9%)	2	1	(0.5%)	1	-	-	-
Hot Flush	2	(0.9%)	2	1	(0.5%)	1	-	-	-

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

Test: New formulation
Reference: Old formulation

Source: Appendix 16.2, Listing 16.2.7.1, Section 15.3, Table 15.3.1. and Table 15.3.1.3

12.2.3 Analysis of Adverse Events

Overall, the incidence of TEAEs was similar for the new and the old formulation levothyroxine. Furthermore, the number of subjects experiencing at least one TEAE was similar for both the new and the old formulations of levothyroxine (30.1% of subjects [Test] compared with 28.9% of subjects [Reference], with 118 events [Test] compared with 165 events [Reference]) (see Table 12.1).

The most commonly reported TEAEs were within the SOC "Nervous System Disorders", with the most commonly reported TEAE being headache (24 [11.5%] subjects with 35 events [Test] compared with 26 [12.3%] subjects with 44 events [Reference]) (see Table 12.2).

Of the 283 reported TEAEs, just over half (154 [54.4%]) were considered related to IMP (67 events [Test] compared with 87 events [Reference]) and a similar trend in terms of the most commonly reported TEAE was observed (headache was the most frequently reported drug-related event with 16 [7.7%] subjects with 22 events [Test] compared with 16 [7.6%] subjects with 26 events [Reference]) (see Table 12.3).

The majority of TEAEs were considered of mild (86 [39.8%] subjects with 191 events) or moderate severity (50 [23.1%] subjects with 90 events). Only two subjects (Subject [radius fracture] and Subject [elevated CPK]) experienced TEAEs considered of severe intensity; (see Section 15.3.3) (Section 15.3, Table 15.3.1.2). No drug-related TEAEs considered of severe intensity were reported during the trial (see Table 12.4; summary of drug-related TEAEs by intensity).

There were no deaths reported during the trial. Two (2) subjects reported SAEs during the trial; Subject had severe radius fracture and Subject had moderate otitis media; both events led to withdrawal from the trial. In addition, 4 subjects were withdrawn from the trial due to AE(s); Subject (moderate sinus tachycardia), Subjec (mild dizziness, moderate diarrhoea, and mild nausea), Subject (moderate depressed mood), and Subject (severe increased blood CPK) (Section 15.3.2, Table 15.3.2.1, Table 15.3.2.2, and Table 15.3.2.3; narratives are provided in Section 15.3.3).

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

Two SAEs were reported during the trial (see Section 12.3.2 for further details):

- Subject had an SAE of severe radius fracture considered unrelated to IMP. The event of radius fracture also led to withdrawal of the subject from the trial.
- Subject had an SAE of moderate otitis media considered unrelated to IMP. The event of otitis media also led to withdrawal of the subject from the trial.

12.3.1.3 Other Significant Adverse Events

In total, 6 subjects had either IMP withdrawn, or were withdrawn from trial due to AE/SAE (see Section 12.3.2 for further details):

- Subject was withdrawn from the trial due to an AE of moderate sinus tachycardia considered unrelated to IMP. **Note:** Assessment of non-relationship to IMP was based on the event commencing approximately 35 days after IMP administration.
- Subject was withdrawn from the trial due to AEs of mild dizziness, moderate diarrhoea, and mild nausea; all considered unrelated to IMP. **Note:** Assessment of non-relationship to IMP was based on the events commencing approximately 34 days after IMP administration.
- Subject had IMP withdrawn due to moderate depressed mood considered related to IMP. The event commenced approximately 5 days after IMP administration.
- Subject was withdrawn from the trial due to an AE of severe increased blood CPK considered unrelated to IMP. **Note:** Assessment of non-relationship to IMP was based on the event commencing approximately 35 days after IMP administration.

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

Narratives are provided in Section 15.3.3 for all SAEs and other significant AEs. The CRFs for deaths, other SAEs and withdrawals for AEs are presented in Appendix 16.3.1.

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 (Clinical 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 clinical 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) and Period 2 (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

Except for Subject 1541 (withdrawn due to elevated blood CPK) (see Section 15.3.3.1), there were no noteworthy 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 and Period 2 at 24 hours predose (Day -1), 50 minute predose (Day 1), and at 2, 3, 6, 12, 24, 48, and 72 hours postdose, and at the follow-up examination.

There were no notable differences within any individual subject, or mean or median values of the 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 individual subjects' weight or in mean or median values 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 at follow-up, as documented in Appendix 16.2, Listing 16.2.9.3. No abnormal physical examination was reported during the trial. 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 and Period 2 at 24 hours predose (Day -1), 50 minute 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, 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. Changes in QT interval of >30 msec occurred in a number of subjects, however, no individual change or abnormal individual ECG assessments were considered clinically relevant. Any significantly abnormal ECG findings were to be documented as a TEAE.

12.6 Safety Conclusions

Overall, treatment with both new and old formulations at a total dose of 600 µg levothyroxine as investigated in this trial can be considered as safe and well tolerated. The safety and tolerability were comparable between treatment periods.

Overall, the number of subjects experiencing at least one TEAE was similar for both the new and the old formulations of levothyroxine (30.1 % of subjects [Test] compared with 28.9% of subjects [Reference], with 118 events [Test] compared with 165 events [Reference]). Of the 283 reported TEAEs, just over half (154 [54.4%]) were considered related to IMP (67 events [Test] compared with 87 events [Reference]).

The most commonly reported TEAEs were within the SOC "Nervous System Disorders", with the most commonly reported TEAE being headache (24 [11.5%] subjects with 35 events [Test] compared with 26 [12.3%] subjects with 44 events [Reference]). A similar trend was observed for drug-related TEAEs, with headache the most frequently reported drug-related event (16 [7.7%] subjects with 22 events [Test] compared with 16 [7.6%] subjects with 26 events [Reference]).

There were no deaths reported during the trial. Two (2) subjects reported SAEs during the trial; Subject ad severe radius fracture considered unrelated to IMP, also leading to withdrawal from the trial, and Subject had moderate otitis media considered unrelated to IMP. In addition, 4 subjects were withdrawn from the trial due to AE(s); Subject (moderate sinus tachycardia considered unrelated to IMP), Subject (mild dizziness, moderate diarrhoea, and mild nausea; all considered unrelated to IMP), Subject (moderate depressed mood considered related to IMP), and Subject evere increased blood CPK considered unrelated to IMP).

All TEAEs were resolved by the end of the trial. However, subjects who had only a change in severity had outcomes indicated as "unknown", per SDTM method. The following subject had AE resolution indicated as "unknown" for AEs that worsened in severity: Subjects (nasopharyngitis), (headache), (headache), (headache), (headache), (headache). Subjects who had "unknown" AE resolution for AEs that improved in severity included: Subject (nasopharyngitis), (headache, dizziness), and (musculoskeletal discomfort).

None of the safety laboratory, vital sign or ECG parameters showed any relevant mean or median changes after treatment and none of the individual values were clinically significant.

13 Discussion and Overall Conclusions

The new formulation of levothyroxine (Test) was determined to be bioequivalent to the old formulation of levothyroxine (Reference), in healthy subjects, as the geometric LS mean ratios (Test/Reference) for total T4 $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ were 99.3 and 101.7, respectively. Since the corresponding 90% CIs were within the predefined "strongest condition (third set)" BE margin

of 0.90 to 1.11 for $AUC_{0-72,adj}$ and $C_{max,adj}$, as set by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France, all three bioequivalence tests were successful.

Overall, treatment with both formulations (new and old formulation) at a total dose of 600 µg levothyroxine as investigated in this trial can be considered as safe and well tolerated.

14 Reference List

There are no citations referenced in this clinical study report.

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

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

15.1 Demographic and Baseline Data

Table 15.1.1 Summary of Subject Disposition

Table 15.1.2 Demographic Data (Safety Population)

Merck Serono
EMR 200125-001
Table 15.1.1 Summary of Subject Disposition

	Status	Treatment Sequence 1 (N=108) n (%)	Treatment Sequence 2 (N=108) n (%)	Total (N=216) n (%)
Screened subjects				762
Randomized subjects	Yes	108 (100.0)	108 (100.0)	216 (100.0)
Subject treated	Yes	108 (100.0)	108 (100.0)	216 (100.0)
Subjects who completed the trial	Yes	103 (95.4)	101 (93.5)	204 (94.4)
	No	5 (4.6)	7 (6.5)	12 (5.6)
Subjects who terminated treatment earlier	Yes	5 (4.6)	7 (6.5)	12 (5.6)
	No	103 (95.4)	101 (93.5)	204 (94.4)
Reason for early treatment termination	Adverse Event	2 (1.9)	2 (1.9)	4 (1.9)
	Protocol Non-Compliance	2 (1.9)	3 (2.8)	5 (2.3)
	Withdrawal By Subject	1 (0.9)	2 (1.9)	3 (1.4)

N: The number of subjects dosed with at least one treatment in that treatment sequence, or the number subjects in the safety population for the total summary; n: The number of subjects in the specific category.
%: calculated using the number of subjects dosed with at least one treatment for each treatment sequence, or the number of subjects in the safety population for the total summary.
Treatment Sequence 1: Test/Reference; Treatment Sequence 2: Reference/Test.
Test: 600 µg (3*200 µg tablets) levothyroxine new formulation.
Reference: 600 µg (3*200 µg tablets) levothyroxine old formulation.

/project24/ep/blinded/e210899_merc/stats/versioncontrol/primary/scripts/program/main/TFL programs/Tables/Table 15.1.1.sas

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