
 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	1 of 68


STUDY TITLE	"Prospective, Single-dose, Randomized, Open-label, Crossover, Comparative Study to Establish the Bioequivalence between Levothyroxine's New Formulation vs. Levothyroxine's Approved Formulation (Eutirox® from Merck S.A. de C.V.) – Given Orally at Doses of 3 Tablets of 200 µg to healthy subjects"
Study code:	PPD /MS200125-0008
Sponsor:	Merck S.A. de C.V.
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 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	2 of 68

Content	Page
1. Introduction.....	3
1.1. Summary	3
1.2. Software used	3
1.3. Design and Analysis Methods	3
2. Study Element and Dosage Schedule.....	4
3. Results.....	4
3.1. Demographic Variables (Descriptive Statistics).....	4
3.2. Concentration's Individual Data vs Time	6
3.3. Concentration vs. Individual and Average Time (arithmetic and logarithmic scale).....	10
3.4. Descriptive Statistics of Biological Fluid Concentration Data as a Function of Time and Formulation.....	49
3.5. Pharmacokinetic Parameters	50
3.5.1. Individual Data and Descriptive Statistics of the Pharmacokinetic Parameters	50
4. Variance Analysis (ANOVA).....	53
5. Study Variability.....	54
6. Pharmacokinetic Parameters Outliers Identification.....	54
7. Bioequivalence Statistics	57
8. Statistical Plan Deviation	57
9. Discussion and Conclusion.....	57
10. Annexes	57
11. References.....	68
12. History of Changes	68

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	3 of 68

1. Introduction

1.1. Summary

To determine the bioavailability of two levothyroxine pharmaceutical forms, the *reference drug* (drug A: Eutirox® approved formulation) and the test drug (drug B: Eutirox® new formulation), in male and female healthy subjects, orally, in fasting state at a dose of 600 µg (3 tablets of 200 µg/mL) of each of the study products, and to establish bioequivalence.

The sample size proposed for this protocol was 44 male and female subjects (included allowance for drop-out to ensure 34 completers), who were randomized to each of the treatment sequences where the test and reference formulations were administered in two periods, separated by a 35-day wash-out period. One subject (subject 38) was positive for cannabinoids, prior to the second dosing; therefore, he was withdrawn from the study.

The statistical analysis to conclude the possible bioequivalence between both drugs is included in this report. This was carried out with 43 evaluable subjects (8 females and 35 males),

1.2. As per the sampling schedule, blood samples were collected from each subject and concentration of levothyroxine were determined from plasma. Software used


- Phoenix® WinNonlin® Version 8.2, Copyright © 1998-2018, Certara L.P. All rights reserved.

1.3. Design and Analysis Methods

For conducting the bioequivalence study, a 2-period and 2-sequence crossover-design was used. The estimation of an AUC_{0-48} could be determined with a 48-h sampling-time.

The pharmacokinetic analysis of plasma concentrations was made using the WinNonlin® software, for which a non-compartmental model and real-time were considered.

t_{max} and C_{max} values were obtained directly from the measurements made. The area under the curve of plasma concentrations from t_0 (dosing) to t_n (AUC_{n-t}) was estimated by means of the trapezoid method with linear interpolation. For the determination of the area under the curve from the last sampling time to the infinite time ($AUC_{t-\infty}$), the quotient of the last plasma concentration between the elimination constant was determined by linear regression using the sampling points from a terminal linear logarithm, which provided the best adjustment for a straight line. The $AUC_{0-\infty}$ was determined by the sum of the AUC_{0-t} and $AUC_{t-\infty}$. This value and, everything related to it, is shown for informative purposes only. Due to the sampling times used, it was not possible to determine at least the 80 % of the AUC. Therefore, it is a truncated design at 48 h. It is important to mention that all the pharmacokinetic and statistical results included in this report correspond to the corrected concentration values. Baseline uncorrected values are shown in the appropriate annex to this study report.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	4 of 68

The statistical analysis was performed with WinNonlin® software using least squares with the generalized linear model (GLM) and 90 % confidence intervals were estimated. The intra-subject studentized residual analysis for the pharmacokinetic parameters was made with Excel®.

The following model was used for the analysis:

$$Y_{ijkl} = \mu + S_k + V(S)_{i(k)} + P_j + F_l + e_{ijkl} \dots\dots (Chow \& Liu, 2009)$$

Where:

- Y_{ijkl} Is the response (pharmacokinetic parameters) in the i^{th} subject, the j^{th} period, the k^{th} sequence and the l^{th} treatment.
- μ Is the general mean.
- S_k Is the effect of the k^{th} sequence of administration.
- $V(S)_{i(k)}$ Is the subject's i^{th} effect on the k^{th} sequence is considered a random effect.
- P_j Is the period's j^{th} effect (or administration's phase).
- F_l Is the treatment or formulation's l^{th} effect.
- e_{ijkl} Is the experimental error, intra-subject variability, and it is a random effect assumed with normal distribution, mean zero, the constant and independent variance of the subject nested in the sequence.

Based on the error mean square determination and the geometric means determination, the estimation of the classical confidence intervals at 90 % for the test to reference ratio was made, in logarithmically-transformed previous data.

2. Study Element and Dosage Schedule

Table 1 shows a description of the drugs administered to the clinical research subjects.

Table 1. Study Drugs' Description

Information	Test drug (B)	Reference drug (A)
Drug substance name or analyte determined	Levothyroxine	Levothyroxine
Dosage Form	Tablets	Tablets
Trademark	Eutirox® new formulation	Eutirox® approved formulation

3. Results

3.1. Demographic Variables (Descriptive Statistics)

Tables 2 and 3 show the individual values and the descriptive statistics for the demographic variables of the subjects who were recruited in the study, respectively.


 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	5 of 68

Table 2. Individual data for demographic variables.

Subject	Sex	Age (years)	Weight (Kg)	Height (m)	BMI (Kg/m ²)	Sequence
1	Woman	27	61	1.68	21.6	BA
2	Man	28	80	1.76	25.8	BA
3	Woman	40	57.5	1.62	21.9	BA
4	Man	21	73	1.80	22.5	AB
5	Woman	26	65	1.56	26.7	AB
6	Man	29	79	1.82	23.8	BA
7	Man	31	70	1.78	22.1	AB
8	Man	22	58	1.66	21.0	AB
9	Man	22	67	1.78	21.1	AB
10	Woman	30	64	1.59	25.3	AB
11	Man	35	70	1.66	25.4	AB
12	Man	24	74.2	1.72	25.1	BA
13	Man	22	75.5	1.70	26.1	AB
14	Man	29	72	1.71	24.6	BA
15	Man	21	74	1.74	24.4	BA
16	Man	23	81	1.76	26.1	BA
17	Man	22	73	1.72	24.7	AB
18	Man	28	76	1.75	24.8	BA
19	Woman	51	55	1.56	22.6	AB
20	Man	20	55	1.63	20.7	BA
21	Man	21	66	1.68	23.4	BA
22	Man	28	76.5	1.88	21.6	AB
23	Man	20	72	1.72	24.3	BA
24	Man	24	55.5	1.60	21.7	AB
25	Man	34	71	1.75	23.2	AB
26	Man	24	75.5	1.83	22.5	AB
27	Man	21	84	1.80	25.9	BA
28	Woman	25	59	1.55	24.6	BA
29	Man	30	76	1.78	24.0	BA
30	Man	23	61	1.76	19.7	AB
31	Man	24	72	1.73	24.1	AB
32	Man	26	81	1.74	26.8	AB
33	Woman	22	52	1.58	20.8	AB
34	Man	22	61	1.65	22.4	AB


 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	6 of 68

Table 2. Individual data for demographic variables. (Continued)

Subject	Sex	Age (years)	Weight (Kg)	Height (m)	BMI (Kg/m ²)	Sequence
35	Man	30	69.5	1.80	21.5	AB
36	Man	22	52	1.60	20.3	BA
37	Man	27	65	1.68	23.0	BA
38	Man	27	67	1.74	22.1	BA
39	Woman	22	50	1.53	21.4	BA
40	Man	23	68	1.76	22.0	BA
41	Man	31	59	1.60	23.0	BA
42	Man	23	72	1.74	23.8	AB
43	Man	21	73	1.84	21.6	BA
44	Man	20	68	1.72	23.0	AB

Table 3. Descriptive statistics for demographic variables.

	Age (years)	Weight (Kg)	Height (m)	BMI (Kg/m ²)
Arithmetic Mean	25.93	67.87	1.71	23.26
Standard Deviation	5.93	8.75	0.09	1.86
%CV	22.86	12.89	5.09	7.98

3.2. Concentration's Individual Data vs Time

Levothyroxine plasma concentration data versus time, for each subject, as well as its mean value are shown in tables 4 and 5 for the reference and test drugs, respectively. Since this is an endogenous molecule, baseline levels are expected. Therefore, concentrations shown in this report correspond to the adjusted levels; i. e., the average value obtained from 3 pre-dose concentrations. The mean of the pre-doses values (corresponding to the times -0.5, -0.25 and 0.0) was subtracted from each of the individual values after administration. Any negative value obtained from the initial correction were designated as zero (0), for reference product (A), twenty seven (27) data were designated as zero, sixteen (16) cases, after the pre dose adjustment had concentration greater than zero. For the test product (B), twenty-five (25) data were designated as zero, eighteen (18) cases, after the pre dose adjustment had concentration greater than zero.

The unadjusted values, including pre-dose values used for baseline adjustment, are presented in Annex section


 PPD	ANALYTICAL UNIT														Issue	10-Mar-2020
															Version	1.0
	STATISTICAL DOCUMENT														Page	7 of 68

Table 4. Table of individual base line corrected concentrations corresponding to levothyroxine (reference drug [A]). Adjusted data. N = 43 subjects

Form	Volunteer	Time																							
		0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00
A	1	0.00	0.00	18.08	25.76	33.62	59.36	73.07	77.18	83.03	73.97	96.39	98.33	89.28	90.42	86.81	79.36	70.08	72.76	66.78	58.76	64.49	57.99	50.27	46.44
A	2	0.95	3.10	19.25	33.71	42.76	45.60	46.32	54.44	52.37	51.29	49.24	55.16	53.62	49.56	59.08	45.50	44.61	44.62	45.91	44.13	38.01	34.60	38.14	39.62
A	3	0.04	5.41	45.45	55.09	61.00	45.19	40.08	52.74	36.22	32.34	40.98	43.74	42.37	35.11	31.35	32.92	32.87	40.23	29.26	23.10	27.04	22.63	22.89	19.76
A	4	0.24	2.22	15.74	39.37	55.52	56.51	59.29	52.39	51.70	67.12	49.86	62.41	59.12	47.28	48.65	51.19	41.04	45.56	47.40	37.83	38.98	30.15	29.06	23.10
A	5	0.00	1.31	22.68	32.52	36.69	37.64	53.06	45.51	52.17	47.12	51.78	51.68	52.20	48.46	46.44	48.39	41.28	34.87	33.99	32.68	26.28	25.10	19.42	28.01
A	6	0.00	2.13	4.16	21.55	49.91	64.49	63.06	57.44	57.84	58.86	49.98	57.66	51.39	55.90	53.28	53.25	52.89	55.45	53.91	44.06	42.77	36.80	32.71	28.96
A	7	0.00	3.04	16.50	28.04	29.99	34.44	57.68	48.23	54.39	64.47	56.21	63.47	49.44	53.45	41.29	40.28	43.31	41.76	53.16	33.20	27.71	38.43	28.84	30.49
A	8	0.00	3.03	31.05	44.07	58.34	64.72	57.08	63.33	49.74	58.34	60.40	60.22	57.79	55.20	61.69	54.74	61.39	47.24	51.10	45.10	39.51	32.40	24.89	23.33
A	9	0.00	7.14	11.53	15.62	12.87	19.26	26.65	47.89	54.01	64.75	59.99	77.35	76.86	84.71	80.43	71.34	71.58	62.30	60.40	49.55	39.32	46.23	37.58	38.79
A	10	0.00	0.00	1.86	36.34	52.20	58.30	62.78	71.37	70.04	56.75	74.84	79.08	75.58	81.77	61.19	74.82	63.72	58.42	62.81	55.65	48.99	41.36	31.64	30.82
A	11	0.00	0.00	14.75	27.54	68.86	40.49	52.38	55.51	51.51	55.85	61.42	60.76	64.98	59.66	58.66	58.59	51.79	41.77	39.55	36.52	30.60	40.18	43.35	25.62
A	12	0.00	6.19	26.38	50.30	54.73	63.00	69.82	61.41	63.27	65.19	60.02	65.76	56.83	51.26	52.95	55.53	54.36	47.84	57.10	45.06	42.70	40.25	32.52	29.49
A	13	0.00	7.13	29.24	59.72	46.49	62.06	60.77	60.84	58.21	50.85	40.75	60.79	53.75	54.37	50.33	55.28	52.64	41.59	48.04	47.04	35.90	42.43	43.72	34.56
A	14	1.25	3.33	24.00	43.40	49.00	61.37	54.90	63.59	57.32	59.44	62.16	63.16	56.87	69.84	61.81	55.00	58.65	55.78	58.93	29.87	48.92	40.85	32.00	31.63
A	15	0.22	0.00	5.43	0.00	13.29	25.09	22.85	30.79	43.23	41.27	36.76	40.83	44.14	40.51	51.95	42.80	39.20	34.20	31.48	41.79	36.83	23.05	15.76	25.49
A	16	0.00	8.00	26.69	33.12	35.23	55.66	56.88	66.06	67.07	61.11	56.07	49.65	49.91	58.86	48.93	60.42	55.01	53.01	37.59	40.86	36.36	30.10	20.19	29.89
A	17	0.00	4.78	11.47	14.59	24.96	42.11	66.14	60.41	54.70	50.91	59.30	62.16	46.06	52.30	58.93	50.21	49.20	54.71	54.37	43.89	41.10	36.45	23.89	14.73
A	18	0.00	2.12	33.99	44.44	52.12	58.14	63.81	61.51	60.94	67.71	63.07	61.82	58.70	56.20	55.17	58.14	56.91	47.85	48.84	42.38	45.57	39.15	29.68	29.96
A	19	0.09	4.33	43.58	51.94	49.37	59.52	60.20	58.16	64.98	60.57	49.71	73.11	55.00	52.70	51.18	55.10	42.80	45.87	49.52	39.35	39.24	50.09	35.00	34.00
A	20	0.00	6.32	34.84	68.56	71.10	66.47	74.56	67.80	74.61	68.09	68.12	67.57	64.24	63.56	67.60	67.08	59.46	56.90	60.97	49.31	44.45	48.93	49.42	37.82
A	21	0.00	2.99	27.13	56.35	53.46	61.00	68.61	64.96	62.32	62.87	68.94	65.30	65.99	60.89	58.27	57.45	43.04	48.99	54.87	38.81	35.62	40.28	34.92	32.53
A	22	0.00	0.00	5.47	10.20	13.43	18.87	24.83	24.02	34.94	35.63	30.05	32.89	50.81	27.92	26.94	30.33	31.08	30.71	24.96	31.68	24.79	24.17	23.12	14.56
A	23	0.00	2.03	36.97	47.98	46.30	49.23	47.93	48.24	44.80	50.16	45.70	48.89	45.05	37.36	44.33	40.72	37.82	34.38	36.27	28.80	21.73	25.25	26.87	19.00
A	24	0.00	0.00	23.24	45.18	53.90	75.62	66.74	63.45	71.36	69.87	65.15	66.94	55.11	53.43	49.25	55.26	46.69	41.32	41.62	34.62	35.28	39.99	22.34	19.02
A	25	0.00	0.00	32.21	53.96	47.94	53.88	29.00	43.37	37.39	37.45	41.45	59.68	41.38	45.81	35.74	42.69	43.87	40.04	38.76	29.82	26.81	24.73	26.95	26.58
A	26	3.32	4.41	10.30	27.04	37.86	49.47	40.82	46.52	36.61	42.67	34.47	39.69	35.68	30.91	36.29	43.15	35.12	42.01	51.65	37.41	33.72	36.45	34.34	25.45
A	27	0.65	0.00	17.31	34.50	41.84	42.94	48.06	46.90	44.91	46.60	42.51	47.33	40.83	33.39	36.48	42.11	42.24	39.78	37.72	36.08	30.58	29.83	23.78	23.70
A	28	0.00	5.77	15.58	47.72	61.94	68.74	121.16	65.30	80.02	71.97	68.57	57.51	63.91	52.81	77.31	46.12	54.33	56.03	52.65	51.64	51.99	41.44	56.27	41.17
A	29	0.74	12.68	11.63	31.89	56.96	65.35	39.34	55.86	54.04	41.67	55.05	53.18	50.24	46.79	41.93	42.84	36.96	36.07	49.20	36.21	31.70	41.18	28.21	20.81
A	30	1.66	4.82	24.29	33.91	29.16	52.40	32.50	68.08	55.06	63.72	53.08	58.09	57.83	52.74	51.52	49.09	43.36	40.22	48.23	42.74	42.01	40.28	48.76	37.67
A	31	0.00	4.57	9.30	34.95	34.96	45.12	39.65	40.99	39.33	39.99	38.43	45.02	49.54	48.10	36.09	23.02	30.45	31.71	32.90	17.75	18.83	27.31	10.97	15.01
A	32	3.18	6.59	50.40	53.47	61.04	43.57	39.55	38.07	39.94	44.61	36.54	42.04	36.95	34.54	35.68	39.39	33.26	34.52	34.90	38.95	25.06	30.26	30.86	30.84
A	33	3.27	8.57	37.56	45.26	57.55	76.35	71.51	77.89	82.25	76.90	79.66	86.93	85.56	73.60	81.06	85.56	65.23	73.26	64.06	59.41	64.31	50.72	58.18	55.61
A	34	0.00	0.00	9.17	12.53	22.41	25.61	40.22	48.91	60.92	47.62	48.59	57.50	43.24	44.53	38.47	42.39	36.95	27.96	40.18	31.81	30.39	36.36	22.47	26.44
A	35	0.00	3.18	38.87	59.17	59.46	54.39	53.87	48.81	45.85	45.87	46.05	54.19	44.10	31.48	43.13	45.66	41.79	43.02	47.03	48.06	34.11	39.58	36.52	31.71
A	36	3.49	4.87	51.03	62.19	56.79	52.03	65.33	74.82	61.33	64.84	57.09	59.12	52.43	54.17	51.54	51.65	46.36	45.53	41.02	42.03	35.39	15.52	29.58	30.34
A	37	0.00	0.00	36.37	47.22	60.30	55.05	54.15	57.78	59.60	55.54	52.78	54.60	52.35	47.95	49.44	53.06	53.52	47.45	48.10	38.77	42.02	36.21	33.56	29.36
A	39	2.71	7.98	81.95	90.27	85.98	100.38	86.78	82.14	79.05	82.19	83.16	89.05	86.73	78.73	73.45	85.70	79.63	77.27	68.79	68.89	64.91	51.98	47.47	49.11
A	40	9.72	5.85	19.24	30.92	38.85	73.16	76.71	80.95	81.27	85.18	84.23	90.55	87.54	83.46	86.80	64.95	86.35	79.86	79.95	70.52	66.20	48.16	49.29	34.43
A	41	0.00	3.33	36.99	51.23	57.14	52.66	64.01	64.35	65.86	59.42	61.18	62.57	72.78	52.99	46.20	40.05	52.40	46.42	48.37	39.45	32.90	46.04	27.53	30.69
A	42	0.00	2.16	6.44	17.24	24.25	20.91	22.88	30.64	39.15	40.03	40.06	44.51	42.99	38.71	35.24	35.24	32.46	34.83	33.72	23.89	22.85	25.08	27.12	27.15
A	43	0.00	9.75	0.00	51.13	47.33	44.91	48.87	41.58	43.98	45.80	46.19	49.97	43.30	45.06	44.44	39.67	40.08	35.99	44.86	30.43	31.86	29.09	34.59	23.61
A	44	1.00	4.89	22.37	35.41	45.79	51.87	48.87	48.92	46.34	44.27	43.36	50.47	44.87	40.22	41.19	38.69	39.78	35.92	30.08	30.31	30.37	27.85	26.68	26.28
Arithmetic Mean		0.76	3.81	24.20	39.66	46.34	52.39	54.72	56.28	56.36	56.07	55.10	59.79	55.98	52.95	52.29	51.27	48.73	46.65	47.46	40.66	37.87	36.39	32.59	29.62


 PPD	ANALYTICAL UNIT										Issue	10-Mar-2020
											Version	1.0
	STATISTICAL DOCUMENT										Page	8 of 68

Table 5. Table of individual base line corrected concentrations corresponding to levothyroxine (test drug [B]). Adjusted data. N = 43 subjects

Form	Volunteer	Time																											
		0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00				
B	1	0.36	2.79	17.91	31.20	40.46	46.99	54.85	69.43	65.89	84.97	82.64	75.96	75.05	74.65	73.40	58.34	55.21	49.74	58.80	50.79	43.11	40.03	41.77	21.93				
B	2	0.00	3.77	34.31	49.71	55.52	52.76	57.53	48.95	52.17	46.50	47.92	52.87	49.14	47.08	40.16	42.16	59.26	36.21	33.32	27.19	30.20	28.83	23.76	18.41				
B	3	0.00	4.56	42.17	56.41	39.98	44.50	35.97	34.31	41.07	39.67	24.39	34.59	48.09	36.40	36.96	24.59	25.43	20.77	6.44	12.78	13.72	20.74	27.56	24.82				
B	4	0.00	5.29	16.63	39.25	54.71	55.69	63.95	60.72	55.17	54.09	53.89	52.11	47.96	42.13	41.46	42.58	43.26	40.44	41.92	37.87	37.55	30.28	31.89	19.31				
B	5	0.00	3.60	5.15	9.40	9.21	13.56	15.13	20.55	12.57	26.79	23.36	37.49	41.91	59.02	53.80	47.48	40.41	42.82	37.95	30.38	23.75	29.37	27.62	24.90				
B	6	0.24	0.00	4.78	15.29	14.54	16.90	16.01	25.48	28.34	33.35	39.92	48.64	45.53	40.81	33.57	38.87	34.07	33.18	29.28	28.03	30.25	25.72	17.88	23.41				
B	7	0.53	8.73	36.06	41.76	49.65	54.84	69.43	55.04	55.85	42.18	45.25	46.82	50.46	45.27	55.71	51.90	50.42	49.95	43.06	45.35	38.26	40.62	36.32	39.65				
B	8	0.00	22.49	48.49	61.64	66.18	57.51	58.67	60.60	59.30	53.33	53.95	60.19	52.90	54.45	47.68	53.99	49.81	44.60	40.06	38.55	37.62	31.20	44.63	31.79				
B	9	2.13	0.00	25.40	43.56	69.04	86.57	93.54	87.80	97.45	98.59	101.74	104.57	94.06	96.22	97.71	95.00	96.72	80.81	73.49	63.24	63.56	42.01	56.25	35.96				
B	10	0.00	1.43	20.93	48.51	67.80	73.54	79.88	97.25	96.00	79.94	74.34	82.17	85.29	84.34	89.85	70.20	82.59	77.27	76.82	57.96	74.36	52.40	44.80	41.12				
B	11	0.39	4.73	23.43	59.64	67.87	71.66	67.73	72.27	69.20	62.75	61.72	63.41	57.79	63.43	62.11	56.08	64.38	62.71	53.65	51.28	41.67	49.91	50.30	32.51				
B	12	0.00	1.73	24.09	40.62	54.56	63.04	54.30	58.19	57.49	57.61	60.91	69.15	55.95	56.19	53.60	48.72	52.36	44.18	53.11	38.15	35.54	48.57	40.50	27.35				
B	13	0.00	4.26	32.89	49.68	47.43	45.61	49.51	42.51	46.20	36.71	46.03	51.70	46.62	43.99	42.89	43.98	42.76	30.11	40.77	31.17	32.40	19.77	37.89	34.95				
B	14	0.20	6.14	33.16	53.17	55.00	63.97	53.37	56.39	60.64	61.77	62.86	63.12	63.19	61.68	61.09	68.12	65.83	60.17	62.76	55.44	52.45	40.06	50.94	35.83				
B	15	0.00	1.87	19.48	33.62	24.27	41.18	46.90	50.19	44.68	45.12	44.01	53.99	44.32	54.48	39.59	38.31	47.15	39.17	53.60	39.42	38.73	31.88	33.06	36.67				
B	16	6.49	2.41	17.61	33.54	55.03	45.07	44.78	43.47	41.31	39.68	43.17	48.86	46.04	41.85	39.92	45.29	36.25	41.96	38.01	36.47	29.87	43.55	27.70	20.88				
B	17	0.00	2.89	17.25	28.91	44.51	50.85	52.11	42.23	68.33	66.23	58.97	67.80	63.88	51.40	51.40	51.97	45.41	38.59	55.86	42.85	36.91	34.72	34.95	11.84				
B	18	0.00	7.27	35.61	47.18	54.82	65.71	68.11	62.74	63.33	61.82	60.32	65.35	57.65	54.51	55.82	53.49	51.41	51.62	53.01	51.62	47.24	37.26	34.72	30.84				
B	19	0.30	2.50	29.64	42.62	56.02	41.53	52.48	46.66	42.04	38.77	36.36	50.90	47.34	47.19	43.10	45.24	55.43	49.00	41.15	38.82	37.83	29.34	23.85	25.47				
B	20	0.01	7.07	39.40	53.19	56.06	54.98	59.97	56.63	49.46	49.00	48.20	60.44	48.90	42.34	37.45	36.18	39.47	39.90	43.58	32.28	24.00	29.55	33.42	23.14				
B	21	3.56	15.88	35.26	58.93	59.18	66.13	66.40	59.28	65.38	62.22	62.60	67.03	61.85	49.99	53.00	53.79	54.12	59.51	64.38	46.40	43.97	39.84	41.86	24.83				
B	22	1.39	0.00	18.07	34.38	30.99	38.85	43.21	42.46	37.15	39.86	40.72	37.81	36.49	32.74	43.65	35.78	37.49	37.29	30.36	32.87	28.72	28.66	24.22	26.61				
B	23	1.89	11.64	49.76	70.84	68.59	73.24	60.25	66.61	61.33	60.29	61.24	67.83	61.56	54.26	53.77	49.82	48.79	44.34	40.53	40.50	38.97	39.37	32.88	30.72				
B	24	0.76	0.00	0.00	0.00	9.34	11.89	16.72	10.93	12.35	18.55	39.45	55.64	54.80	60.54	51.26	45.55	29.73	33.85	36.69	21.42	26.65	34.25	24.89	26.37				
B	25	0.00	20.25	50.91	60.79	55.35	47.89	56.13	42.26	55.71	62.69	42.97	51.28	40.88	54.72	45.57	57.57	41.01	53.43	44.70	50.85	34.92	47.30	31.89	26.78				
B	26	0.00	0.00	11.65	25.16	35.14	51.11	54.58	50.03	49.19	53.50	48.08	46.87	46.09	46.22	47.47	45.86	40.73	45.93	49.16	42.23	41.84	36.91	35.69	25.87				
B	27	0.00	1.22	26.36	39.15	42.23	49.84	44.22	42.60	46.63	45.42	51.14	52.34	42.09	38.86	45.57	39.84	46.78	32.39	40.71	30.76	30.65	29.61	24.19	14.63				
B	28	0.00	10.78	40.05	31.95	44.49	35.97	105.75	93.10	57.87	91.63	58.16	46.44	69.72	71.26	80.92	49.71	12.65	45.55	25.46	34.32	40.80	41.93	32.50	24.17				
B	29	0.00	0.46	0.00	0.00	36.95	40.43	41.45	40.61	47.14	44.64	44.35	60.17	57.37	52.35	49.79	49.87	45.56	39.91	44.89	26.18	37.92	34.80	0.00	6.82				
B	30	3.11	3.63	25.34	46.10	42.17	53.40	36.85	65.54	54.82	71.68	55.55	49.89	49.80	47.11	46.88	43.70	41.96	40.53	37.15	36.33	35.24	38.98	41.39	34.86				
B	31	0.00	3.80	33.71	46.73	52.87	51.74	62.01	49.53	53.25	50.33	46.42	46.59	48.00	42.24	56.14	46.41	55.85	38.69	40.30	32.69	30.85	35.30	38.03	24.01				
B	32	0.00	9.47	44.44	56.18	47.62	56.23	57.42	50.04	44.53	62.17	38.50	48.71	47.84	42.93	35.65	38.00	42.37	35.78	39.37	30.91	32.49	36.47	24.68	22.33				
B	33	0.00	20.22	62.72	82.18	79.02	69.15	69.81	61.80	61.79	62.31	64.57	66.39	66.69	60.32	61.34	53.11	54.58	54.40	52.44	42.43	45.74	43.60	28.55	30.88				
B	34	1.28	10.99	30.74	50.42	63.83	70.24	58.56	55.87	57.01	58.08	59.78	68.78	57.30	51.35	47.19	41.26	47.67	40.39	36.00	28.07	38.33	29.43	24.24	17.34				
B	35	0.17	0.00	0.00	16.04	20.92	49.01	52.07	36.70	41.30	49.07	28.33	38.25	44.89	44.85	39.72	35.70	51.67	45.29	37.17	26.76	35.85	36.73	24.02	41.01				
B	36	1.83	17.66	60.21	64.87	70.08	66.77	45.41	52.85	63.36	47.07	57.71	63.12	54.05	56.11	50.51	50.47	40.10	42.39	46.20	42.17	32.18	29.81	35.13	36.58				
B	37	0.00	6.08	3.52	25.64	40.87	52.82	60.91	61.67	62.32	64.41	57.07	61.67	51.50	54.86	57.06	68.30	54.04	50.03	46.56	45.74	43.97	43.70	37.54	39.90				
B	39	0.00	21.11	58.94	82.41	86.16	91.74	86.69	73.80	73.91	84.89	84.48	70.66	94.09	85.59	77.05	60.60	52.98	58.79	62.34	55.82	45.68	48.10	33.44	35.15				
B	40	0.00	0.00	16.31	31.43	43.30	58.76	65.02	68.52	74.09	71.22	70.39	78.08	75.35	70.39	72.83	71.95	65.40	65.58	65.92	59.63	58.56	42.80	37.96	38.58				
B	41	0.00	14.77	39.58	62.91	57.36	79.08	49.75	52.69	57.46	38.34	54.72	63.73	47.79	41.76	36.95	59.50	40.42	34.98	63.09	26.06	40.04	32.28	25.61	17.70				
B	42	0.00	5.13	20.63	29.26	20.68	31.73	33.98	30.70	33.13	32.32	31.38	33.26	26.93	29.62	29.99	27.70	27.90	27.14	31.69	23.39	20.83	27.09	24.76	27.53				
B	43	0.98	5.77	41.87	50.89	50.10	56.81	46.08	50.09	47.69	54.80	50.80	48.40	41.95	40.31	46.32	40.53	37.32	32.31	36.35	33.93	29.34	22.89	21.13	30.42				
B	44	0.00	5.77	37.85	47.59	41.39	37.75	41.29	37.34	38.76	39.51	36.07	41.87	43.03	39.25	36.83	39.01	39.51	33.49	34.83	27.96	28.45	28.68	16.07	27.54				
Arithmetic Mean		0.60	6.47	28.66	43.09	48.40	53.33	54.62	53.17	53.55	54.51	52.43	57.09	54.47	52.68	51.69	49.01	47.59	44.47	45.18	38.26	37.47	35.68	32.10	27.71				
Standard Deviation		1.26	6.44	16.39	18.77	17.54	17.09	18.05	17.42	16.73	17.20	15.71	13.97	14.10	14.12	14.93	12.97	14.27	12.34	13.45	11.31	10.93	7.32	10.24	8.06				
%CV		211.29	99.62	57.18	43.57	36.23	32.05	33.05	32.76	31.24	31.56	29.97	24.48	25.89	26.81	28.88	26.4	29.99	27.57	29.77	29.56	29.18	22.18	31.89	29.95				



 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	9 of 68

Table 6. Subjects with concentrations other than 0.00 ng/mL at time zero.

Subject	Form	Pre-dose concentration (ng/mL)	C _{max} (ng/mL)	% pre-dose concentration with respect to C _{max}
2	A	0.95	59.08	1.60
3	A	0.04	61.00	0.07
4	A	0.24	67.12	0.36
14	A	1.25	69.84	1.79
15	A	0.22	51.95	0.42
19	A	0.09	73.11	0.13
26	A	3.32	51.65	6.42
27	A	0.65	48.06	1.36
29	A	0.74	65.35	1.14
30	A	1.66	68.88	2.41
32	A	3.18	61.04	5.21
33	A	3.27	86.93	3.76
36	A	3.49	74.82	4.66
39	A	2.71	100.38	2.70
40	A	9.72	90.55	10.74
44	A	1.00	51.87	1.93
1	B	0.36	84.97	0.42
6	B	0.24	48.64	0.50
7	B	0.53	69.43	0.76
9	B	2.18	104.57	2.03
11	B	0.39	72.27	0.54
14	B	0.20	68.12	0.29
16	B	6.49	55.03	11.80
19	B	0.30	56.02	0.53
20	B	0.01	60.44	0.02
21	B	3.56	67.03	5.31
22	B	1.39	43.65	3.19
23	B	1.89	73.24	2.58
24	B	0.76	60.54	1.26
30	B	3.11	71.68	4.34
34	B	1.28	70.24	1.82
35	B	0.17	52.07	0.33
36	B	1.83	70.08	2.61
43	B	0.98	56.81	1.73

As per data shown in table 6, subjects 26, 32, and 40 with the reference formulation (A), and subjects 16 and 21 with the test formulation (B) had pre-dose concentrations higher than 5 % of the C_{max} corresponding value. Thus, as per annex C.5, part a) of the Mexican Official Standard, NOM-177-SSA1-2013, the data of these subjects must be removed from the statistical analysis. Therefore, from now on, all results shown do not include subjects 16, 21, 26, 32, and 40.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	10 of 68

3.3. Concentration vs. Individual and Average Time (arithmetic and logarithmic scale)

The non-adjusted plasma concentration time profiles of levothyroxine for test (B) and reference (A) products are shown from figures 1 to 38 in the arithmetic scale, from 39 to 76 in the logarithmic scale and in figures 77 and 78 those corresponding to the average plots in the arithmetic and logarithmic scale, respectively.

Volunteer=1

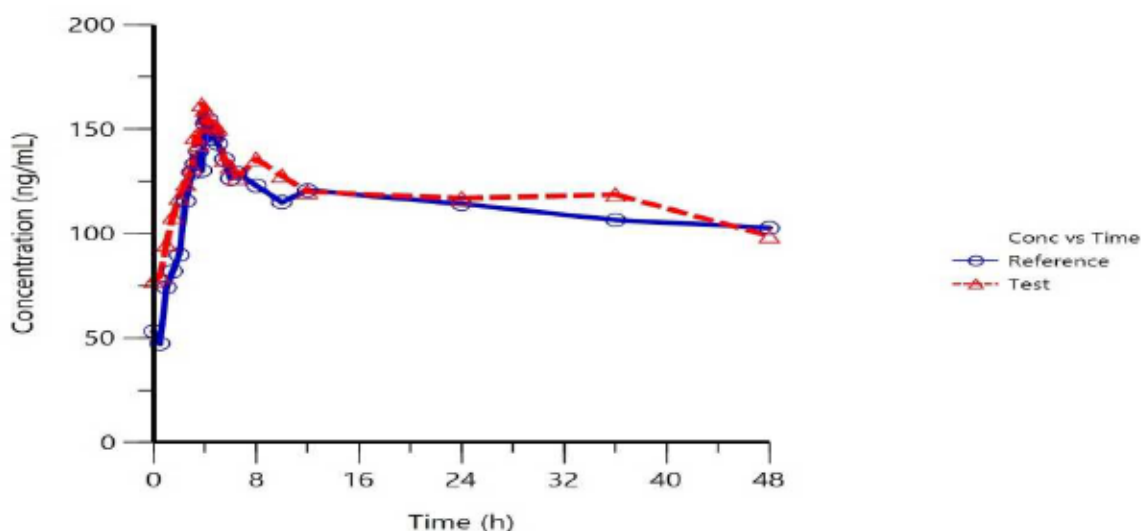


Figure 1. Levothyroxine concentration vs. subject 1's time plot, on an arithmetic scale, post-dose of the test-drug, and reference-drug.

Volunteer=2

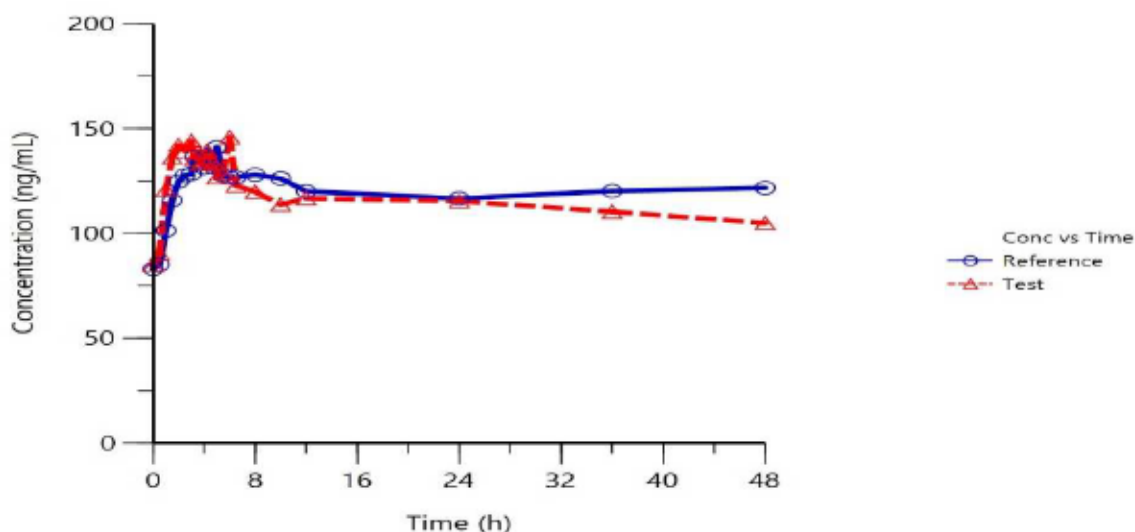



Figure 2. Levothyroxine concentration vs. subject 2's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	11 of 68

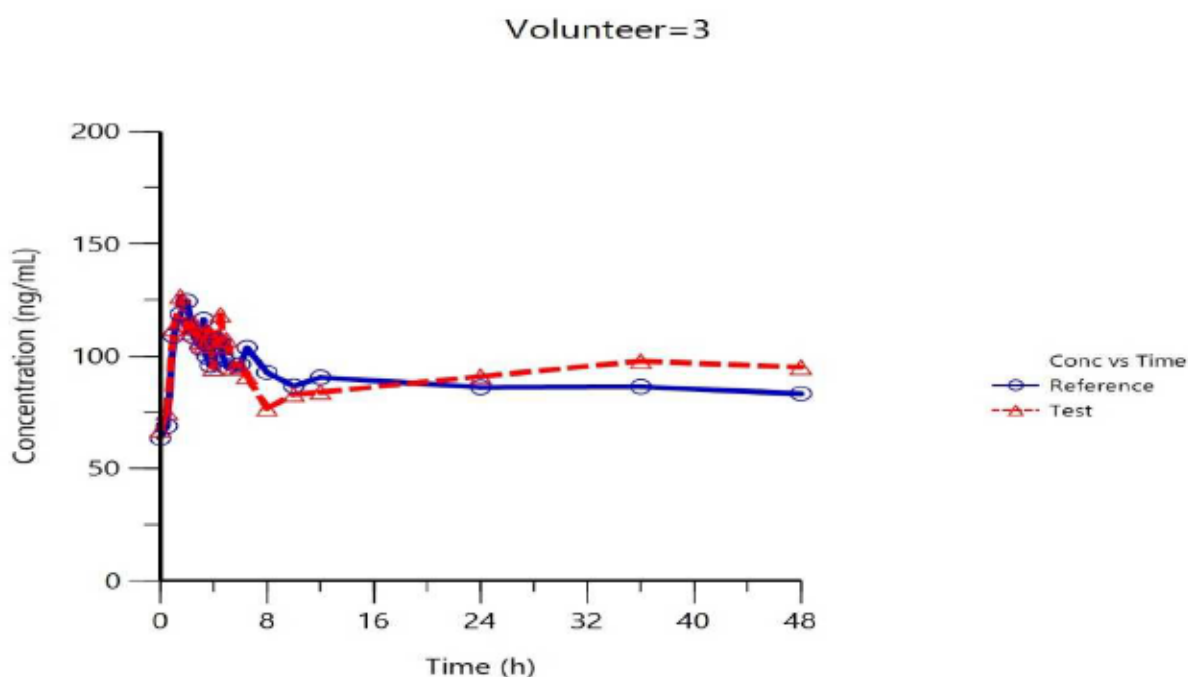


Figure 3. Levothyroxine concentration vs. subject 3's time plot, on an arithmetic scale, post-dose of the test-drug, and reference-drug.

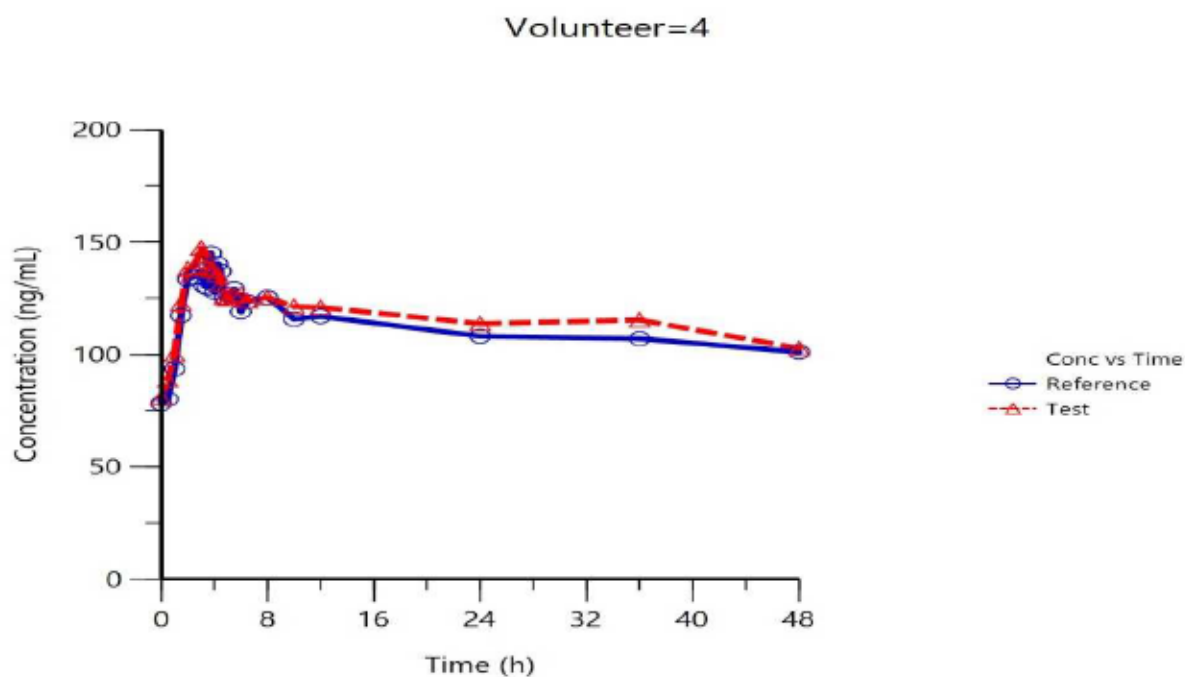



Figure 4. Levothyroxine concentration vs. subject 4's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	12 of 68

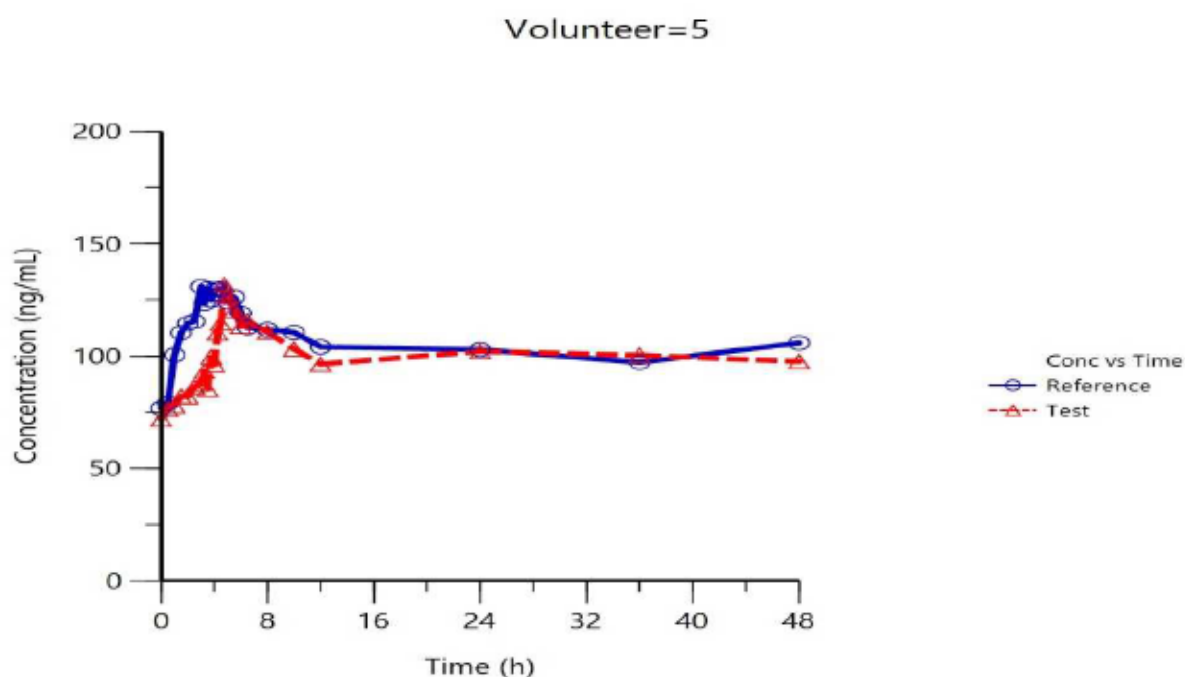


Figure 5. Levothyroxine concentration vs. subject 5's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

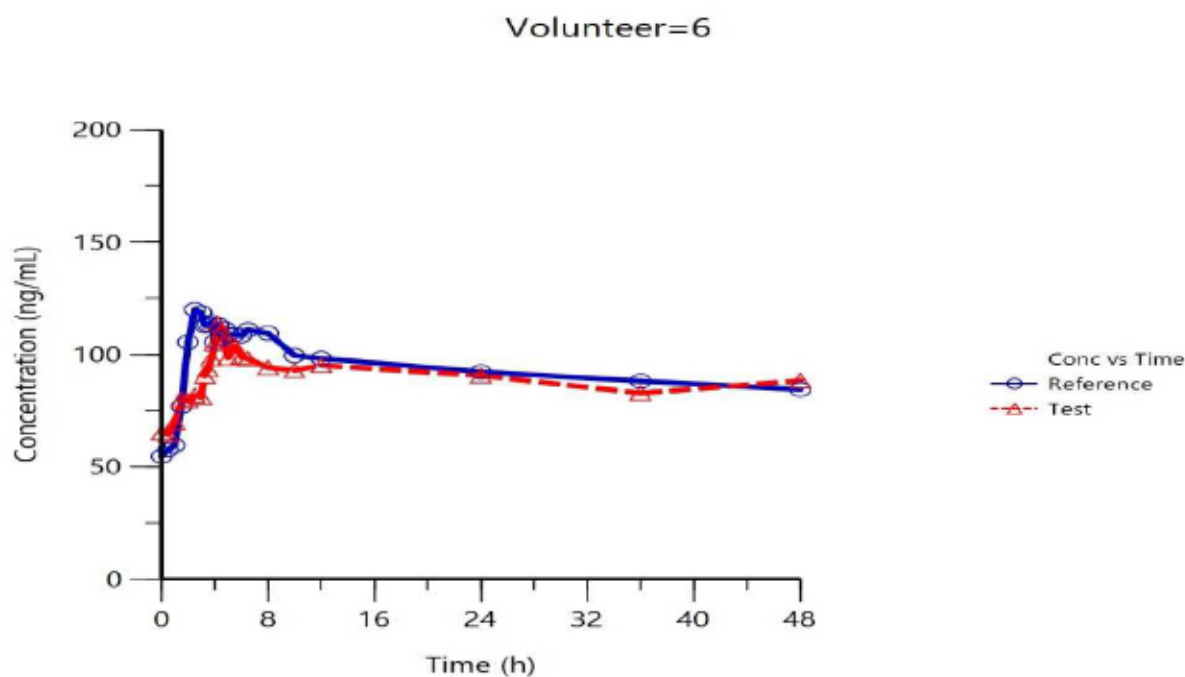



Figure 6. Levothyroxine concentration vs. subject 6's time plot, on an arithmetic scale, post-dose of the test-drug, and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	13 of 68

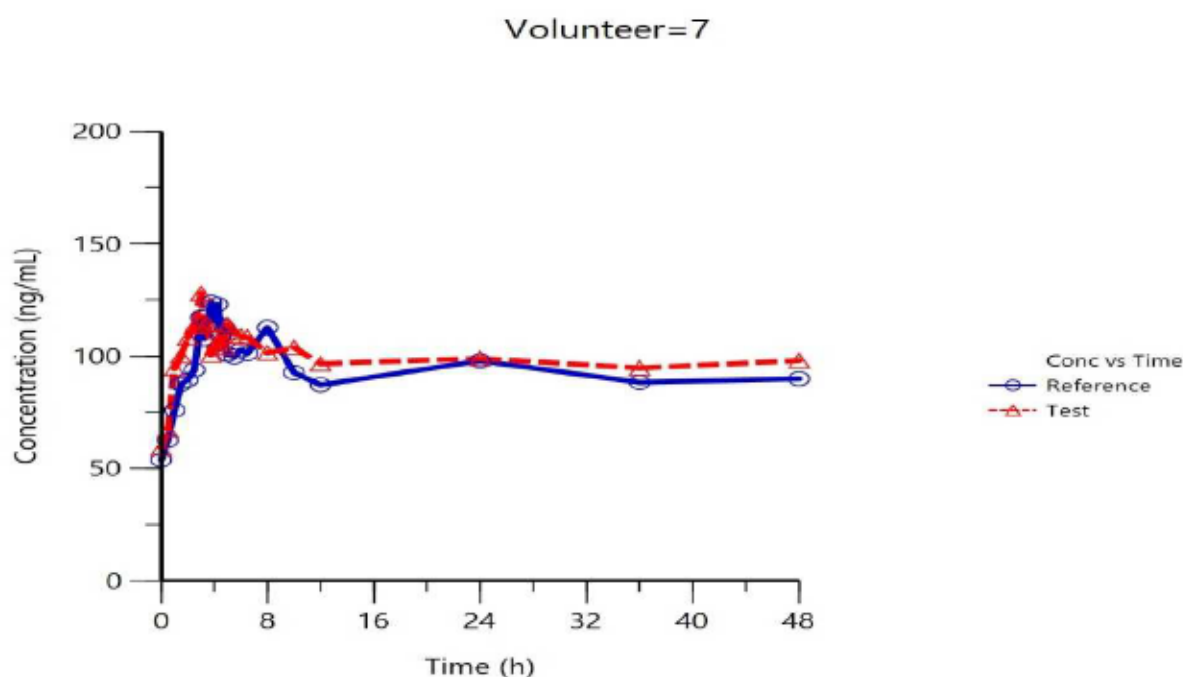


Figure 7. Levothyroxine concentration vs. subject 7's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

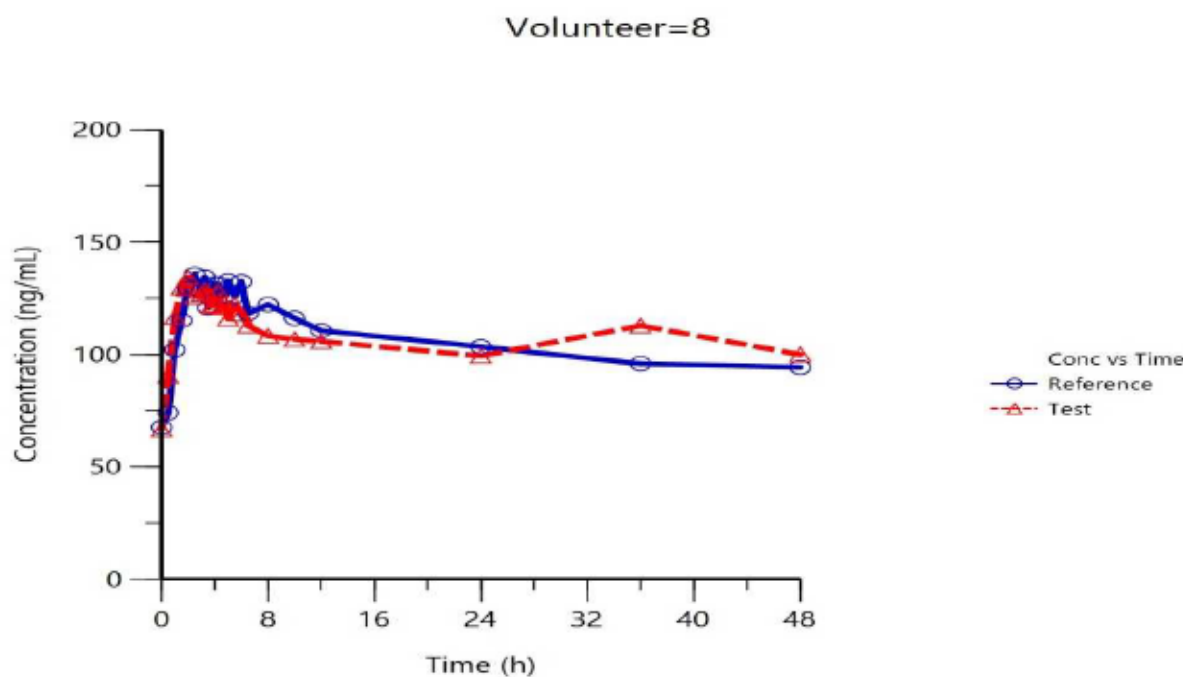



Figure 8. Levothyroxine concentration vs. subject 8's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	14 of 68

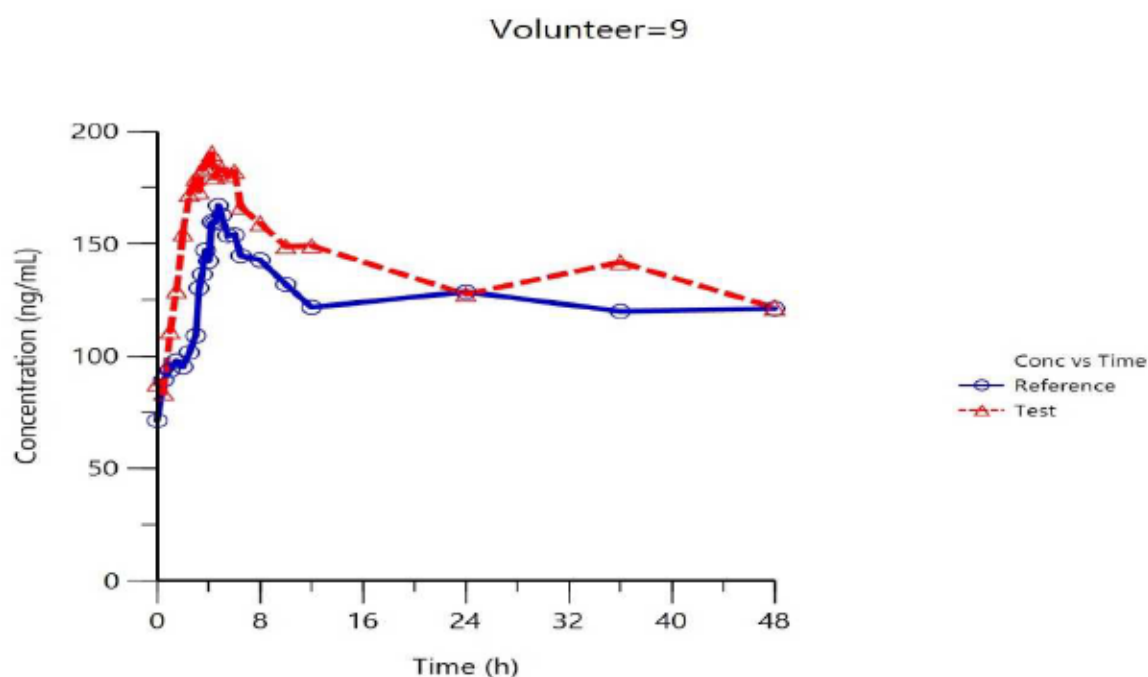


Figure 9. Levothyroxine concentration vs. subject 9's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

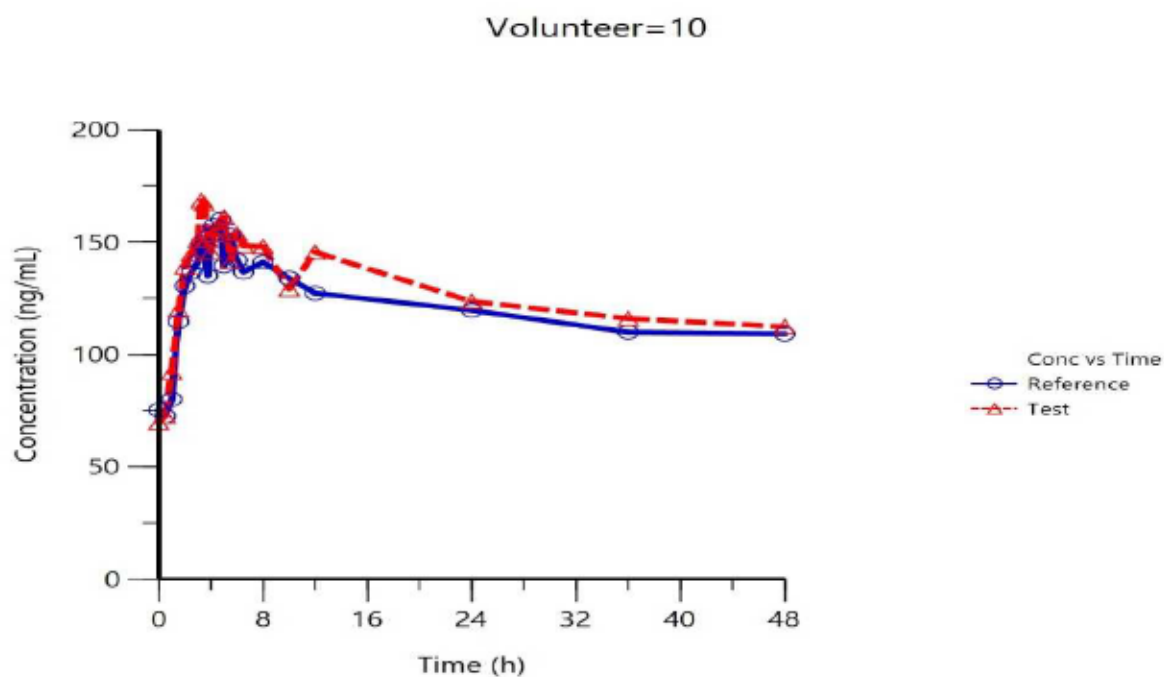



Figure 10. Levothyroxine concentration vs. subject 10's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	15 of 68

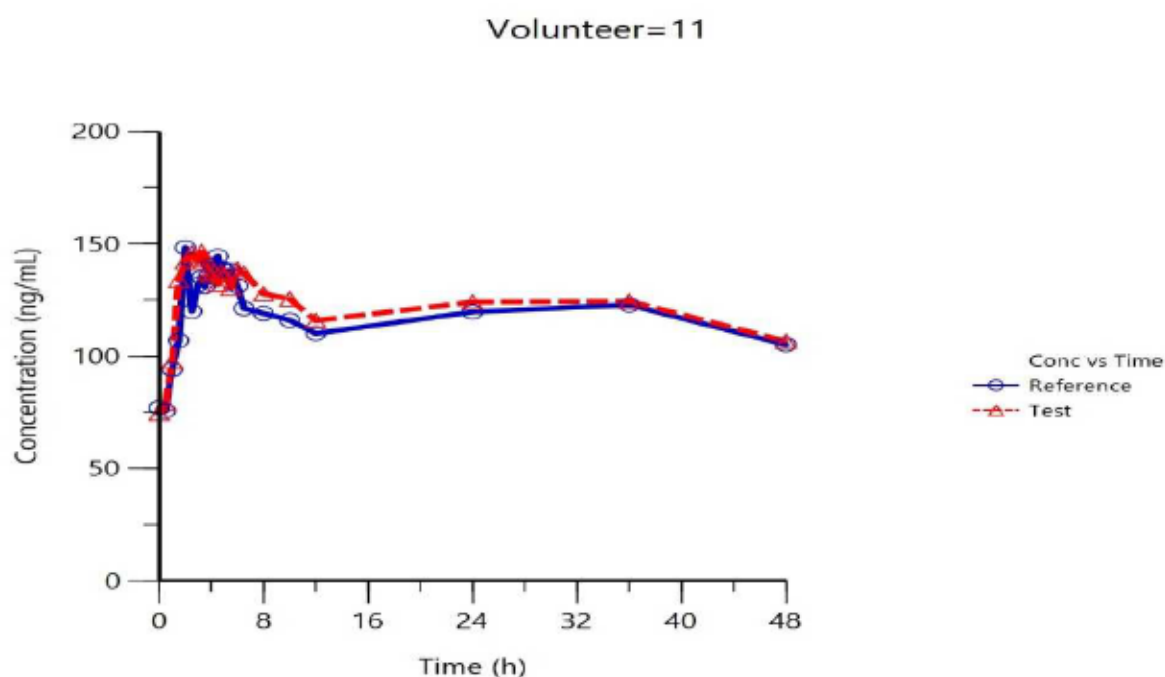


Figure 11. Levothyroxine concentration vs. subject 11's time plot, on an arithmetic scale, post-dose of the test-drug, and reference-drug.

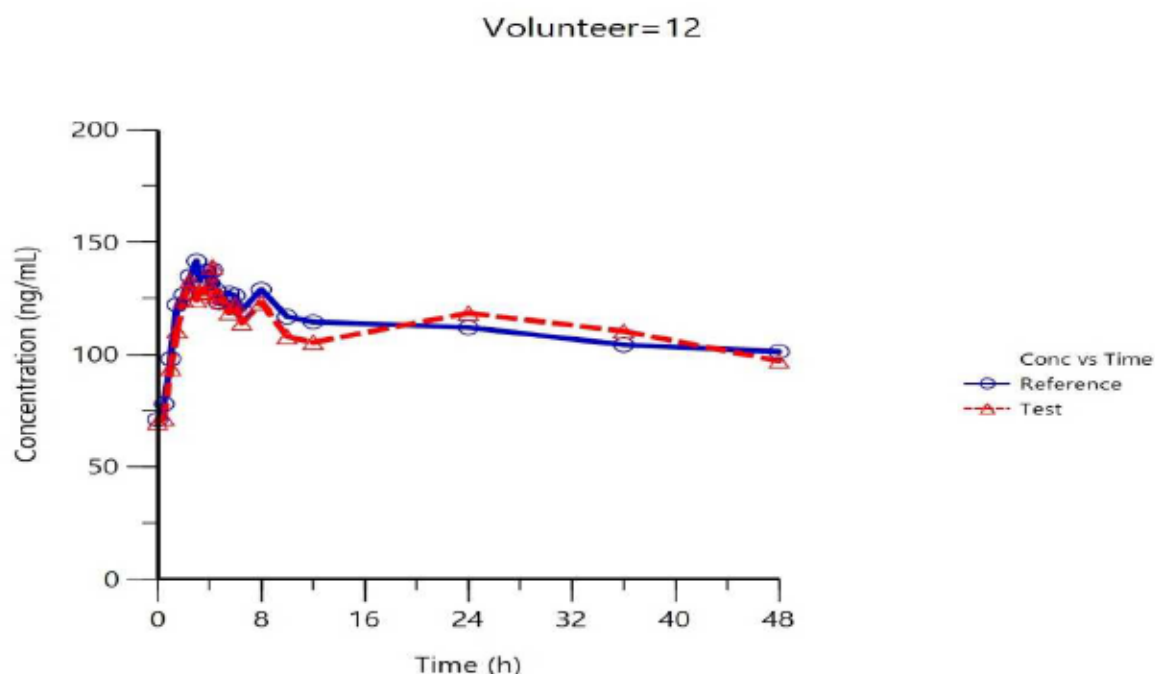



Figure 12. Levothyroxine concentration vs. subject 12's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	16 of 68

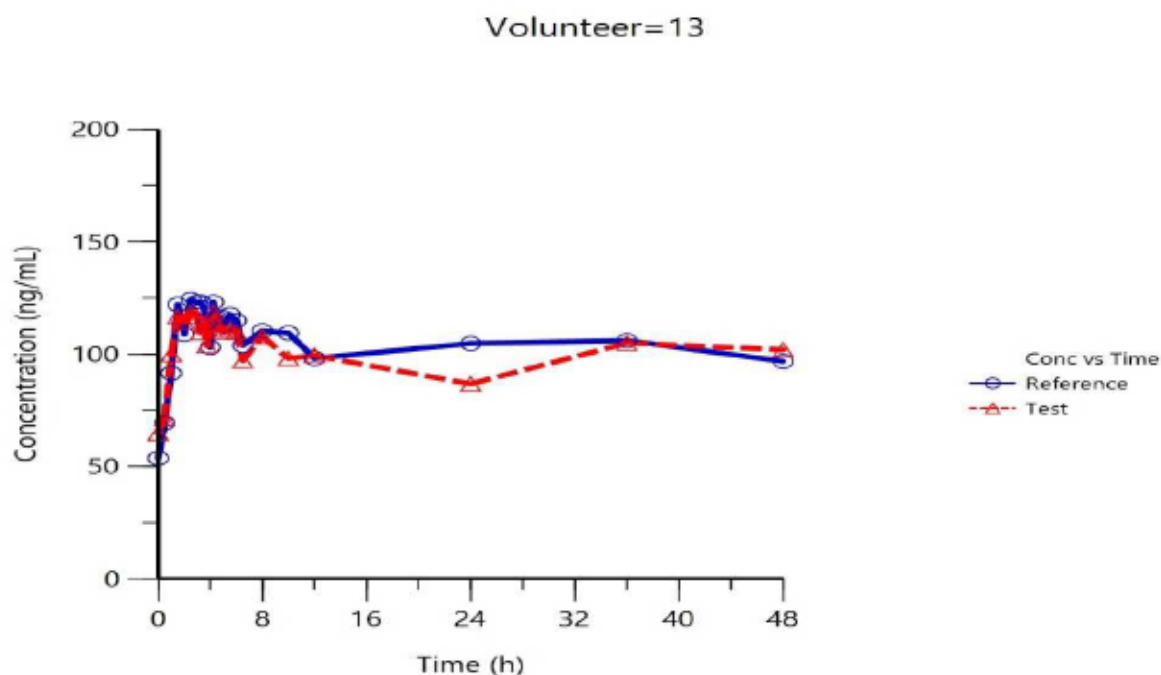


Figure 13. Levothyroxine concentration vs. subject 13's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

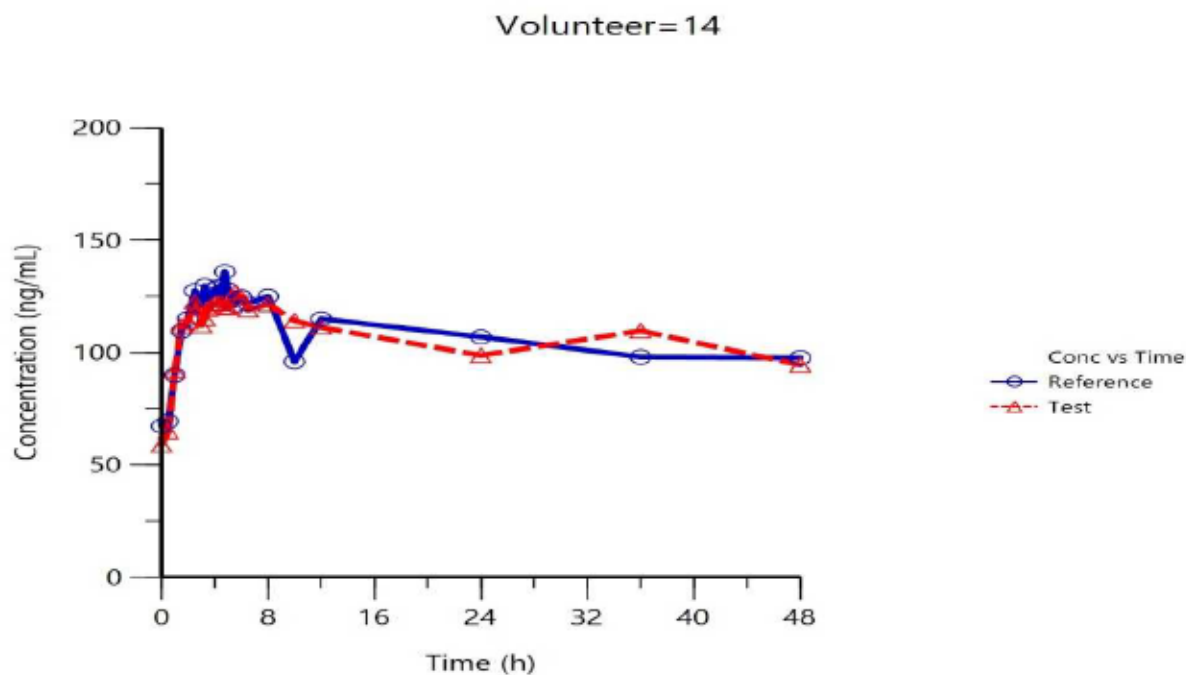



Figure 14. Levothyroxine concentration vs. subject 14's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	17 of 68

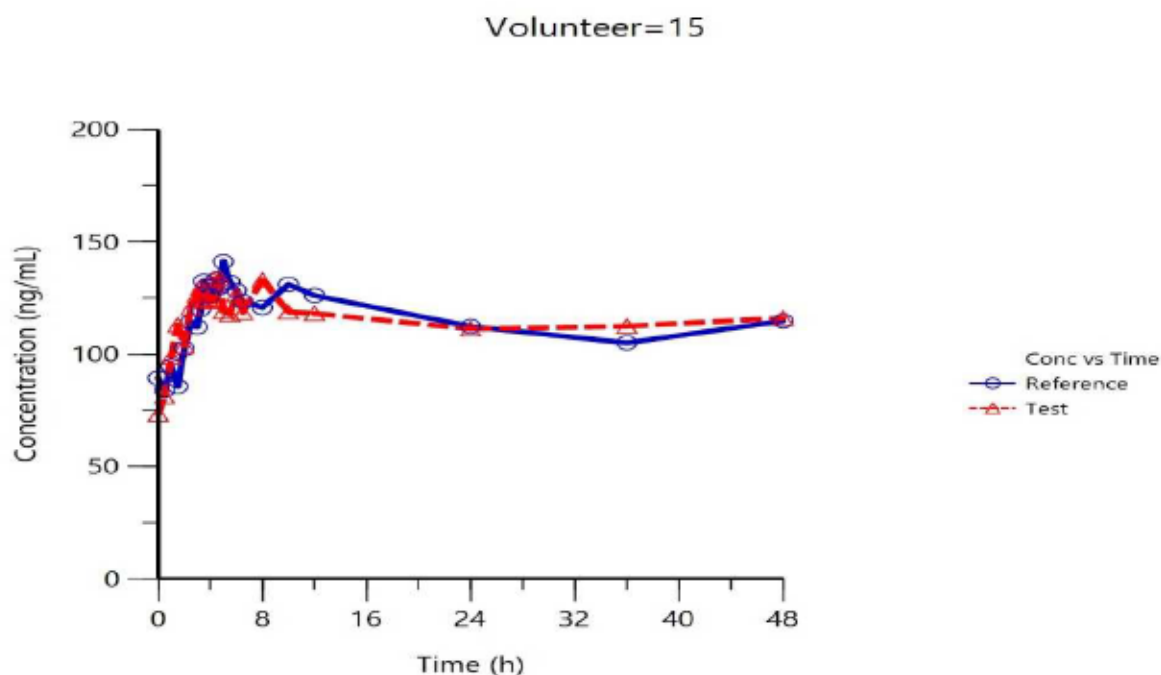


Figure 15. Levothyroxine concentration vs. subject 15's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

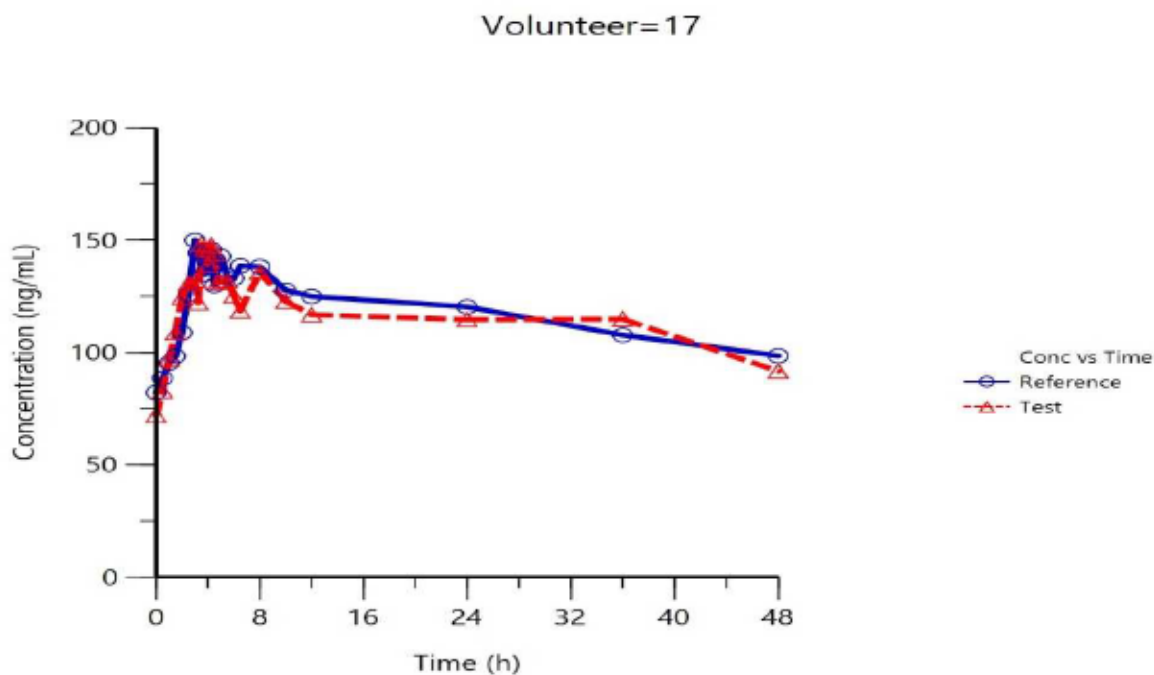



Figure 16. Levothyroxine concentration vs. subject 17's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	18 of 68

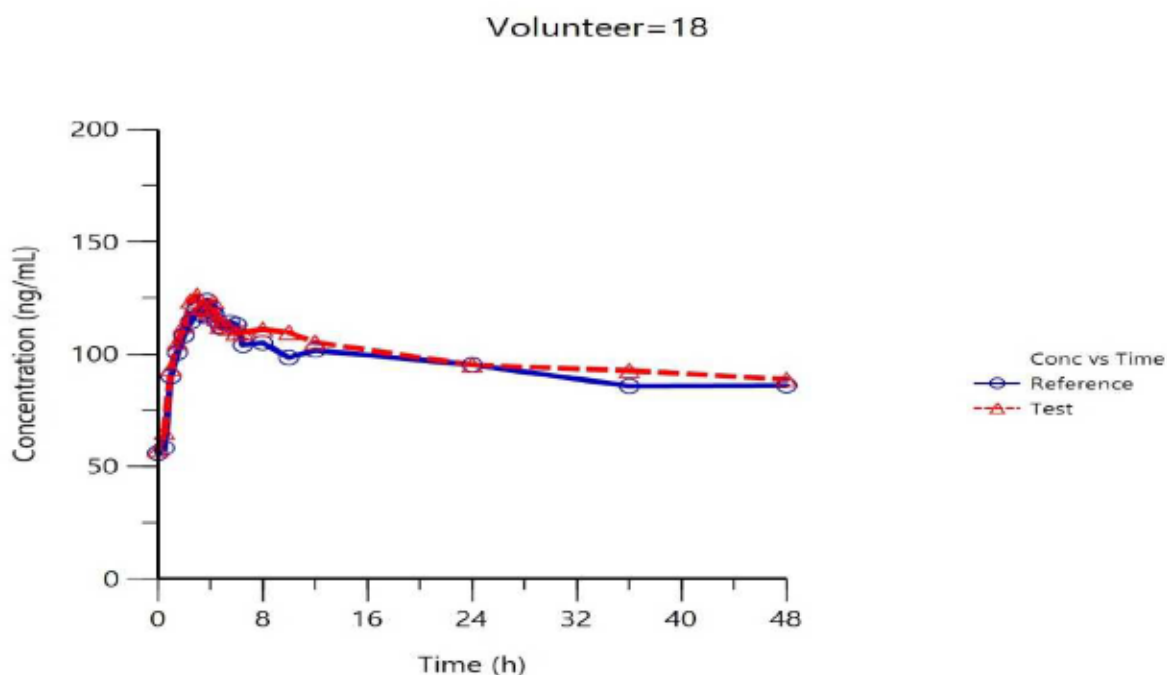


Figure 17. Levothyroxine concentration vs. subject 18's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

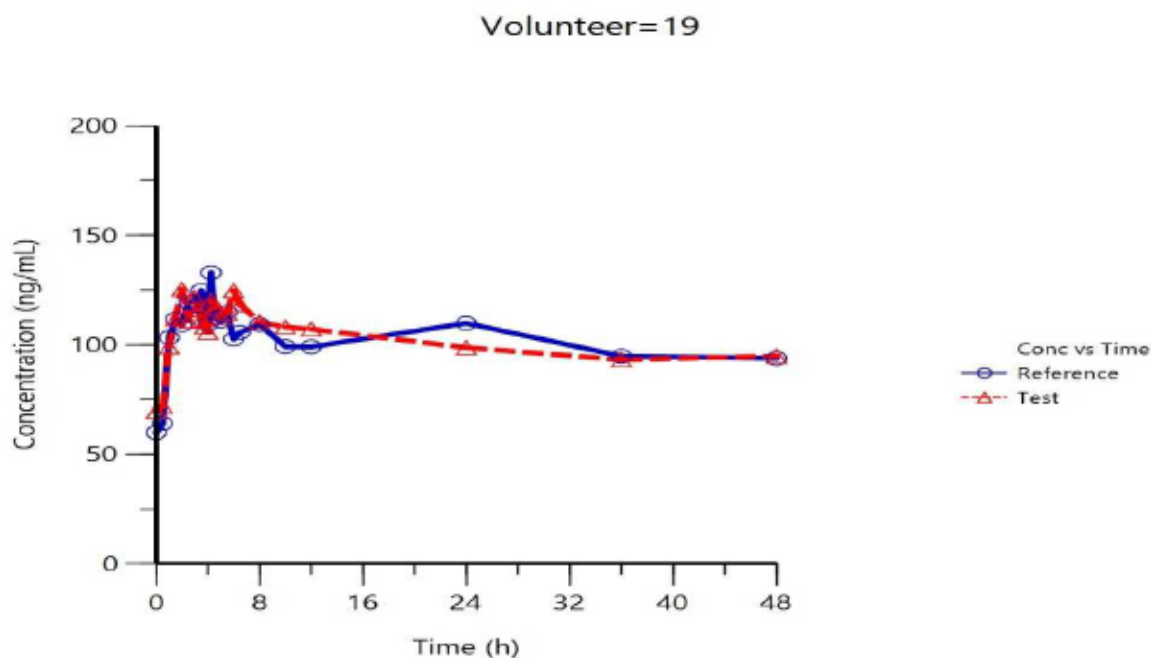



Figure 18. Levothyroxine concentration vs. subject 19's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	19 of 68

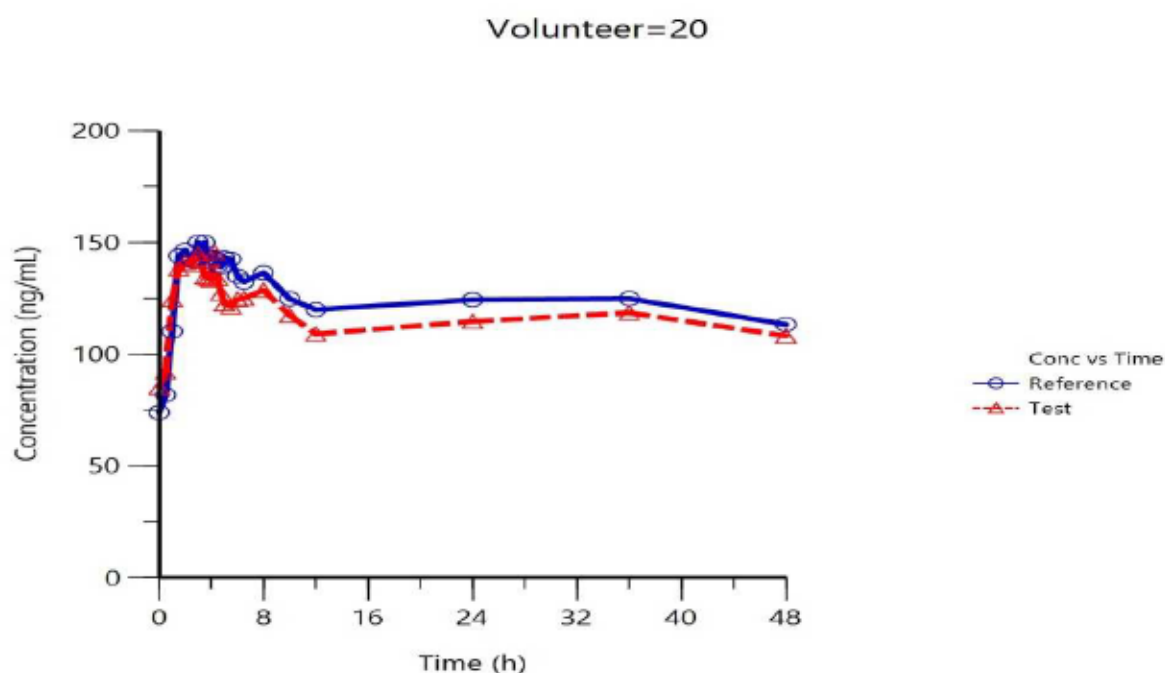


Figure 19. Levothyroxine concentration vs. subject 20's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

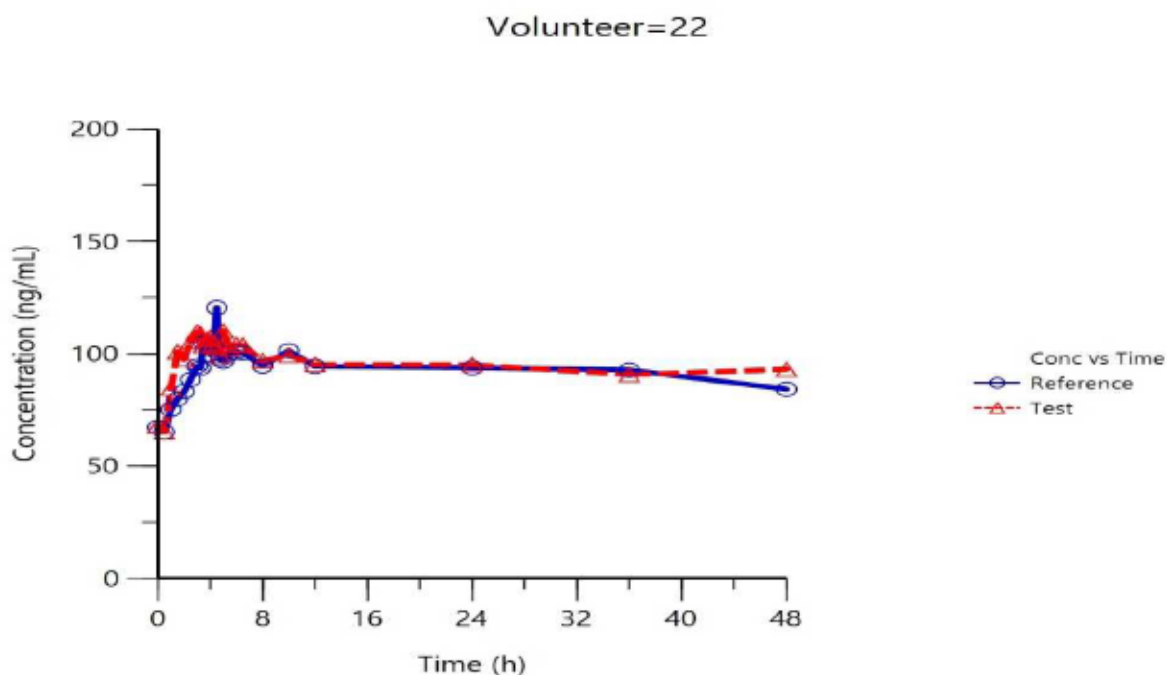



Figure 20. Levothyroxine concentration vs. subject 22's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	20 of 68

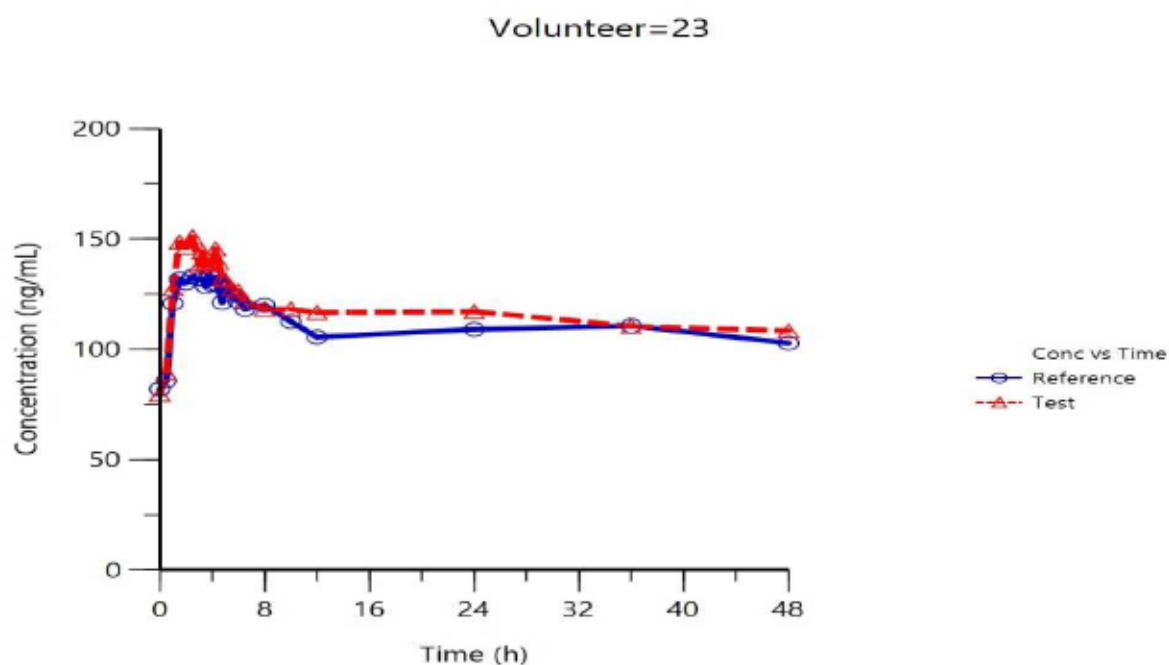


Figure 21. Levothyroxine concentration vs. subject 23's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

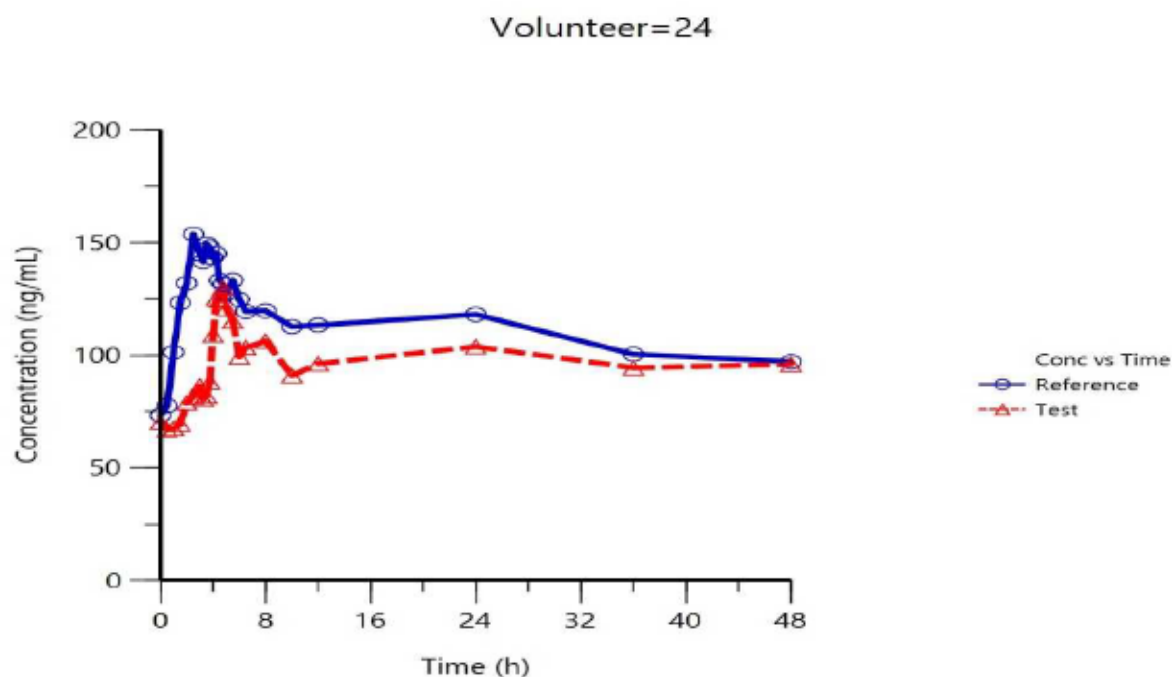



Figure 22. Levothyroxine concentration vs. subject 24's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	21 of 68

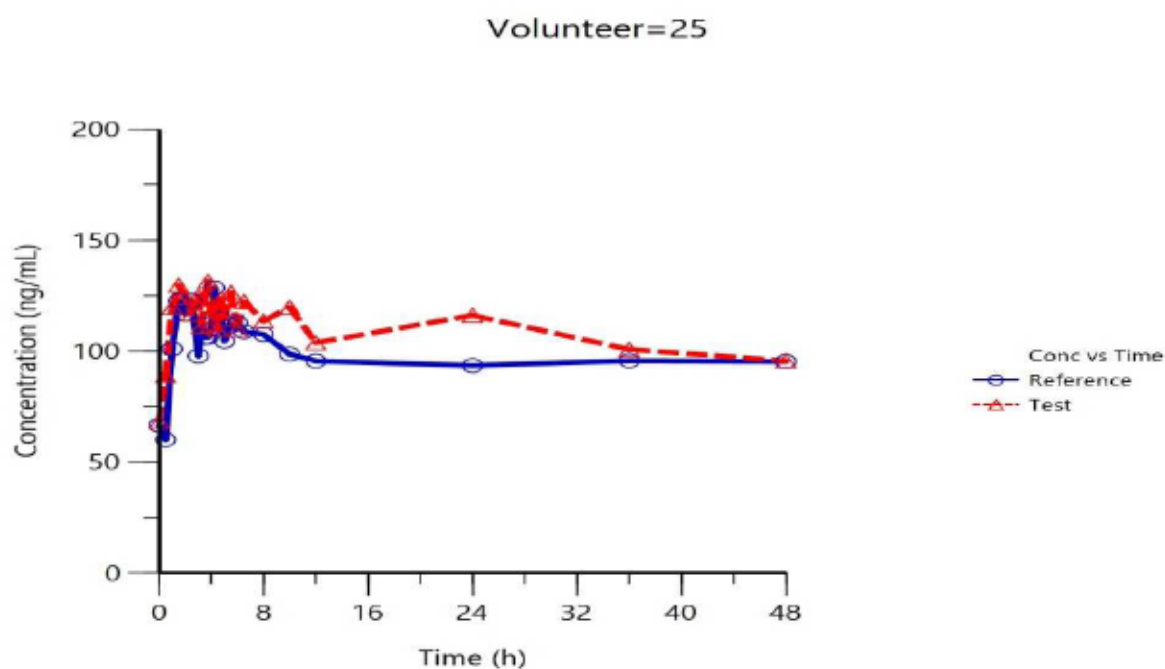


Figure 23. Levothyroxine concentration vs. subject 25's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

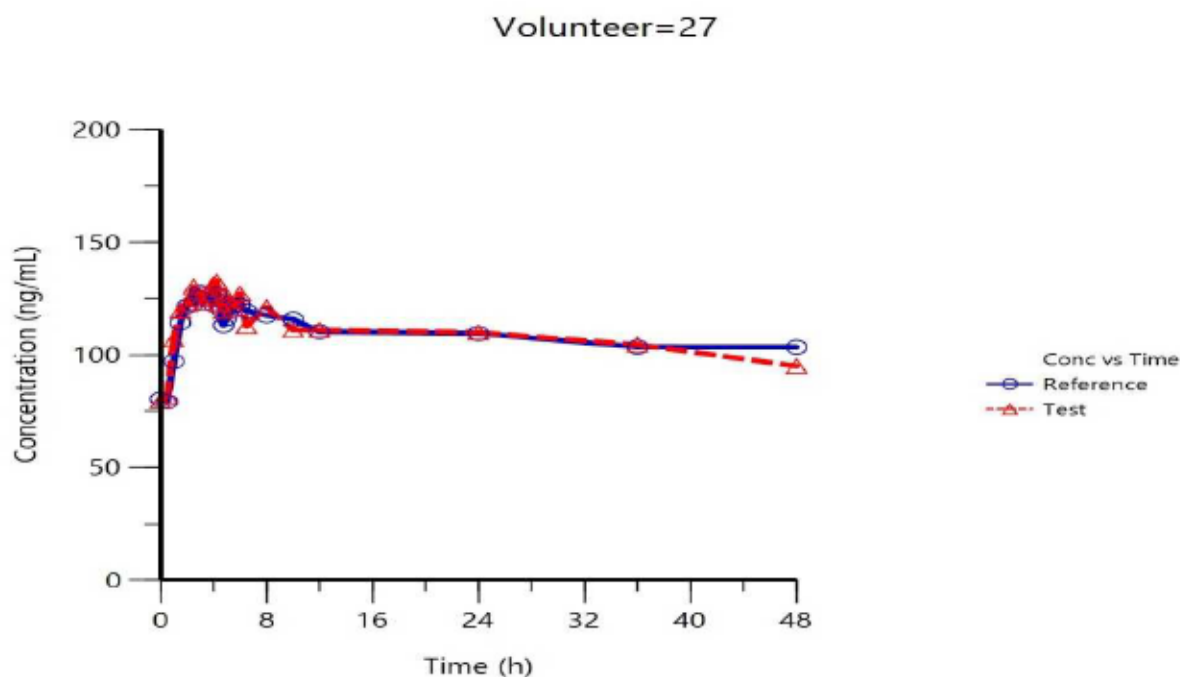



Figure 24. Levothyroxine concentration vs. subject 27's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	22 of 68

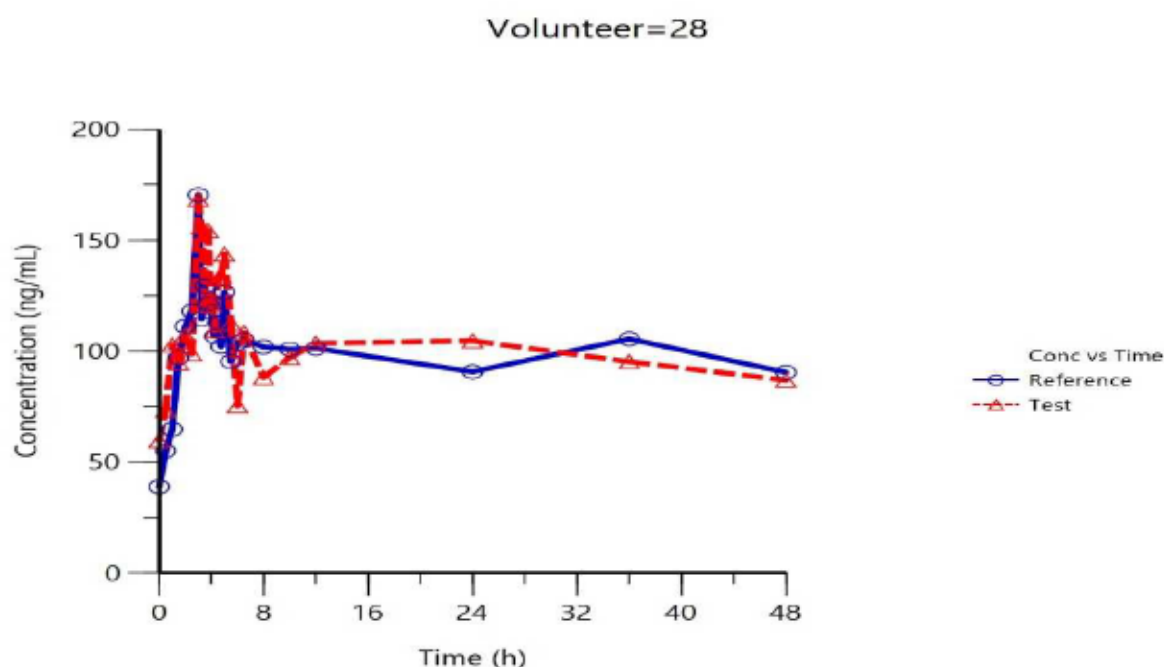


Figure 25. Levothyroxine concentration vs. subject 28's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

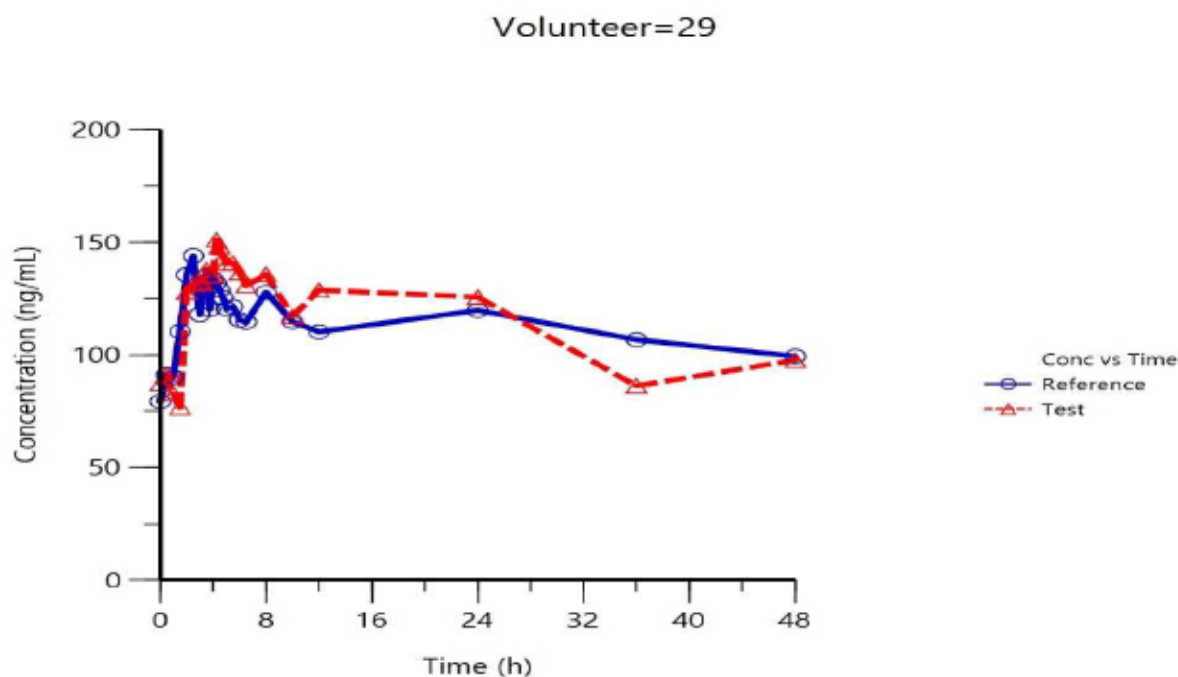



Figure 26. Levothyroxine concentration vs. subject 29's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	23 of 68

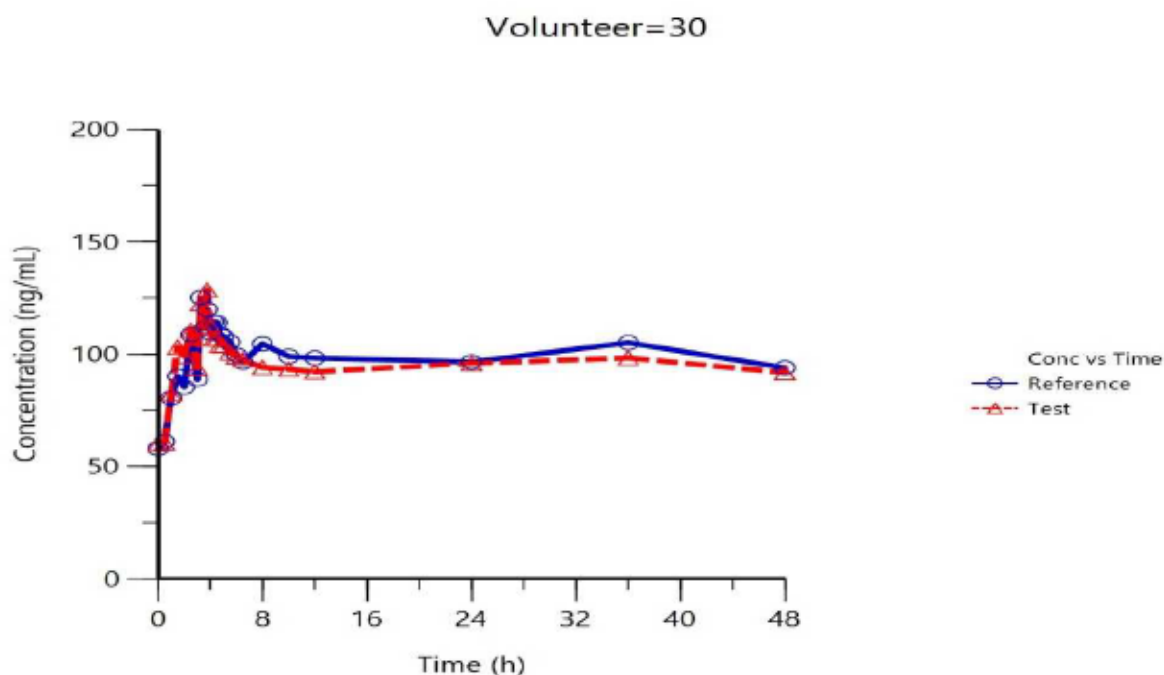


Figure 27. Levothyroxine concentration vs. subject 30's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

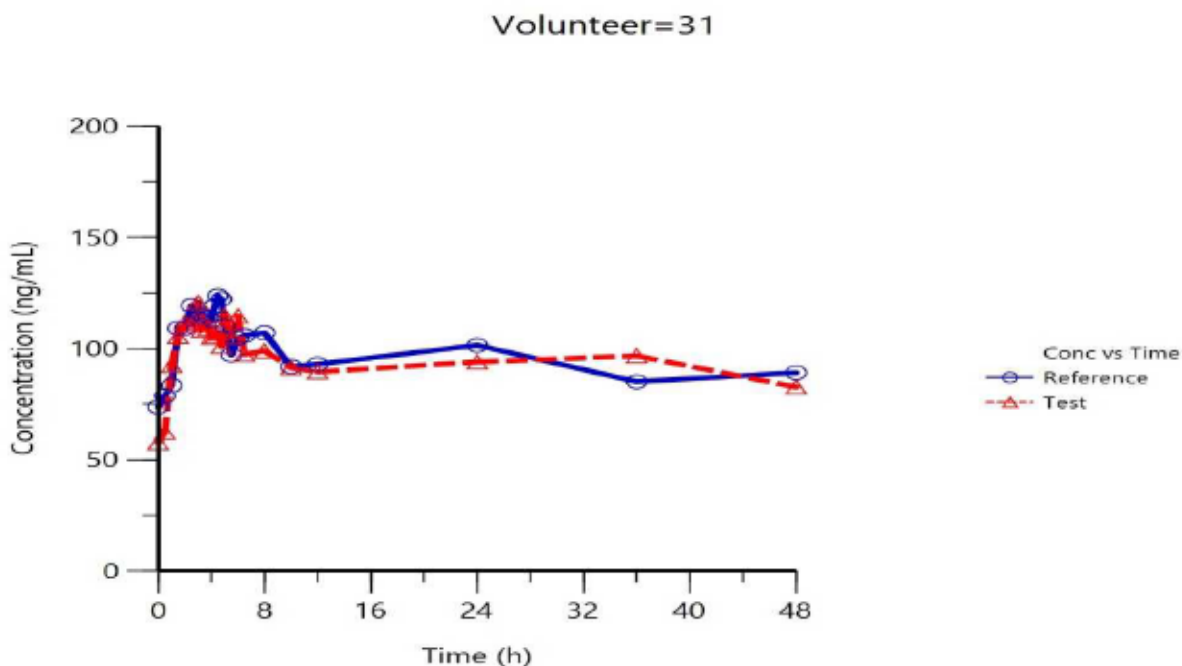



Figure 28. Levothyroxine concentration vs. subject 31's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	24 of 68

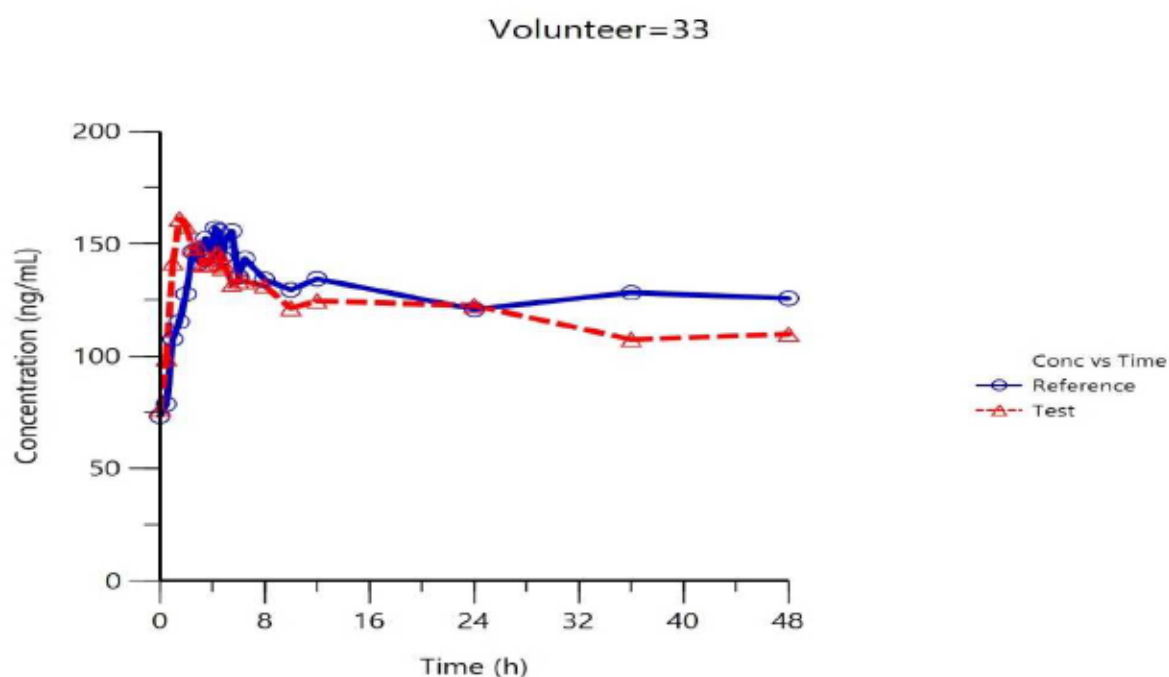


Figure 29. Levothyroxine concentration vs. subject 33's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

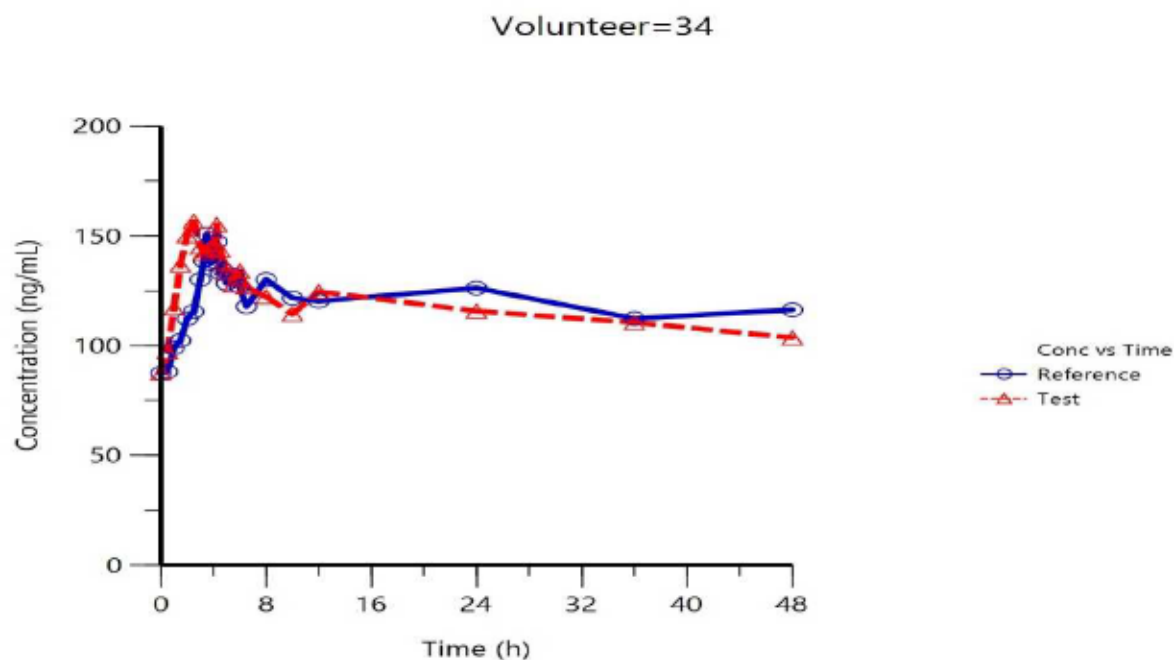



Figure 30. Levothyroxine concentration vs. subject 34's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	25 of 68

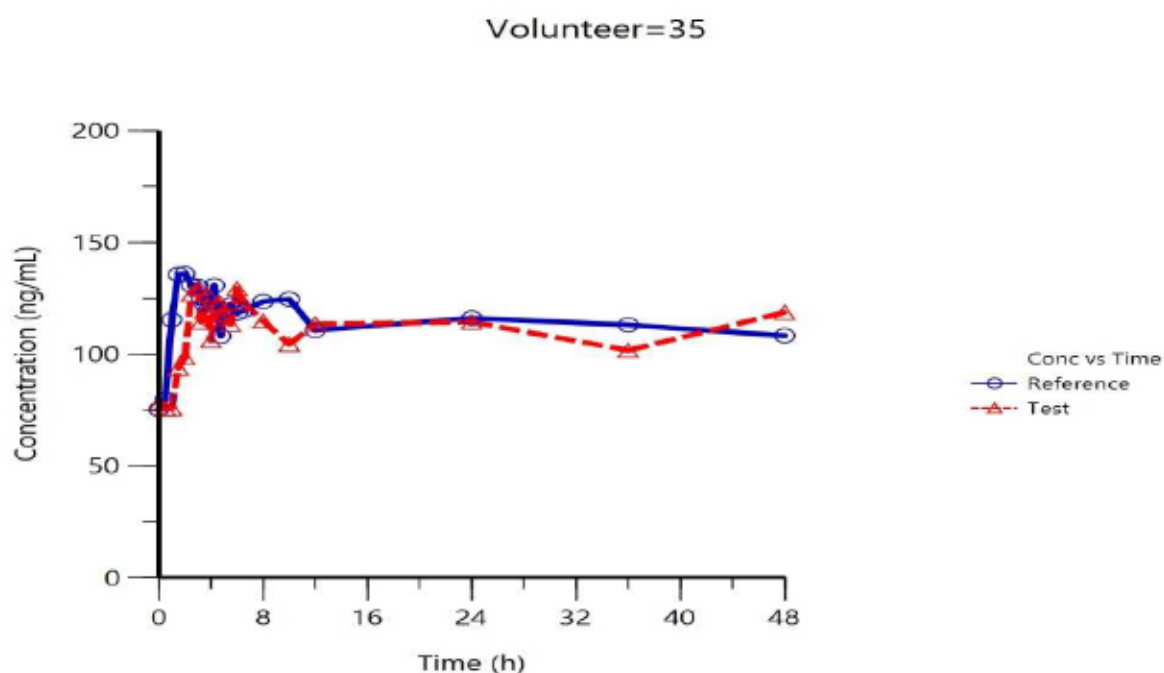


Figure 31. Levothyroxine concentration vs. subject 35's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

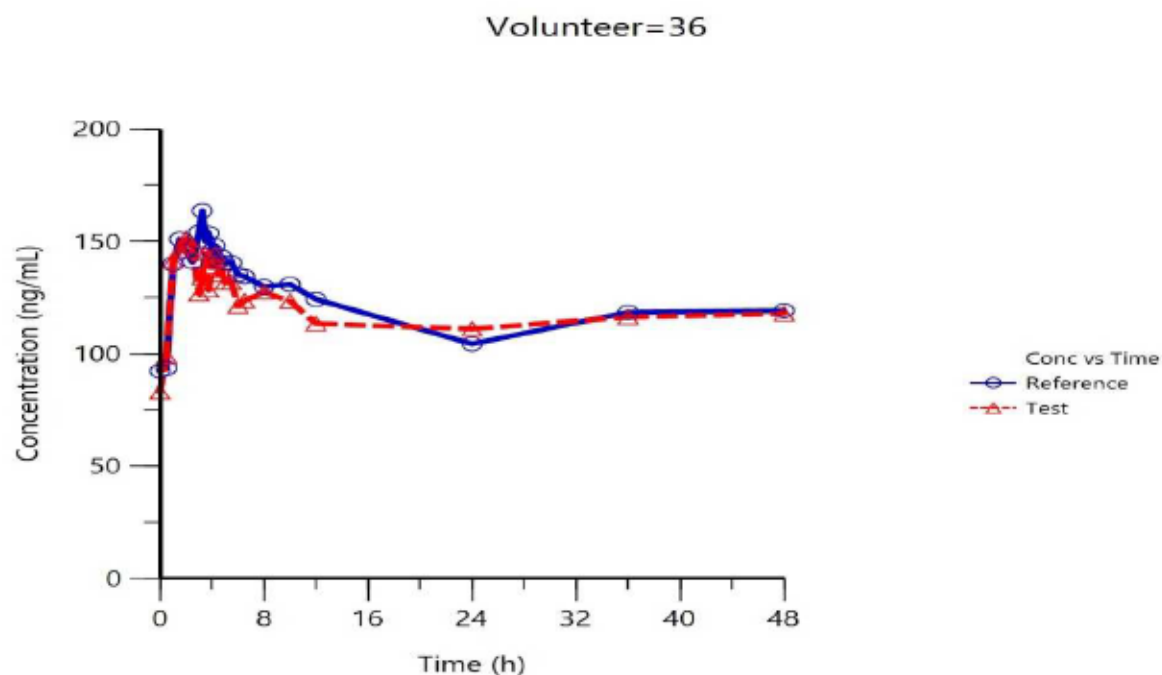



Figure 32. Levothyroxine concentration vs. subject 36's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	26 of 68

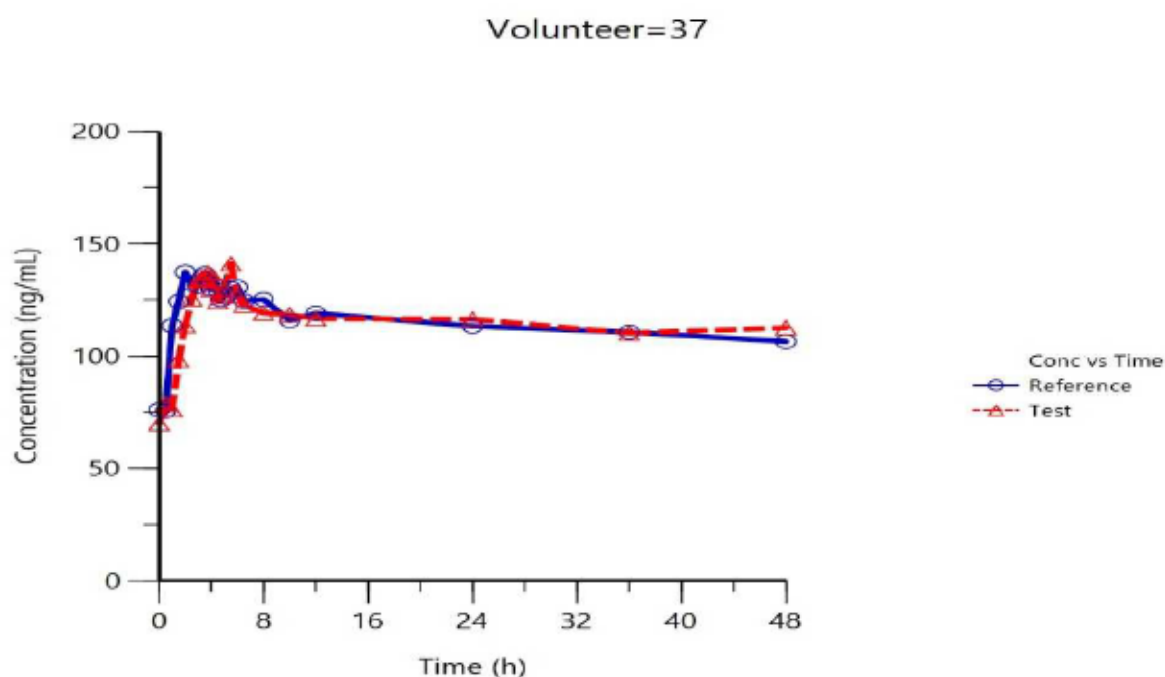


Figure 33. Levothyroxine concentration vs. subject 37's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

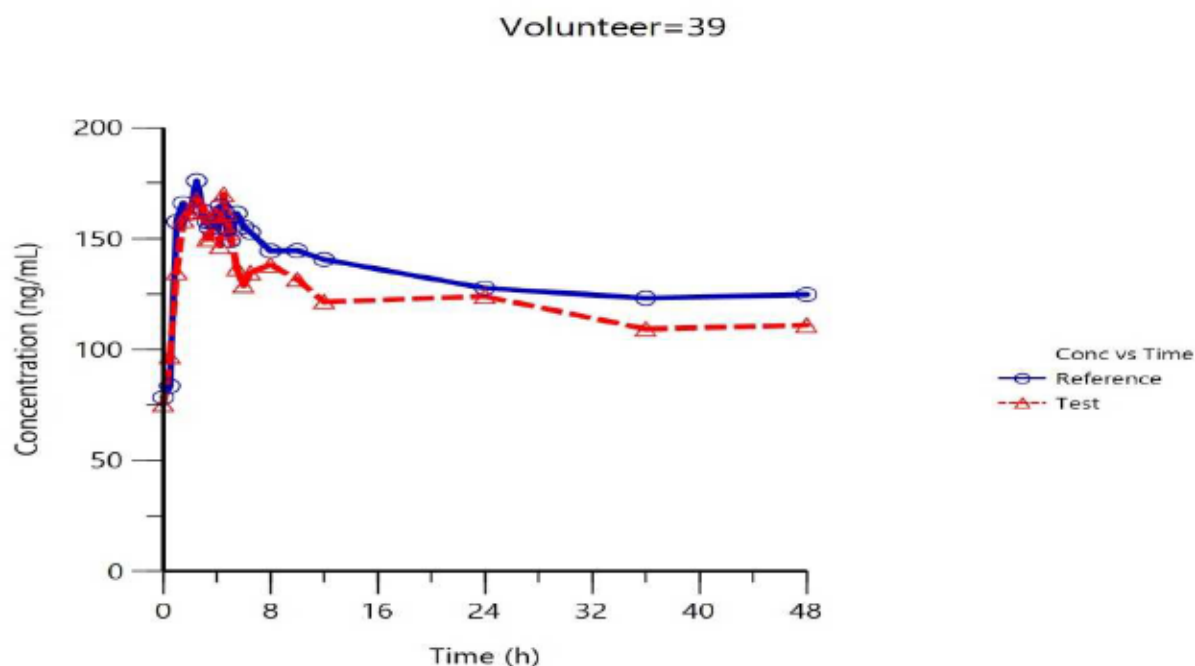



Figure 34. Levothyroxine concentration vs. subject 39's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	27 of 68

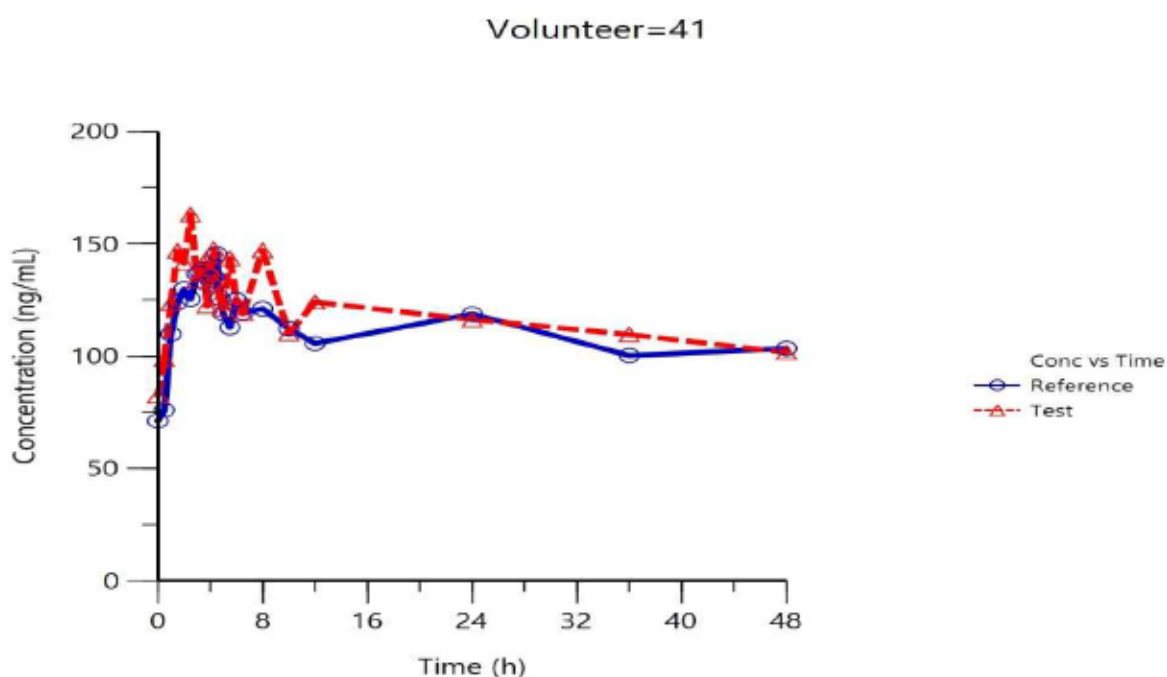


Figure 35. Levothyroxine concentration vs. subject 41's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

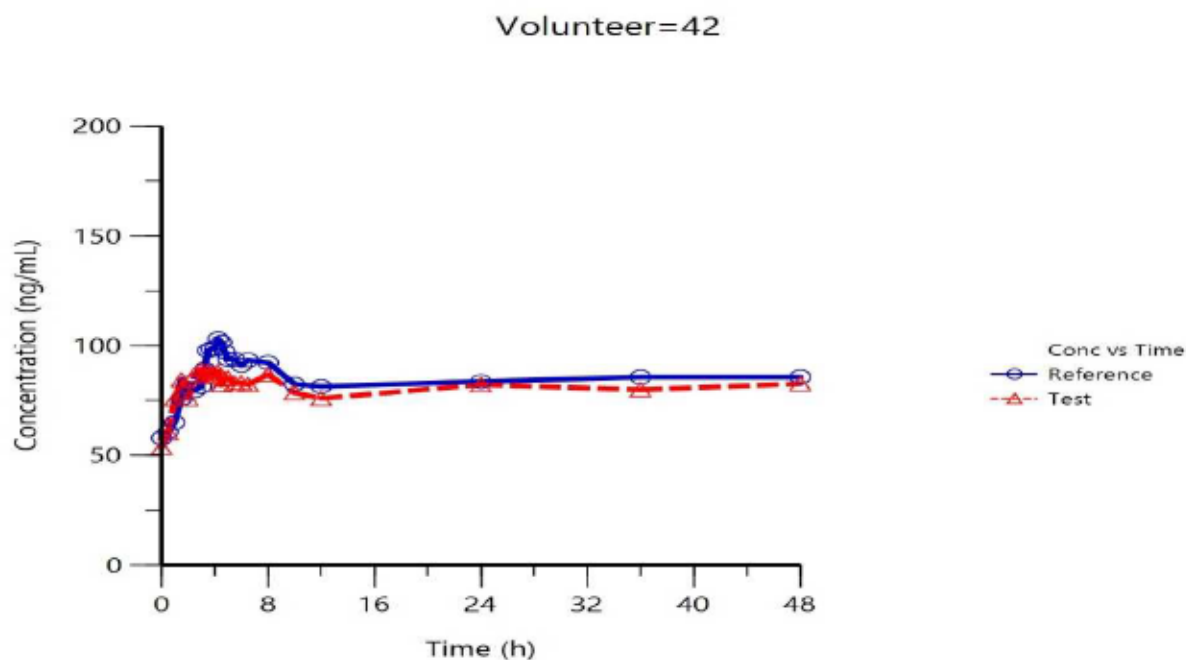



Figure 36. Levothyroxine concentration vs. subject 42's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	28 of 68

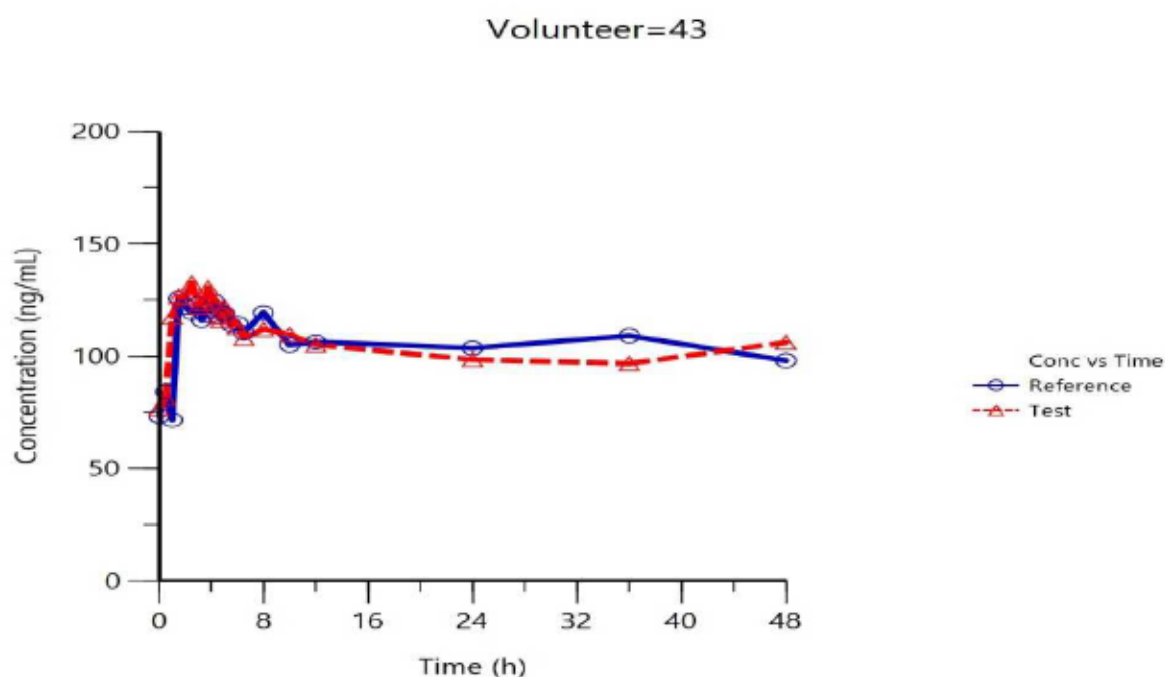


Figure 37. Levothyroxine concentration vs. subject 43's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

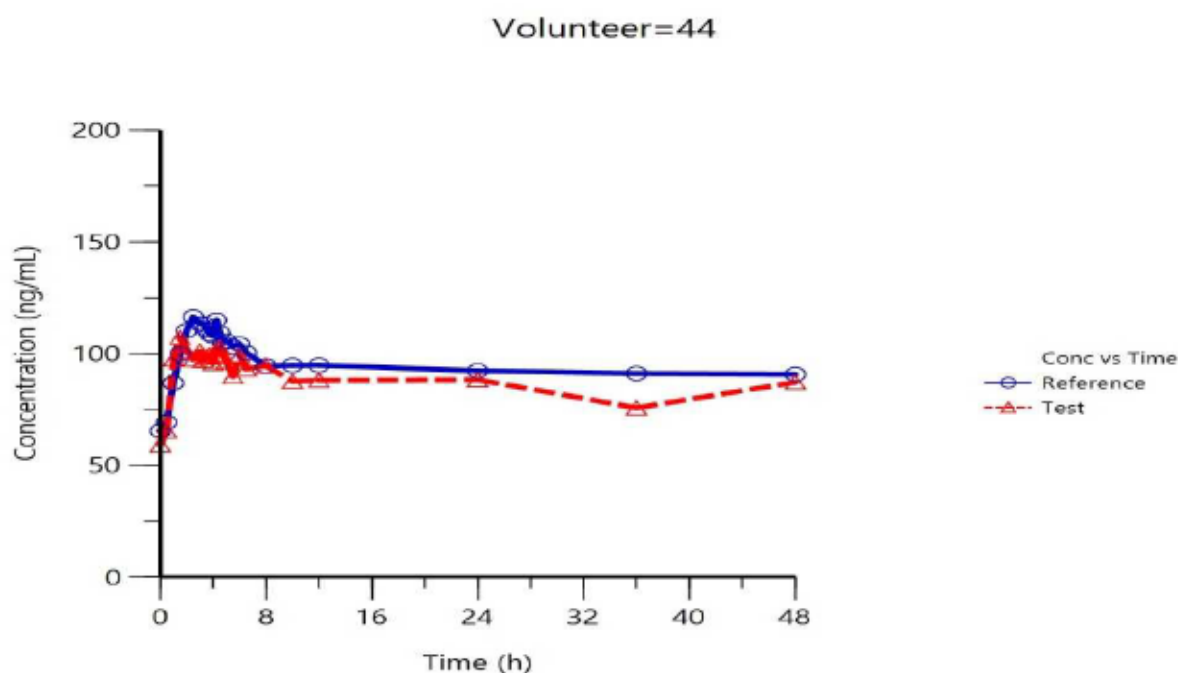



Figure 38. Levothyroxine concentration vs. subject 44's time plot, on an arithmetic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	29 of 68

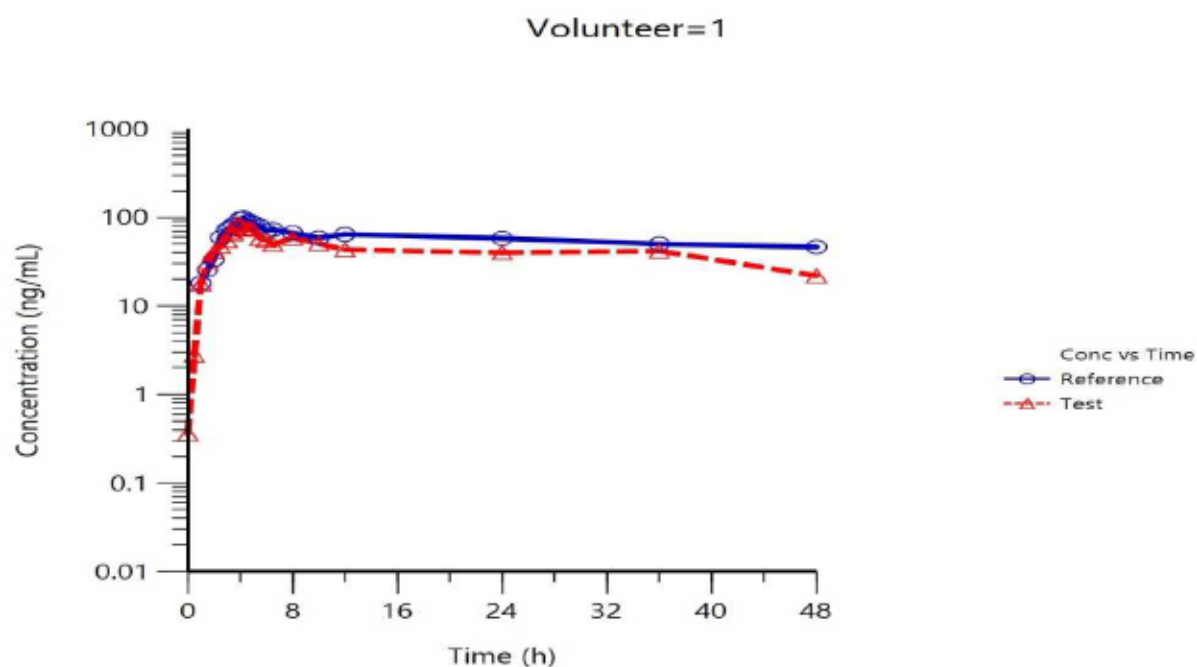


Figure 39. Levothyroxine concentration vs. subject 1's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

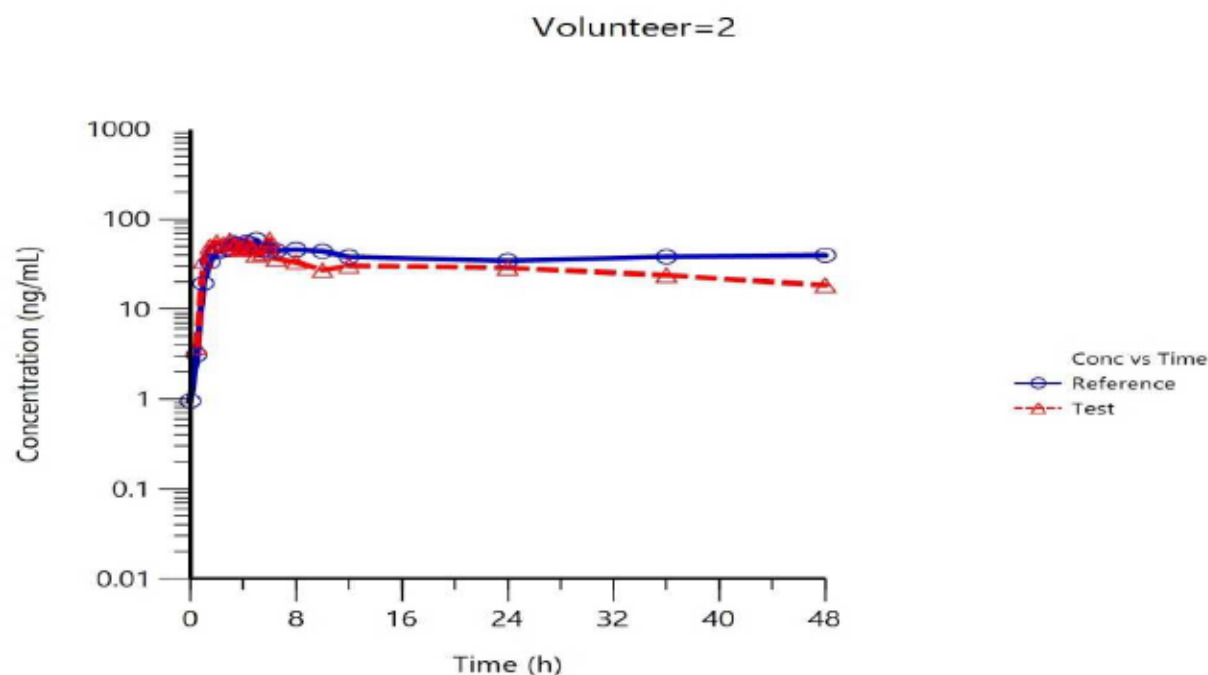



Figure 40. Levothyroxine concentration vs. subject 2's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	30 of 68

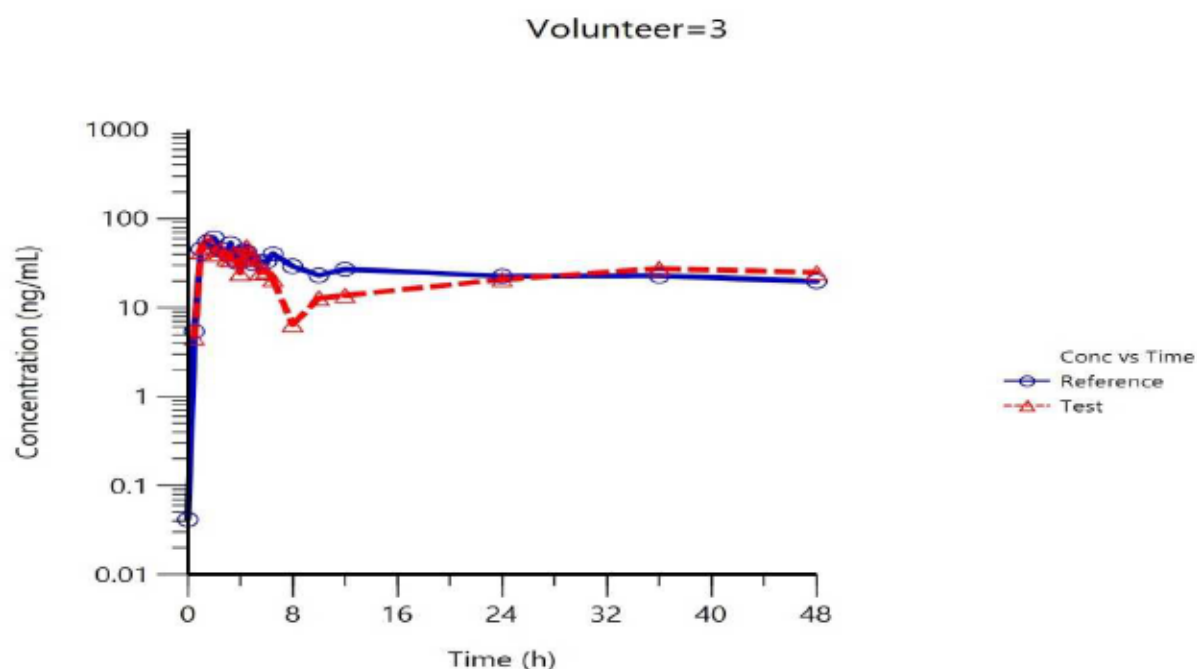


Figure 41. Levothyroxine concentration vs. subject 3's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

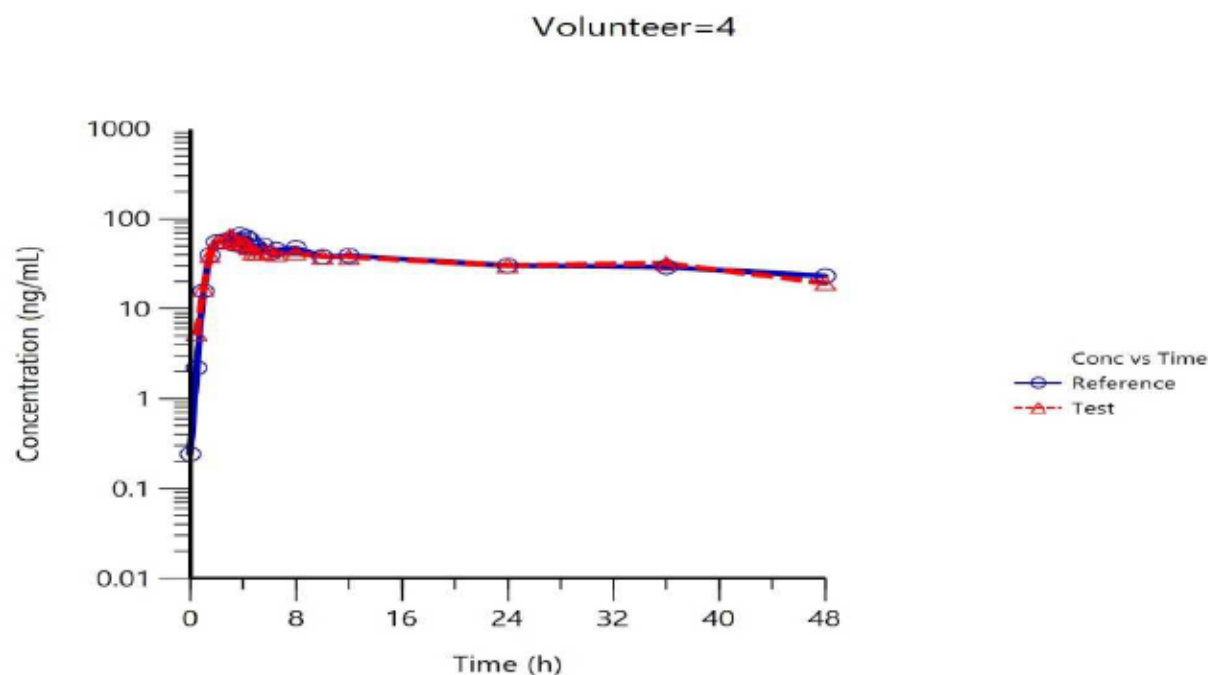



Figure 42. Levothyroxine concentration vs. subject 4's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	31 of 68

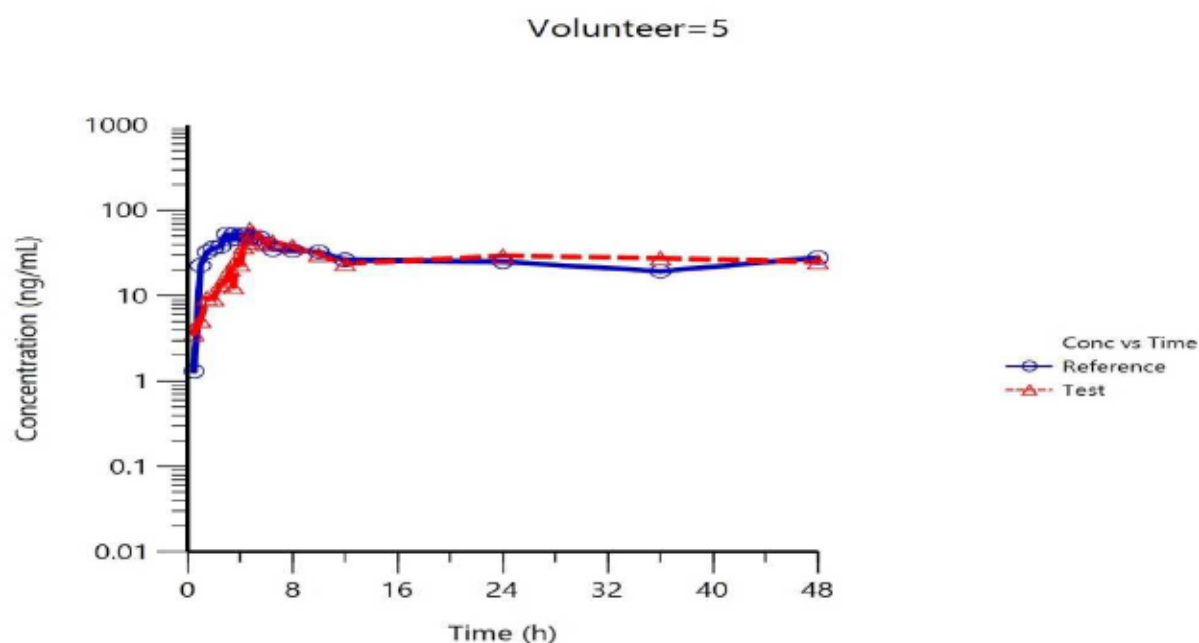


Figure 43. Levothyroxine concentration vs. subject 5's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

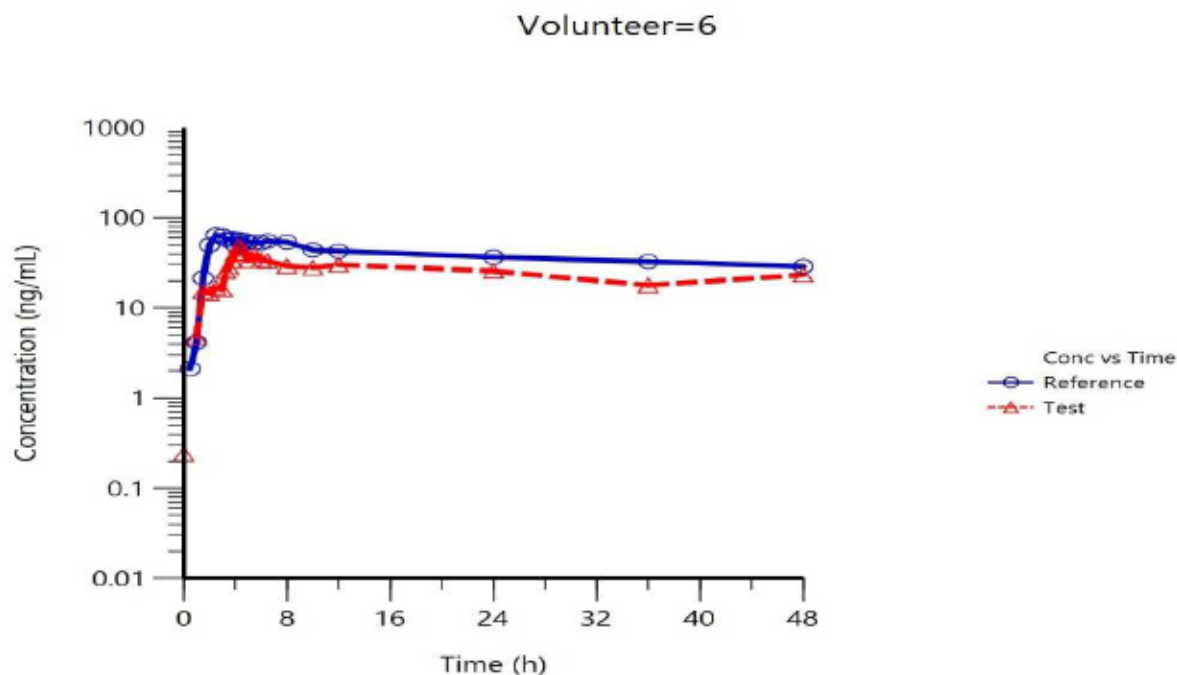



Figure 44. Levothyroxine concentration vs. subject 6's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	32 of 68

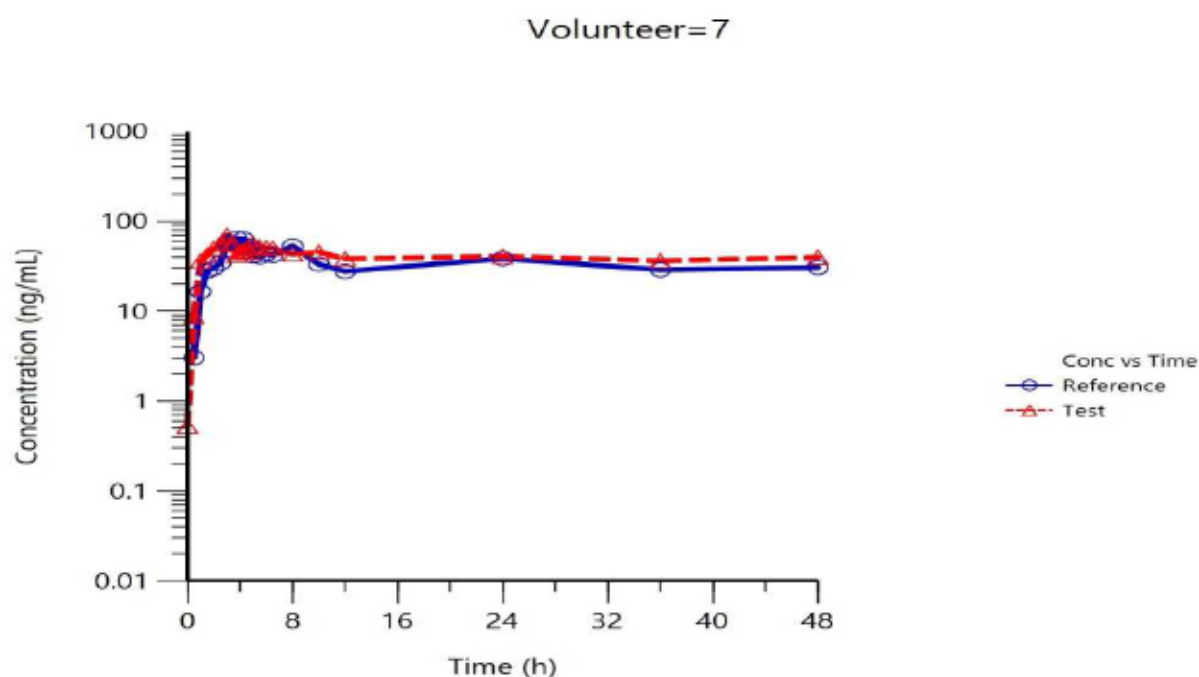


Figure 45. Levothyroxine concentration vs. subject 7's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

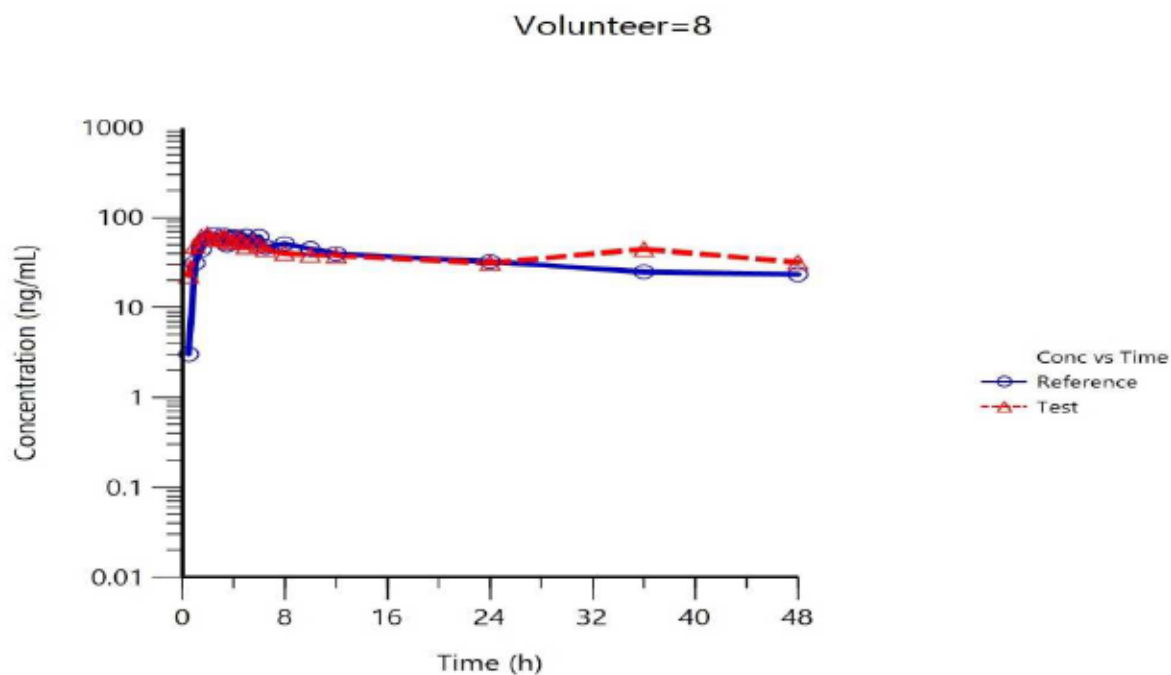



Figure 46. Levothyroxine concentration vs. subject 8's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	33 of 68

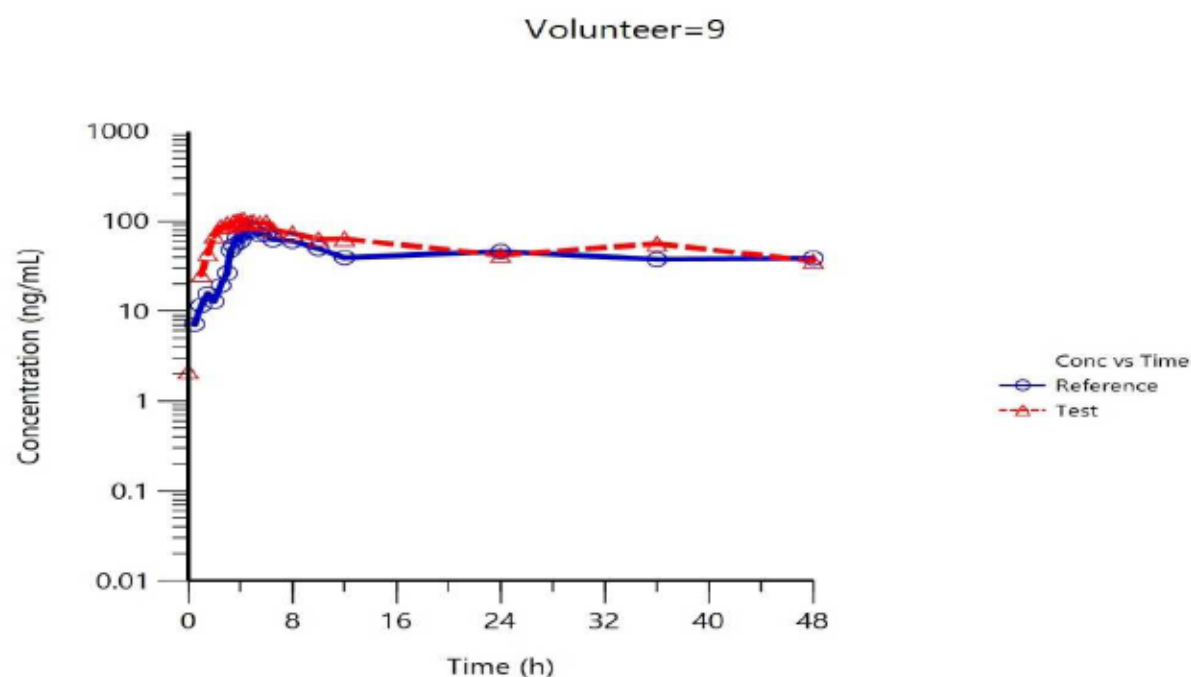


Figure 47. Levothyroxine concentration vs. subject 9's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

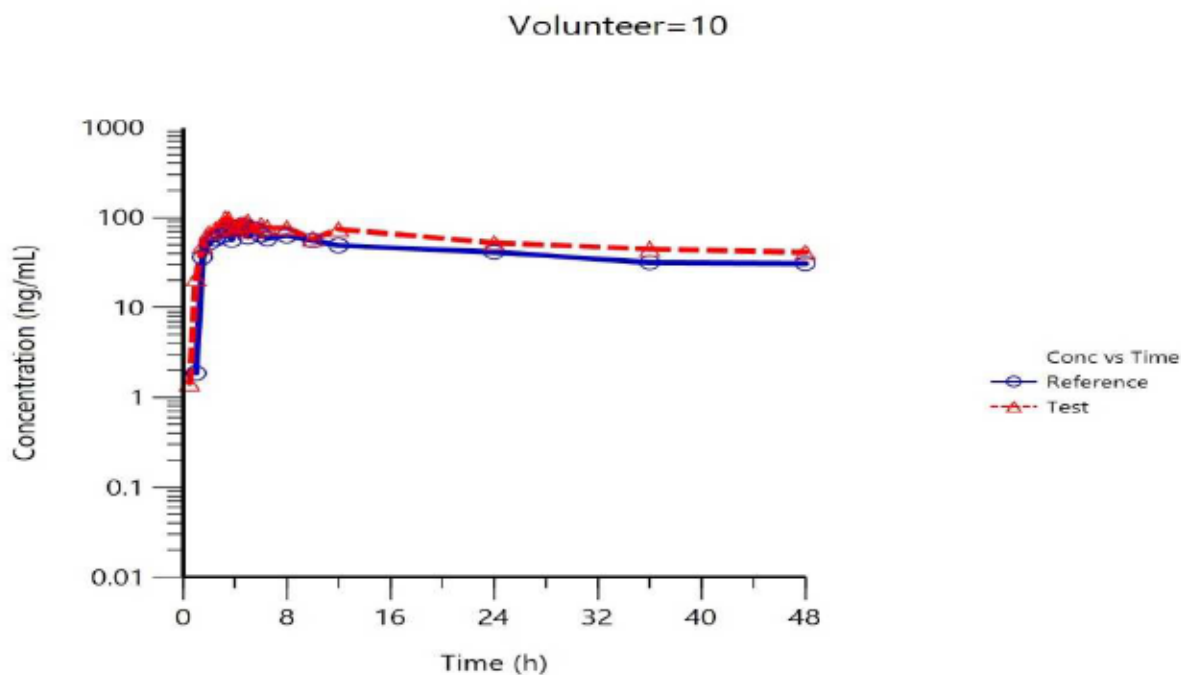



Figure 48. Levothyroxine concentration vs. subject 10's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	34 of 68

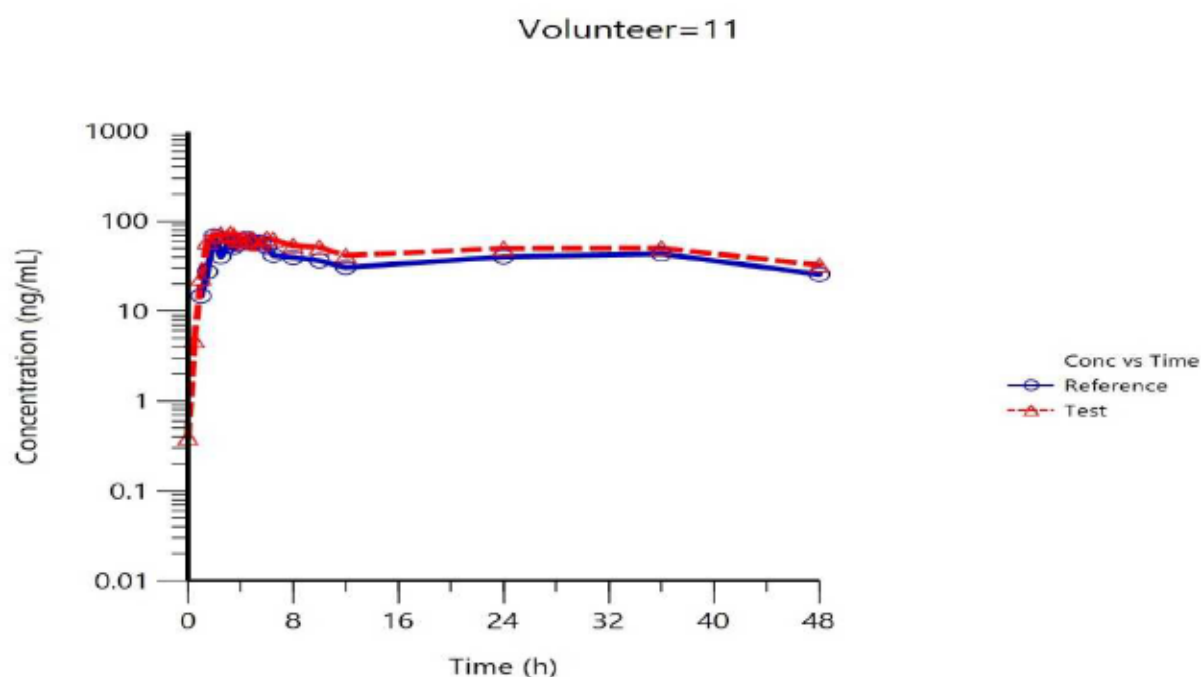


Figure 49. Levothyroxine concentration vs. subject 11's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

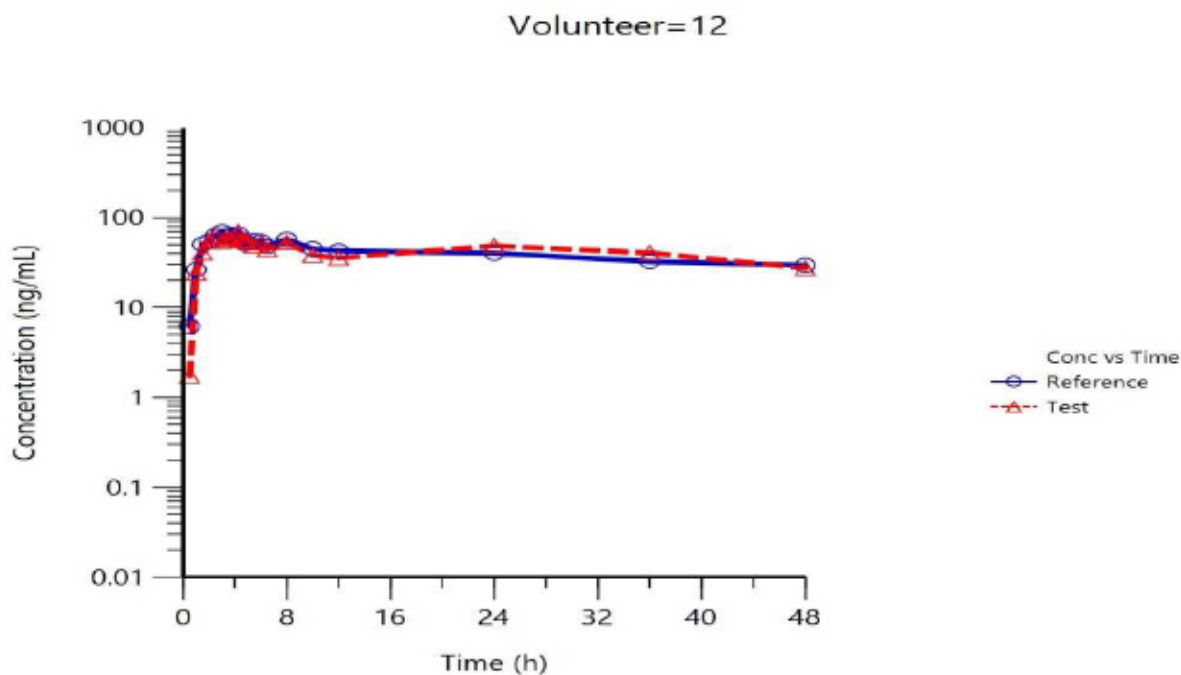



Figure 50. Levothyroxine concentration vs. subject 12's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	35 of 68

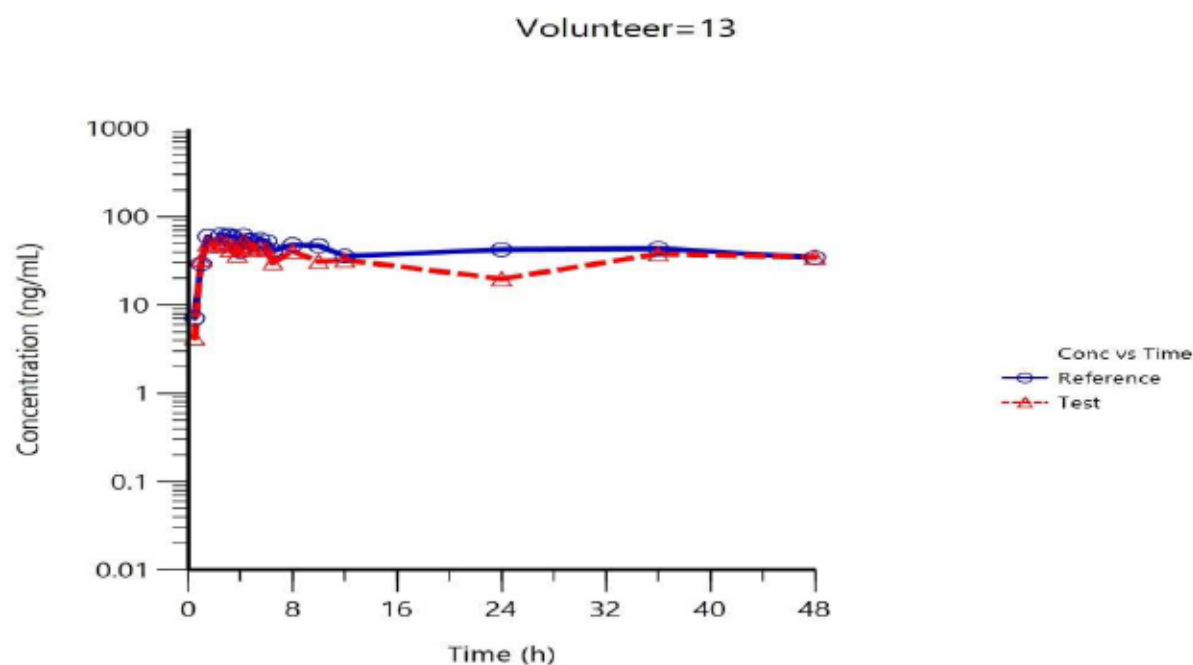


Figure 51. Levothyroxine concentration vs. subject 13's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

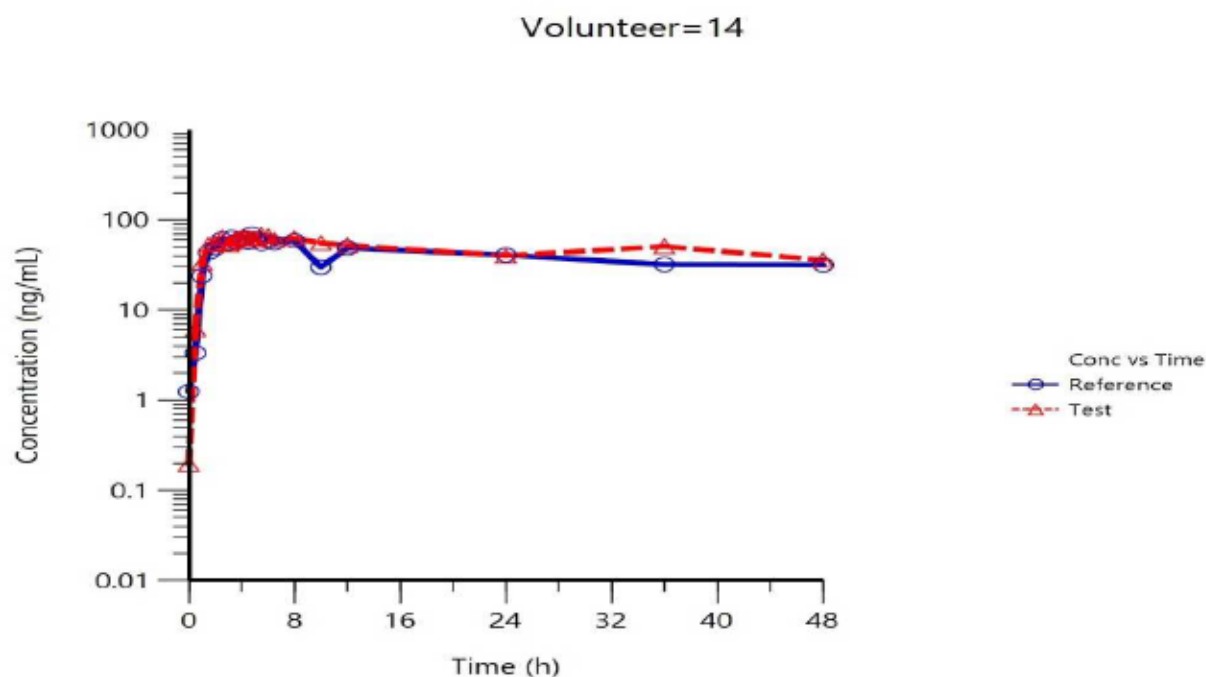



Figure 52. Levothyroxine concentration vs. subject 14's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	36 of 68

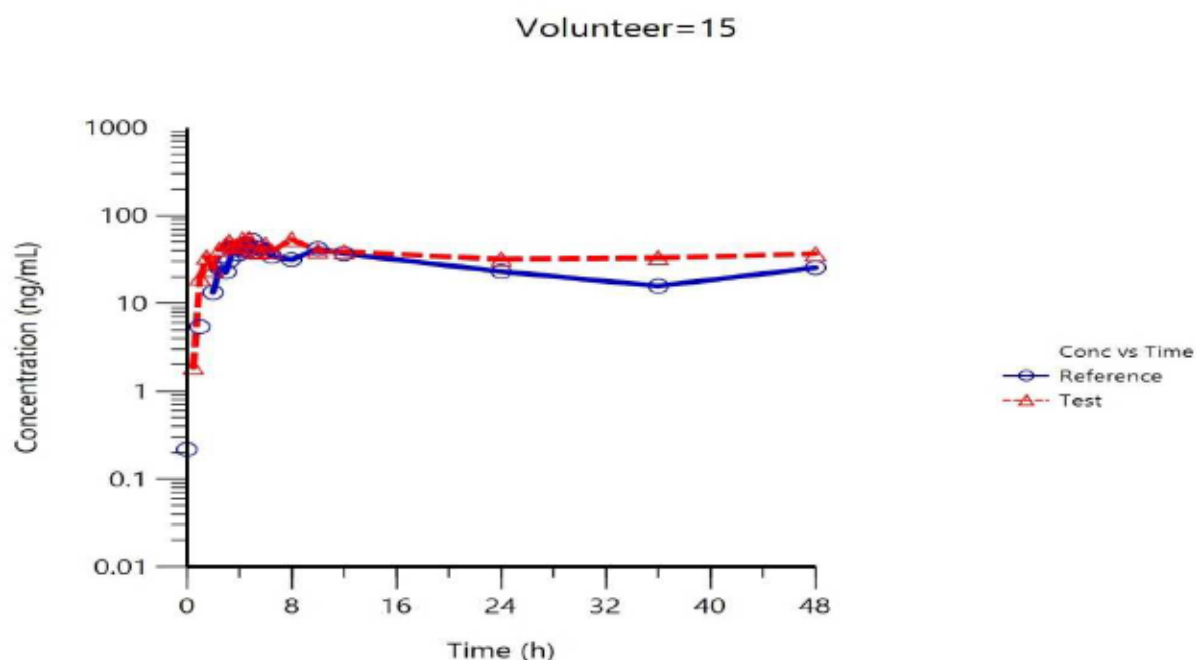


Figure 53. Levothyroxine concentration vs. subject 15's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

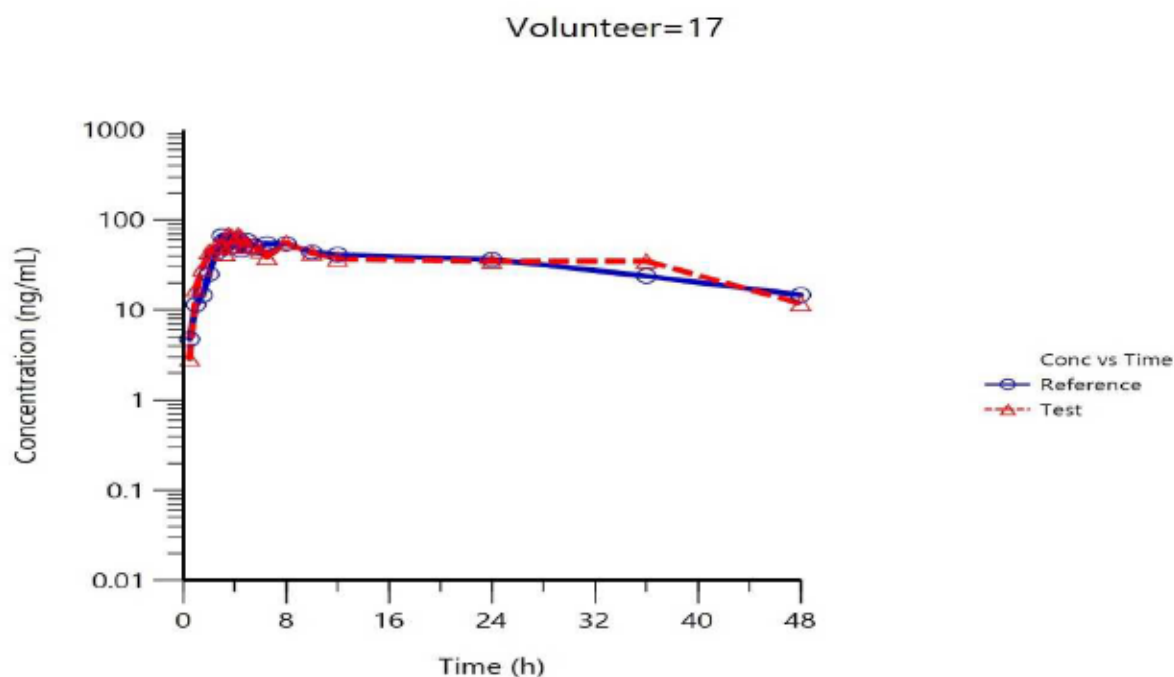



Figure 54. Levothyroxine concentration vs. subject 17's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	37 of 68

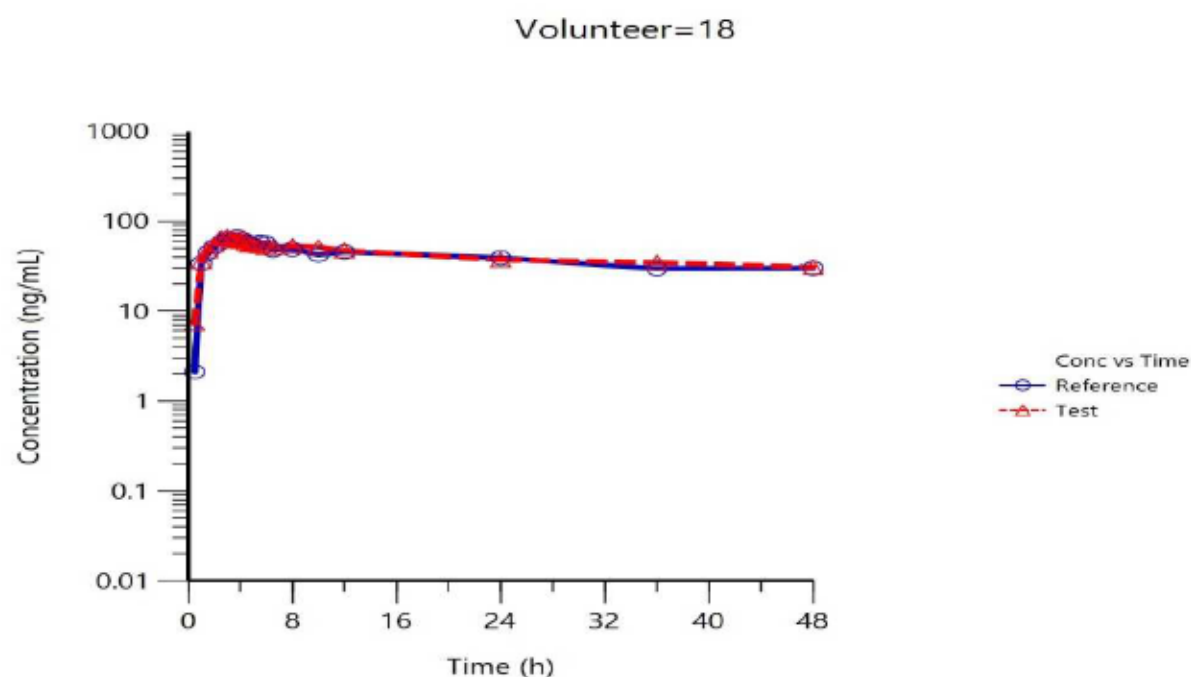


Figure 55. Levothyroxine concentration vs. subject 18's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

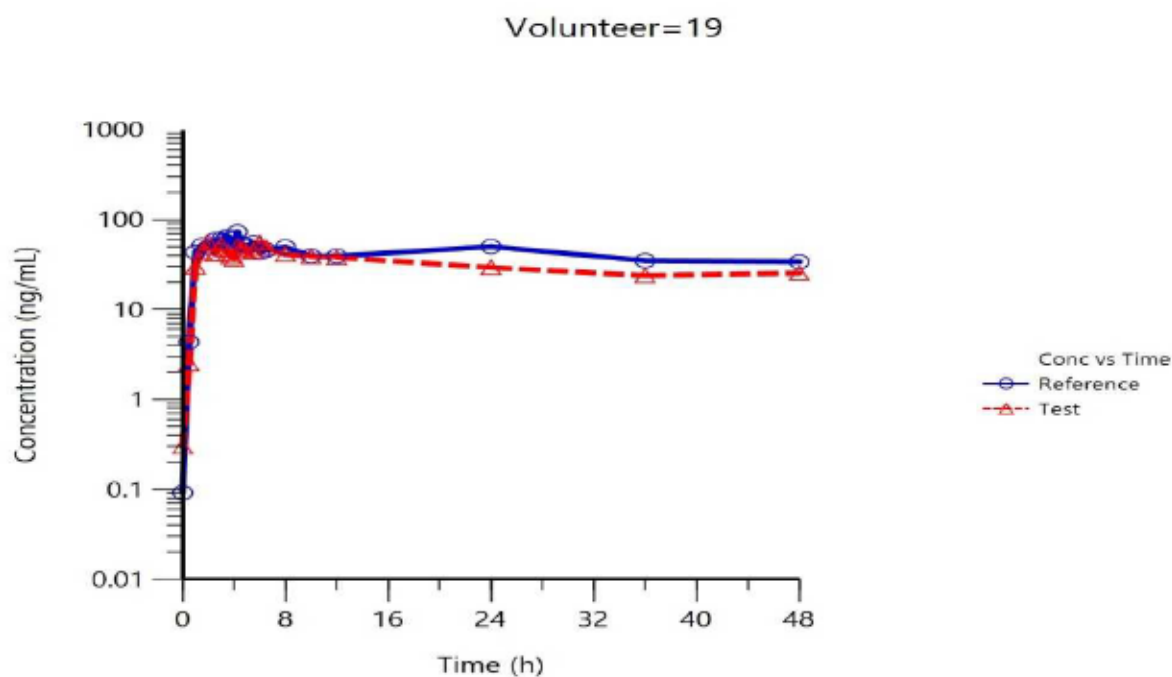



Figure 56. Levothyroxine concentration vs. subject 19's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	38 of 68

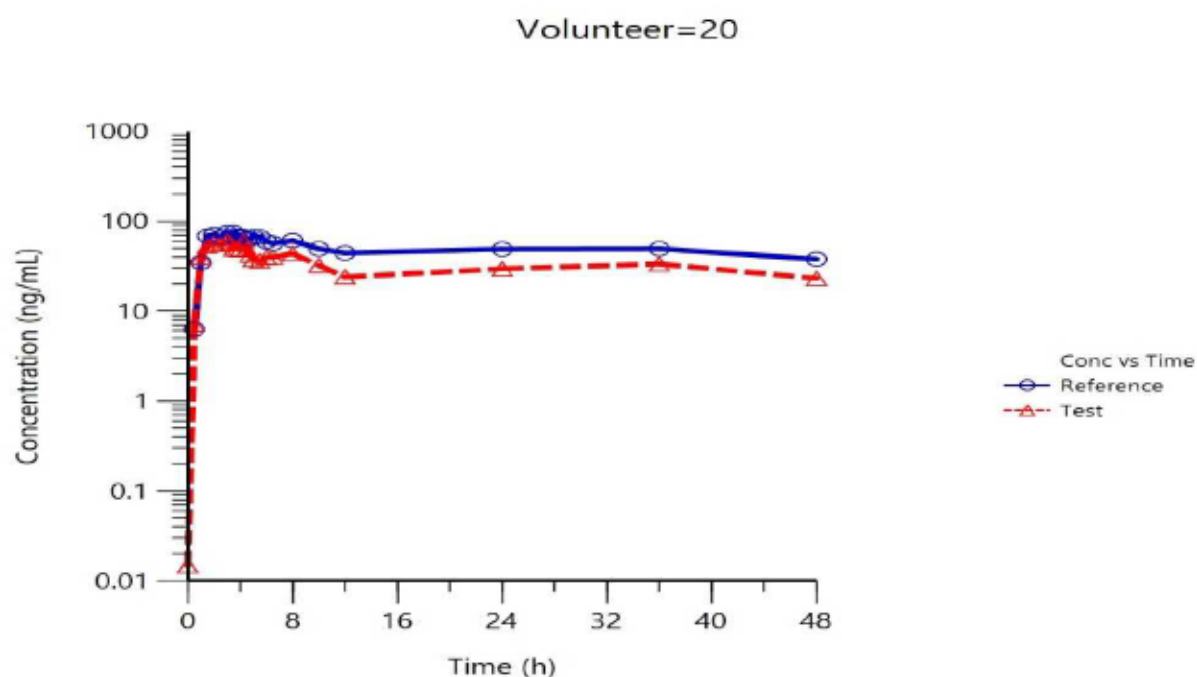


Figure 57. Levothyroxine concentration vs. subject 20's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

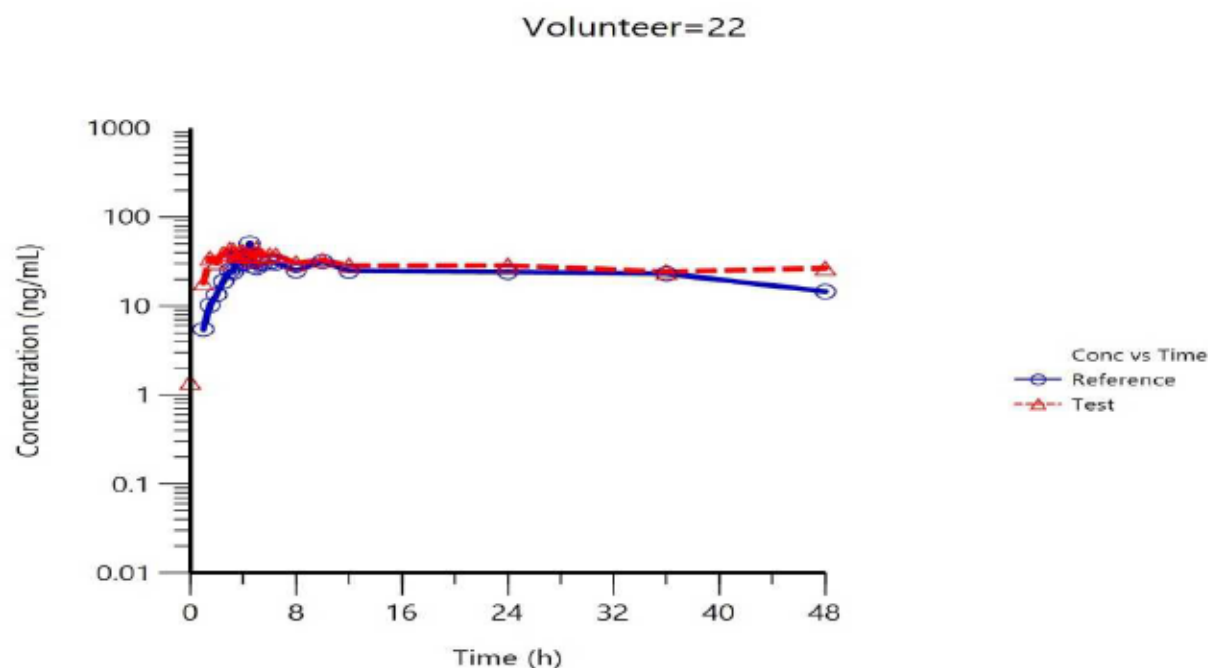



Figure 58. Levothyroxine concentration vs. subject 22's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	39 of 68

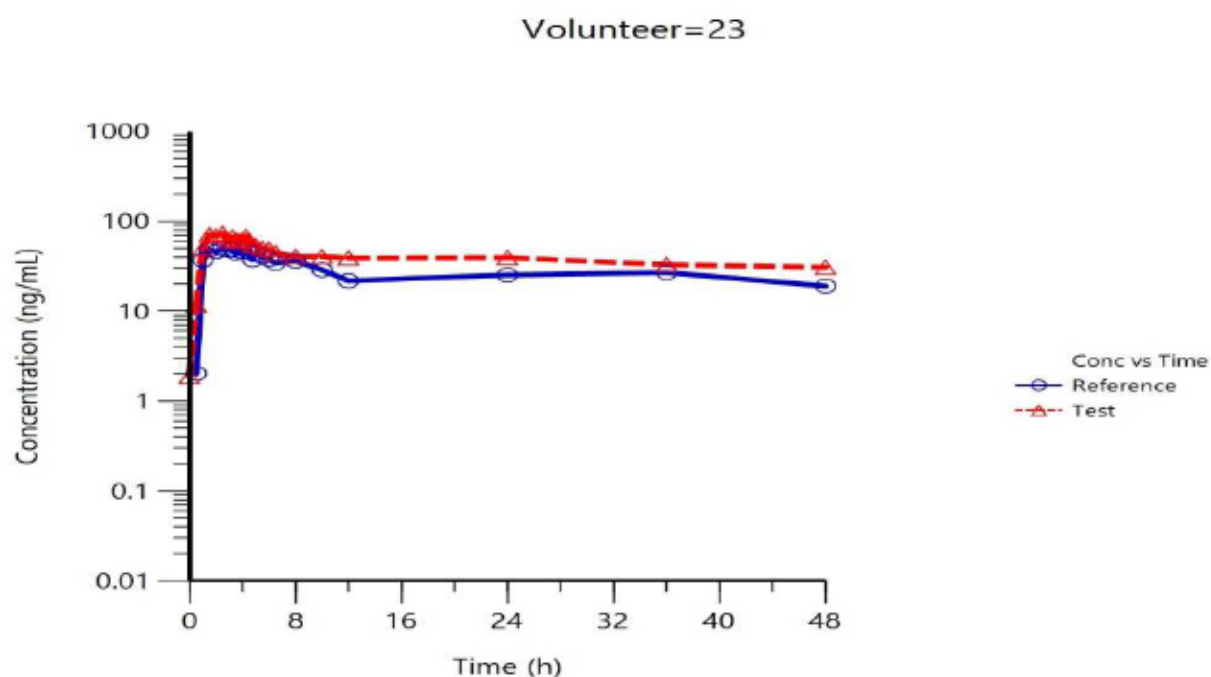


Figure 59. Levothyroxine concentration vs. subject 23's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

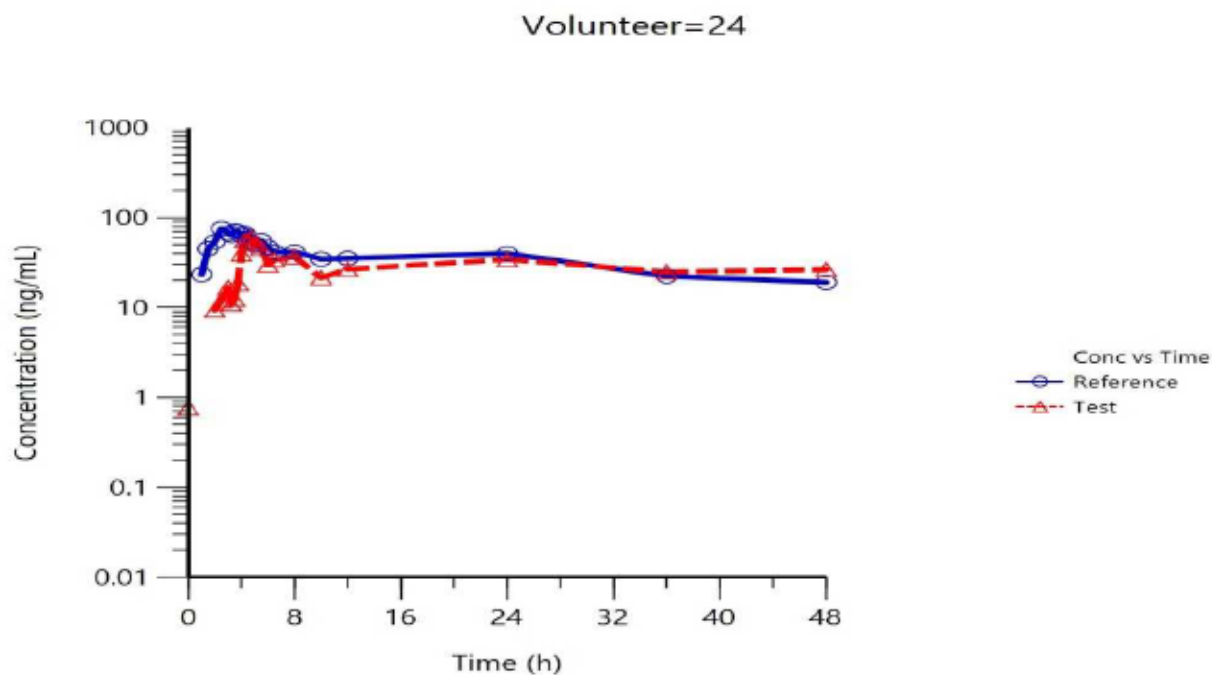



Figure 60. Levothyroxine concentration vs. subject 24's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	40 of 68

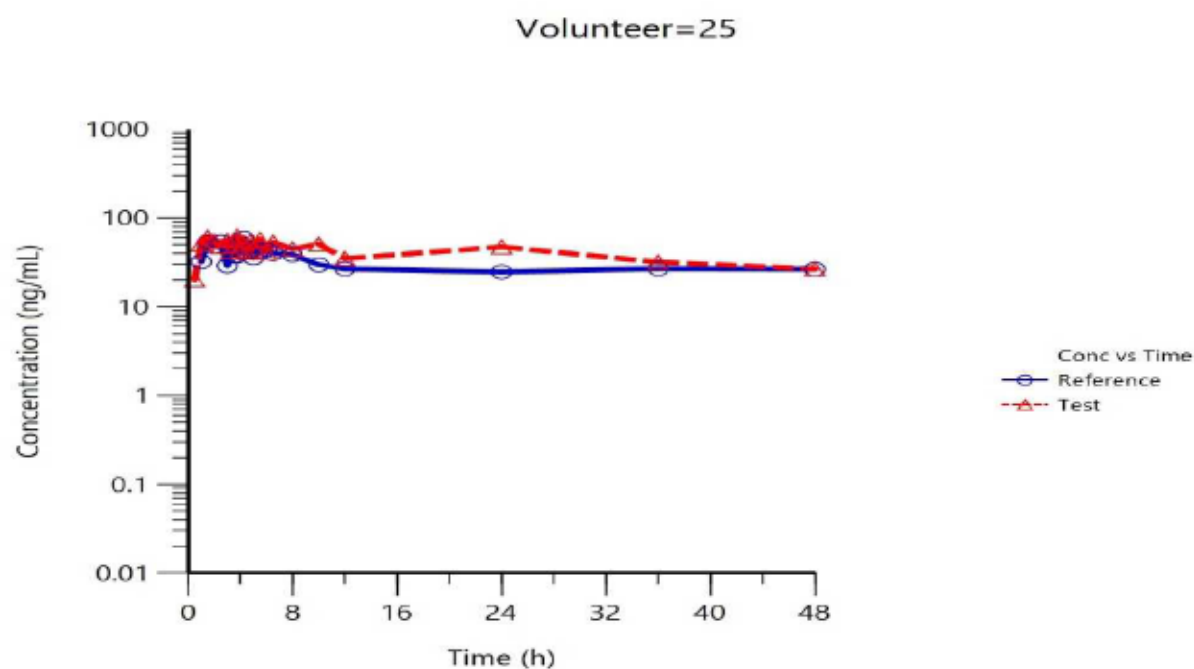


Figure 61. Levothyroxine concentration vs. subject 25's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

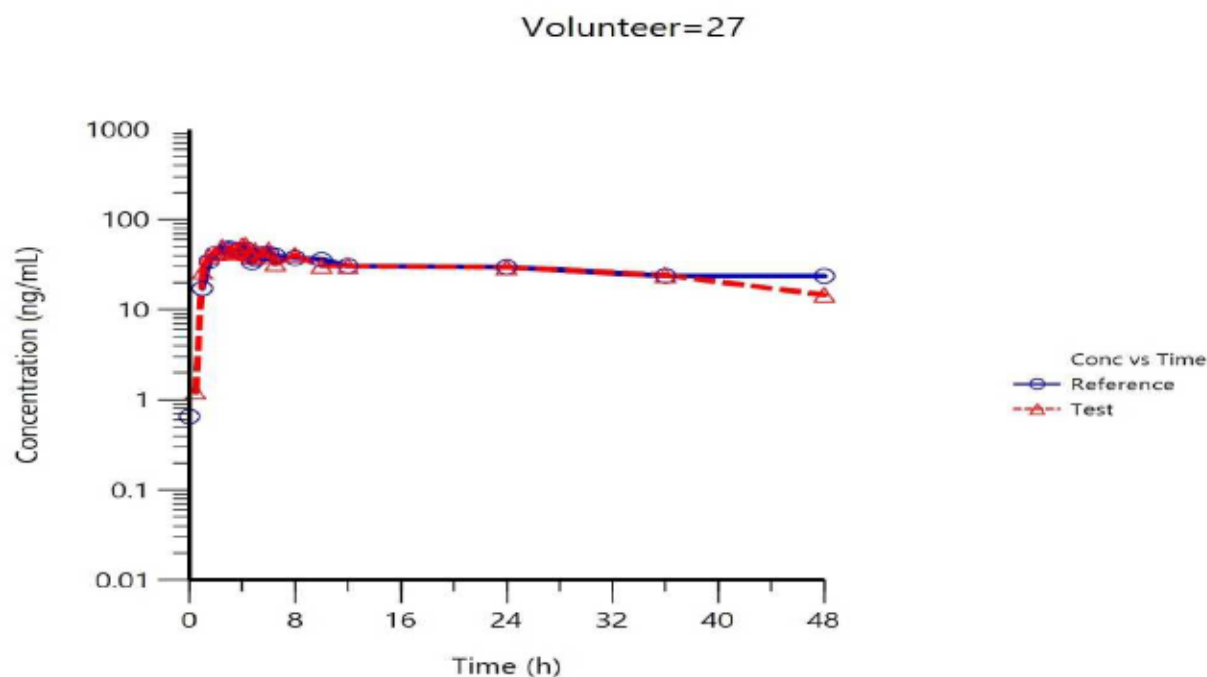



Figure 62. Levothyroxine concentration vs. subject 27's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	41 of 68

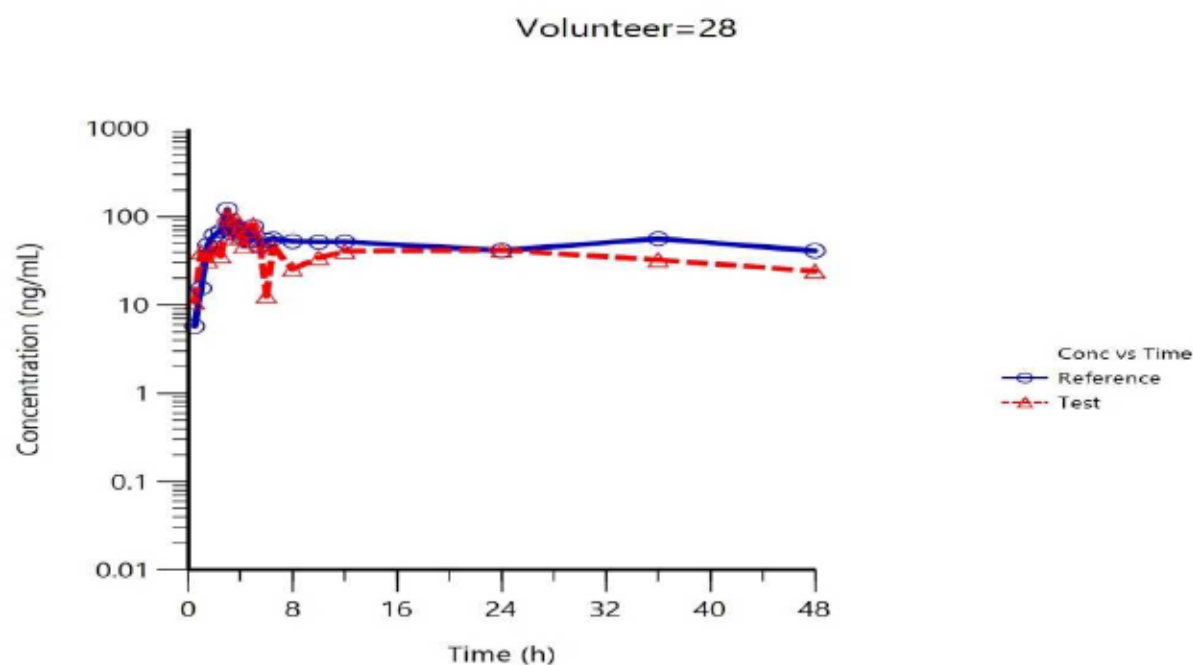


Figure 63. Levothyroxine concentration vs. subject 28's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

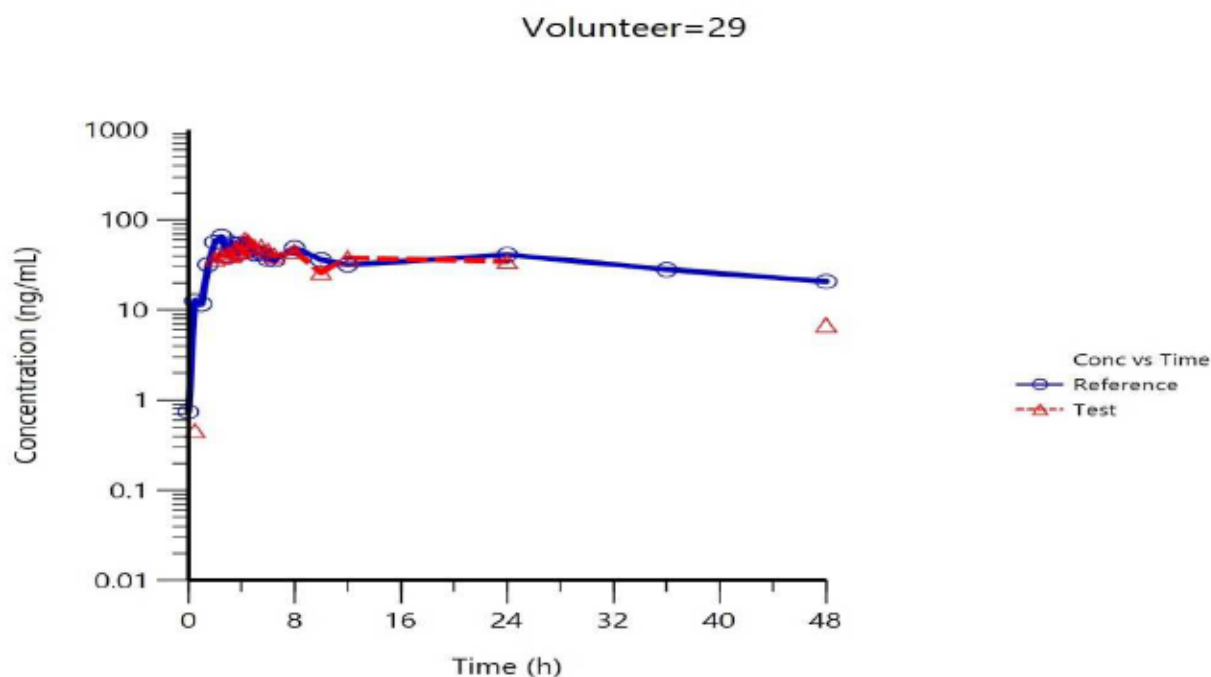



Figure 64. Levothyroxine concentration vs. subject 29's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	42 of 68

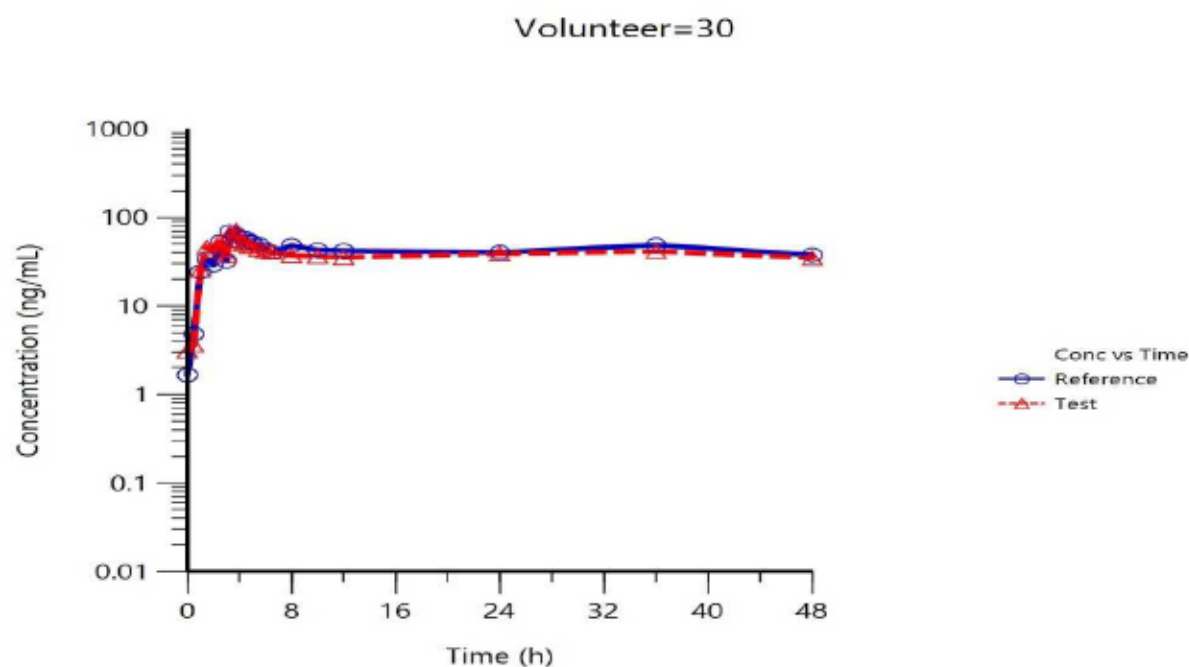


Figure 65. Levothyroxine concentration vs. subject 30's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

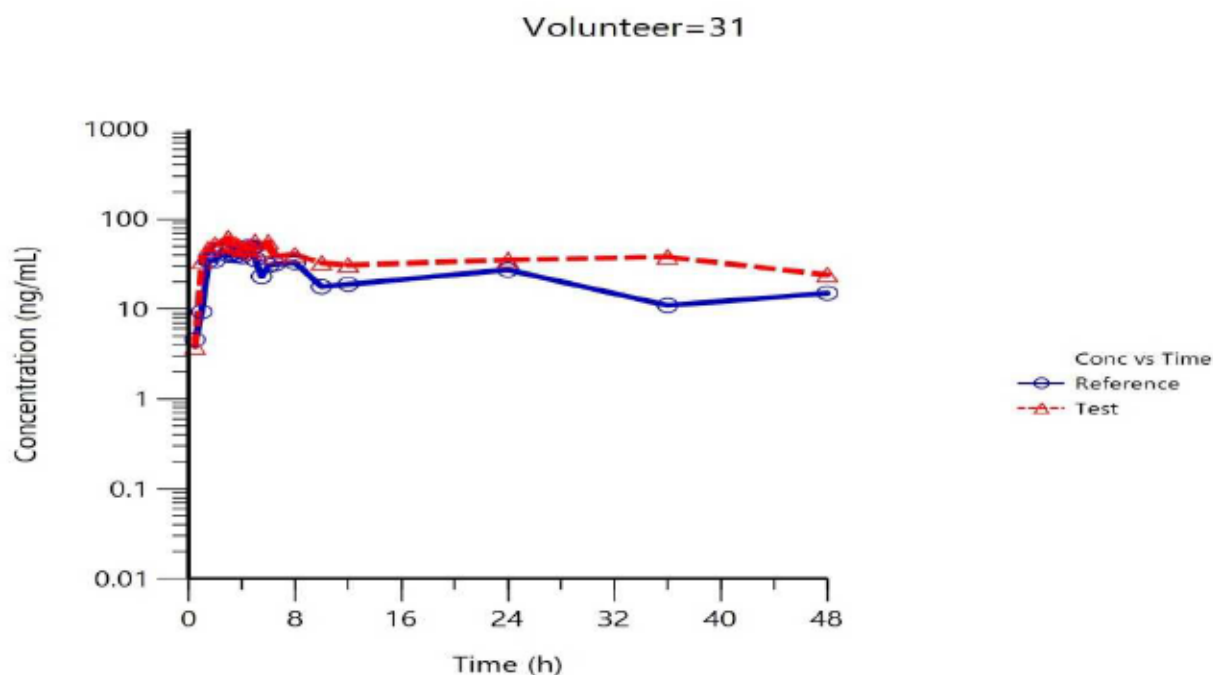



Figure 66. Levothyroxine concentration vs. subject 31's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	43 of 68

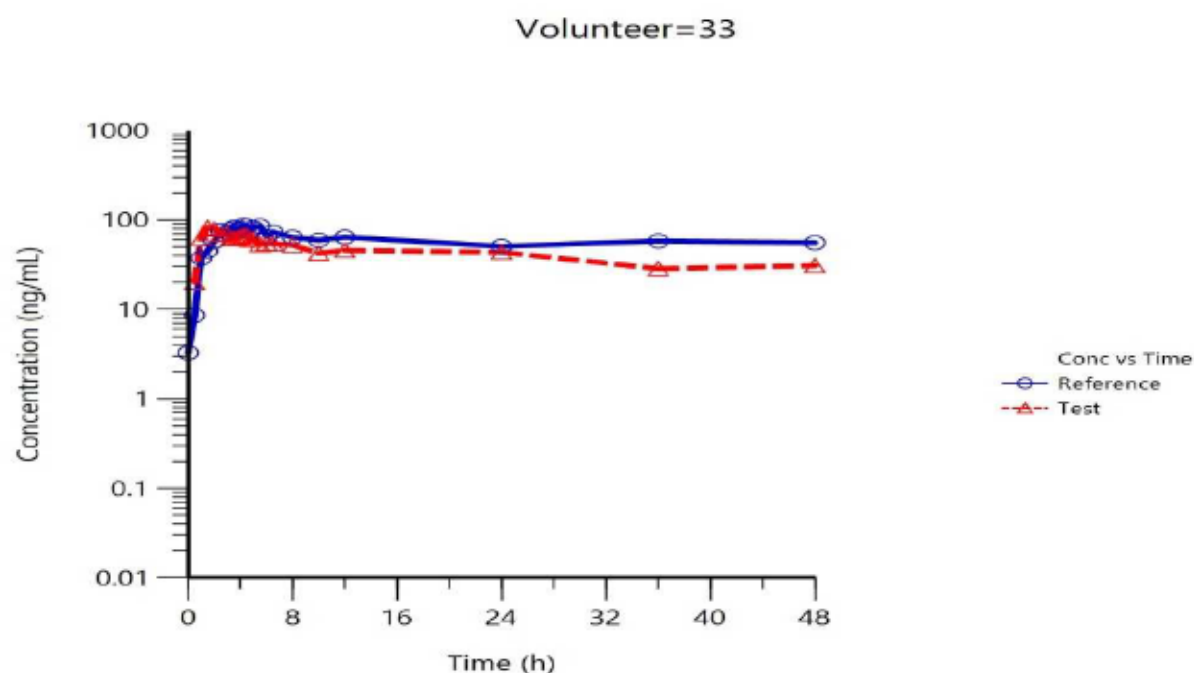


Figure 67. Levothyroxine concentration vs. subject 33's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

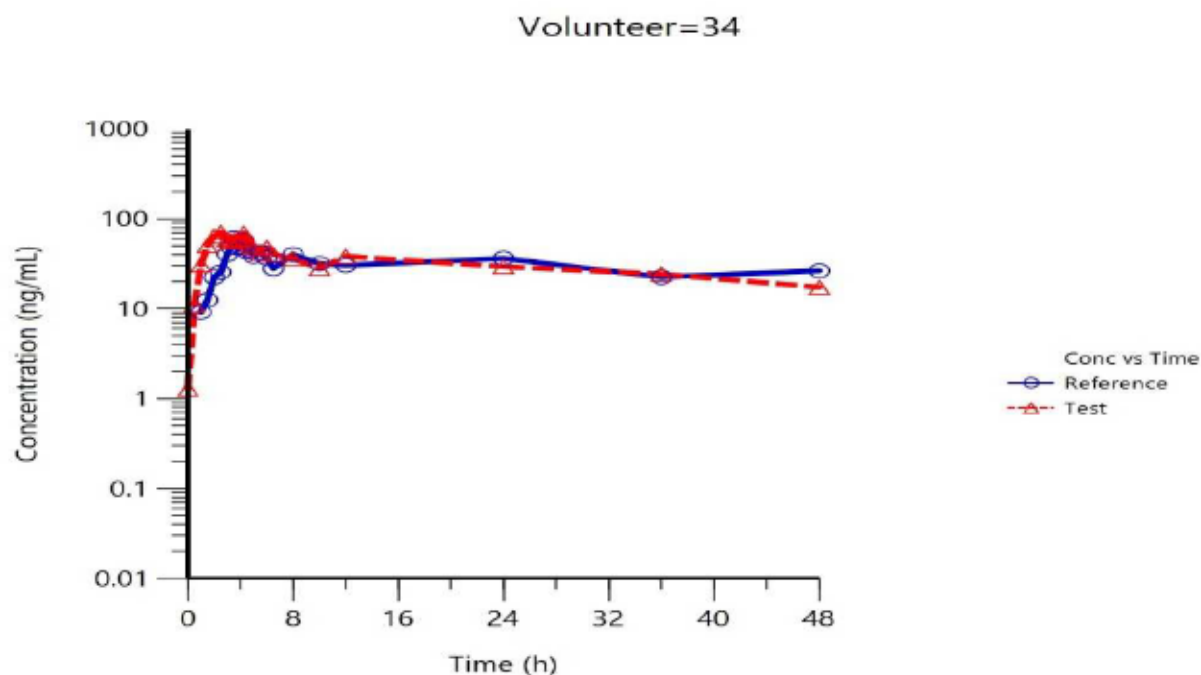



Figure 68. Levothyroxine concentration vs. subject 34's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	44 of 68

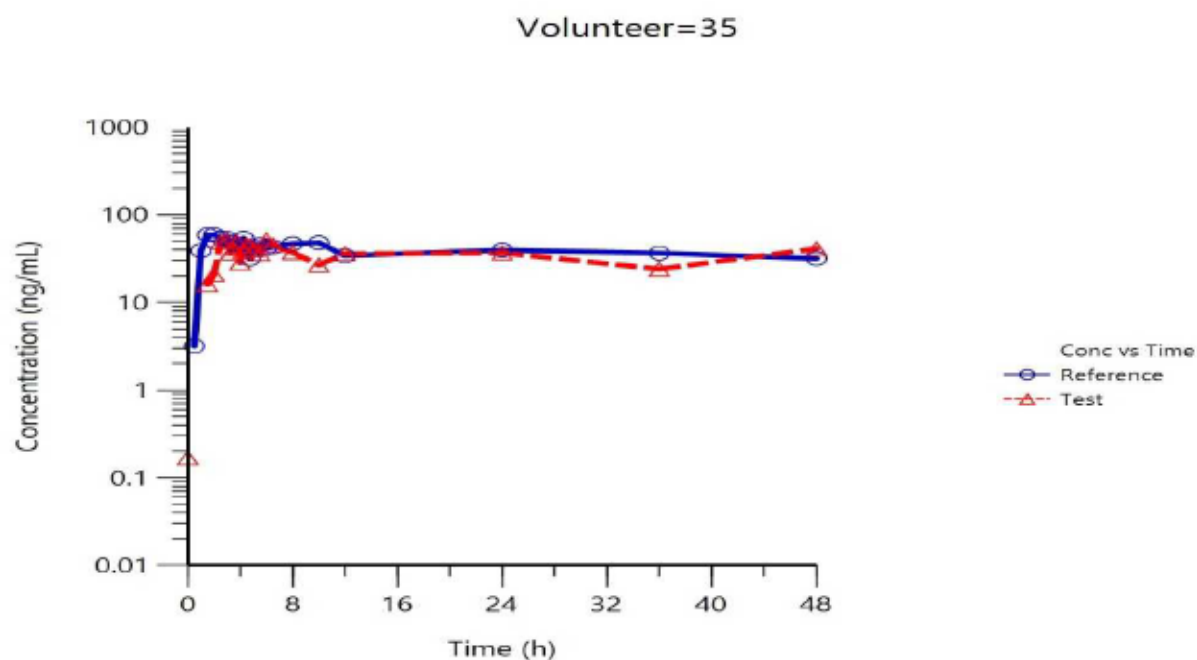


Figure 69. Levothyroxine concentration vs. subject 35's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

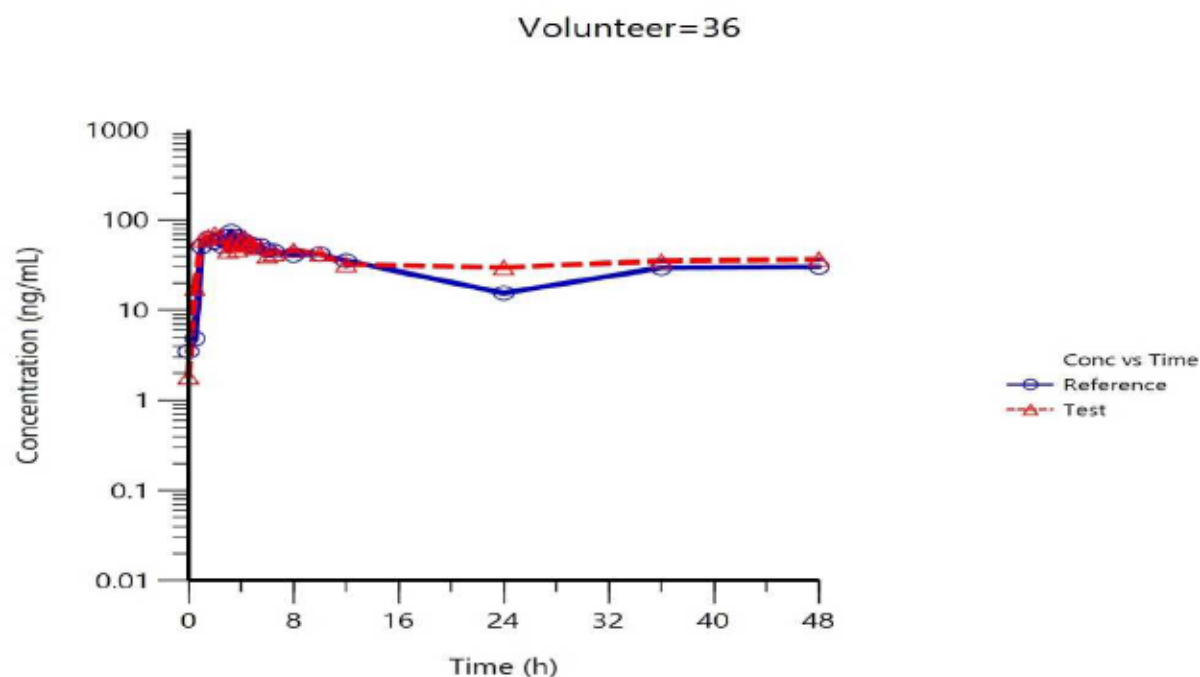



Figure 70. Levothyroxine concentration vs. subject 36's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	45 of 68

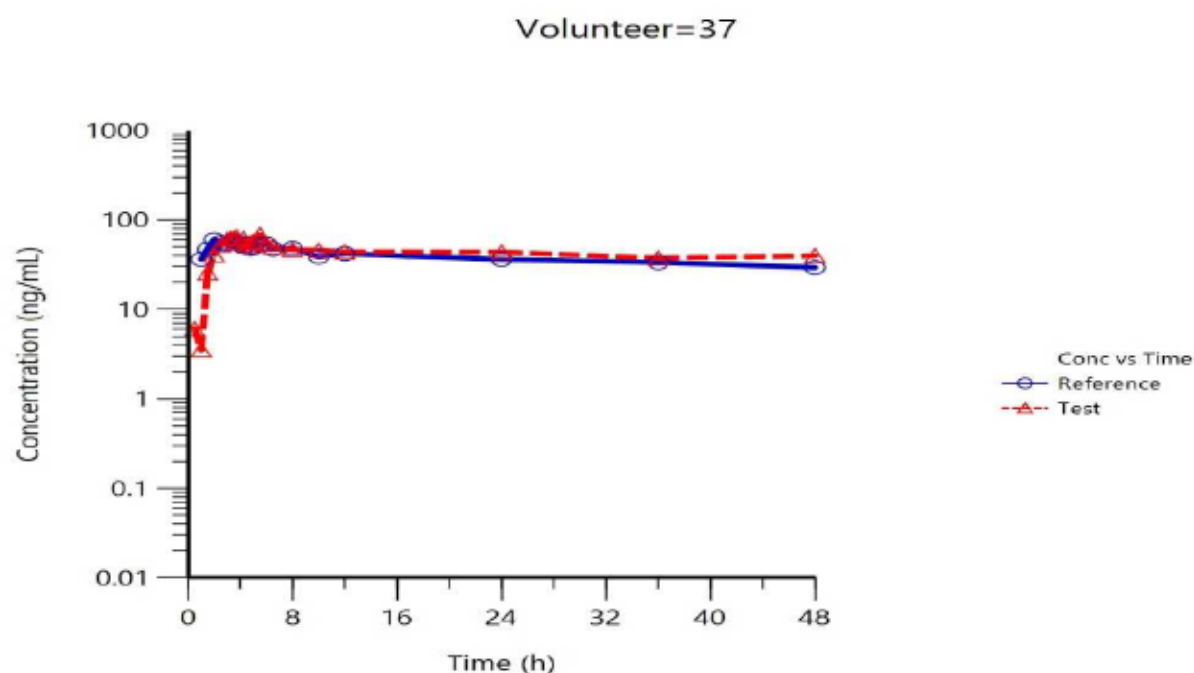


Figure 71. Levothyroxine concentration vs. subject 37's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

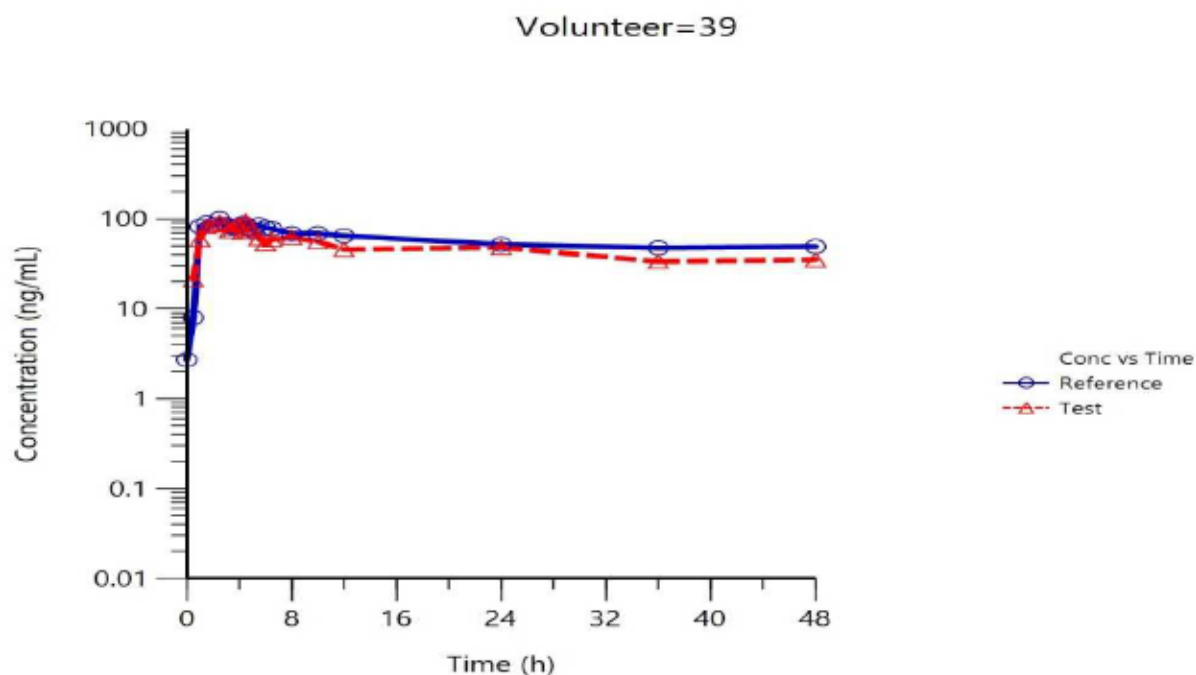



Figure 72. Levothyroxine concentration vs. subject 39's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	46 of 68

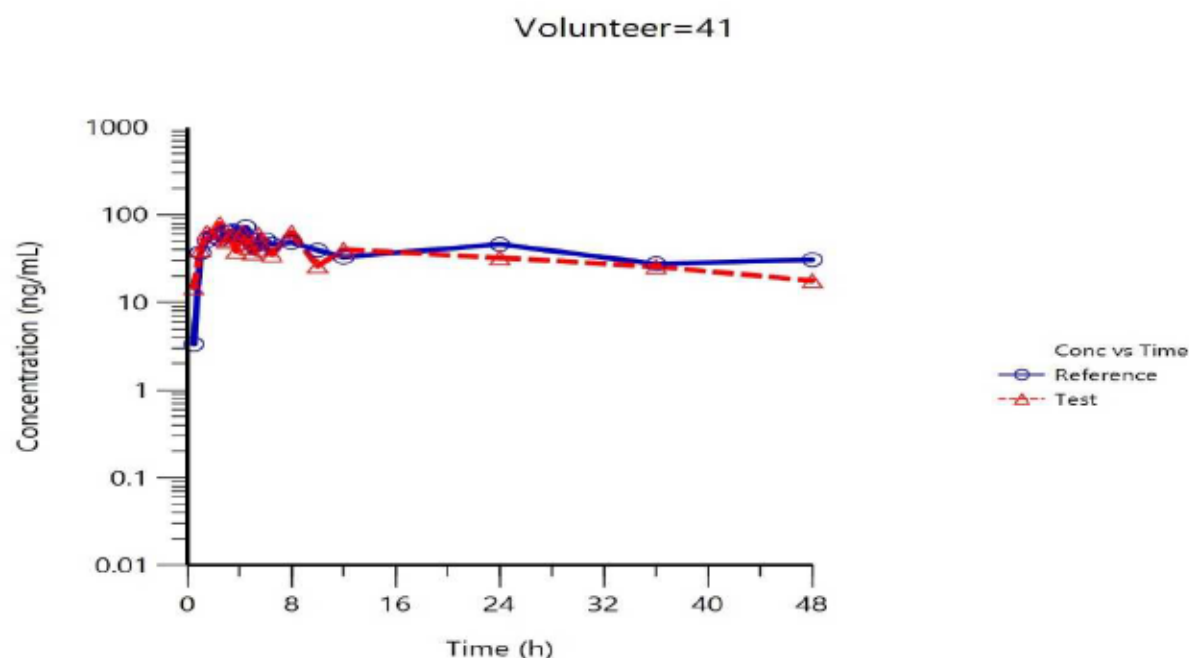


Figure 73. Levothyroxine concentration vs. subject 41's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

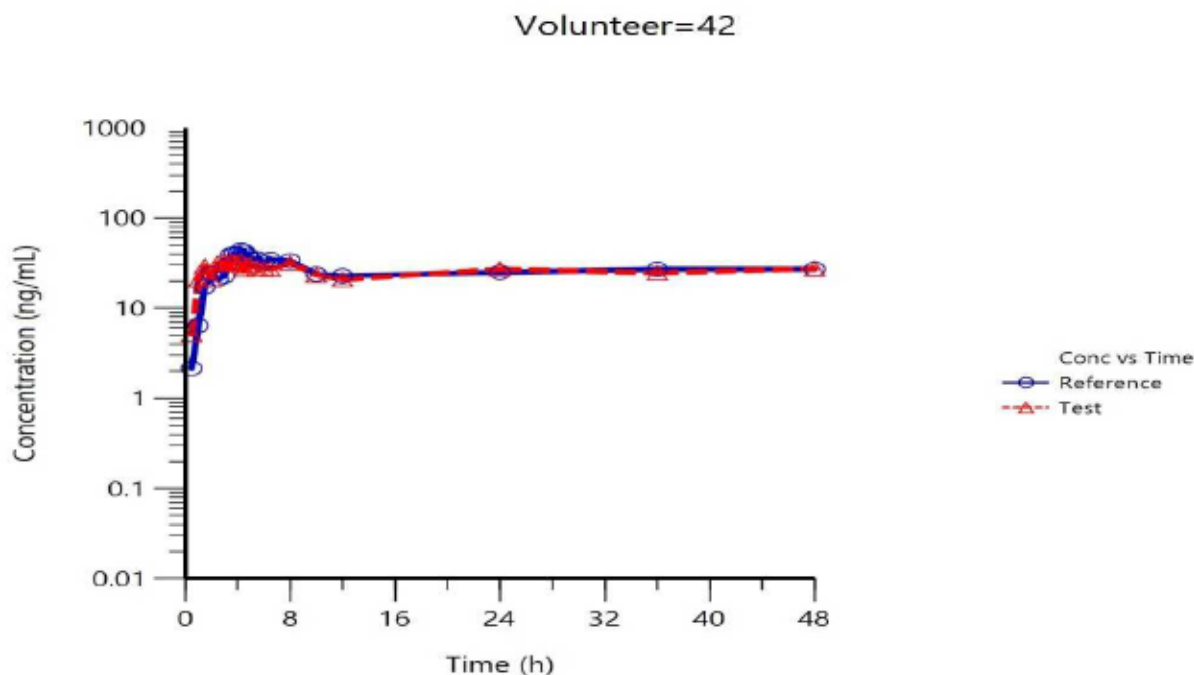



Figure 74. Levothyroxine concentration vs. subject 42's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	47 of 68

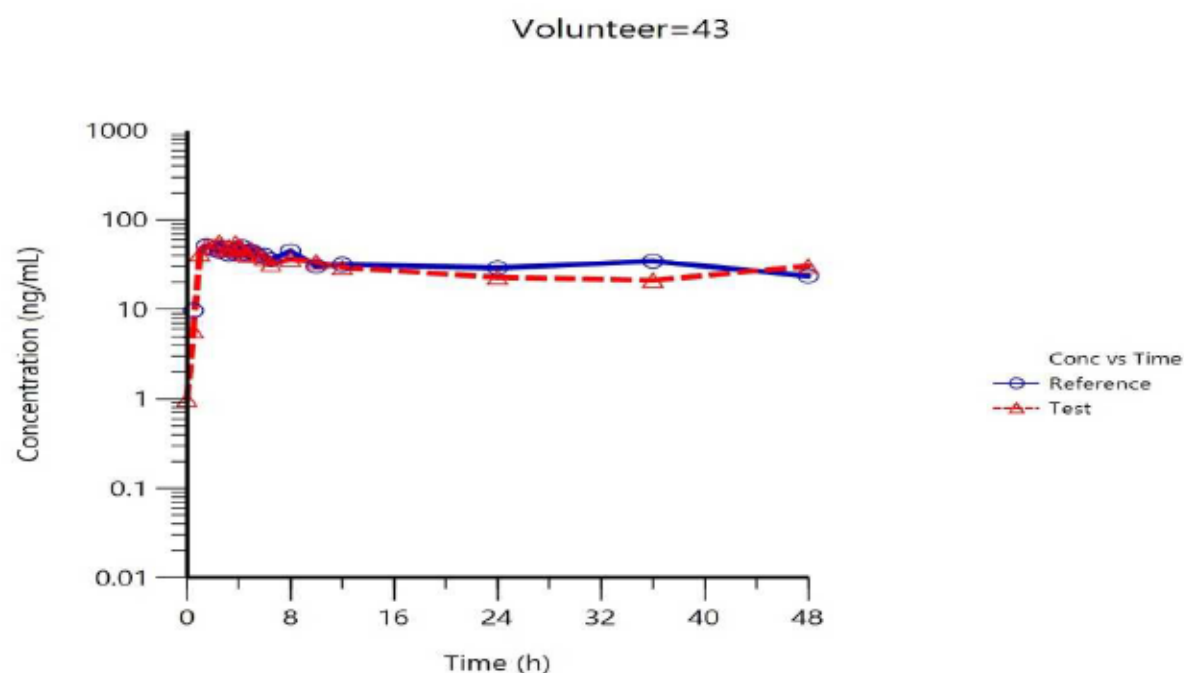


Figure 75. Levothyroxine concentration vs. subject 43's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

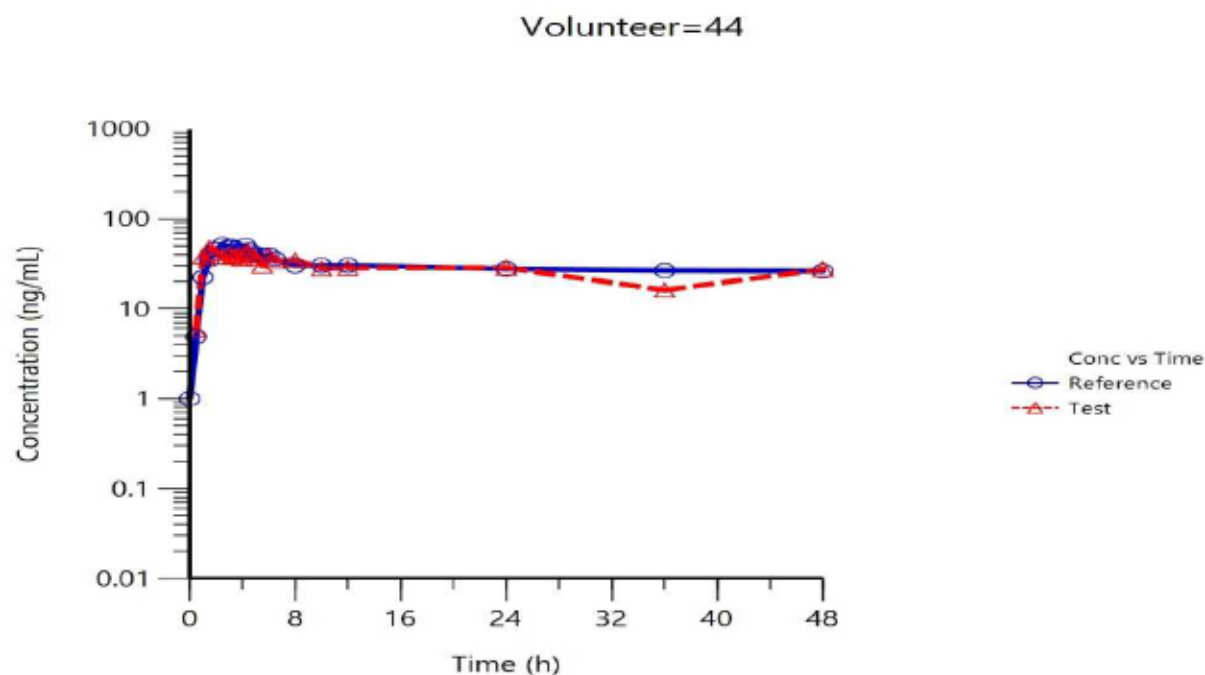



Figure 76. Levothyroxine concentration vs. subject 44's time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	48 of 68

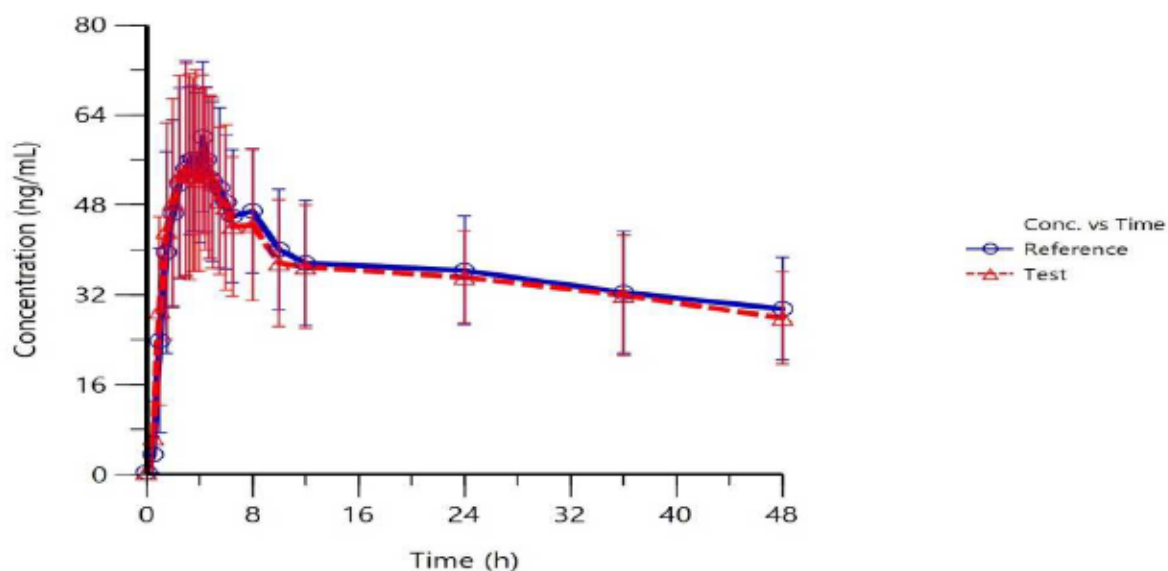


Figure 77. Levothyroxine average concentration vs. time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug (standard deviation bars).

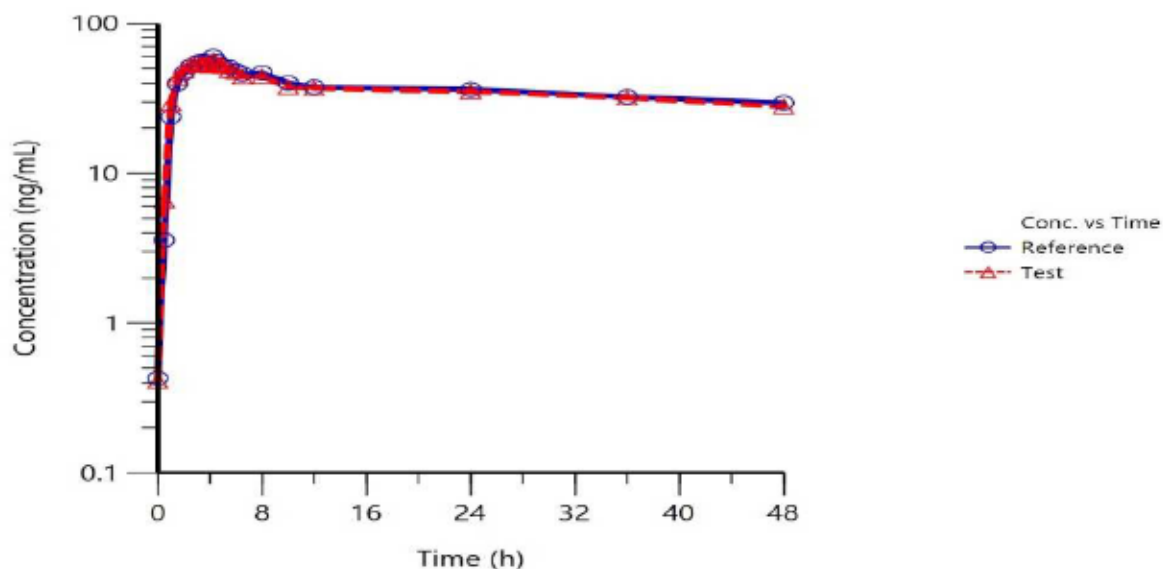



Figure 78. Levothyroxine average concentration vs. time plot, on a logarithmic scale, post-dose of the test-drug and reference-drug (standard deviation bars).


 PPD	ANALYTICAL UNIT					Issue	10-Mar-2020
						Version	1.0
	STATISTICAL DOCUMENT					Page	49 of 68

3.4. Descriptive Statistics of Biological Fluid Concentration Data as a Function of Time and Formulation

Table 7 shows the average values of the levothyroxine concentrations, as well as their descriptive statistics obtained from the assessed products.

Table 7. Descriptive statistics of the levothyroxine concentration in biological fluid, adjusted data. (N = 38).

Time	Eutirox® approved formulation						Eutirox® test formulation					
	Arithmetic mean	Median	Minimum value	Maximum value	Standard Deviation	%CV	Arithmetic mean	Median	Minimum value	Maximum value	Standard Deviation	%CV
0.00	0.43	0.00	0.00	3.49	0.91	211.46	0.41	0.00	0.00	3.11	0.75	182.21
0.50	3.58	3.14	0.00	12.68	3.14	87.72	6.59	4.65	0.00	22.49	6.46	98.09
1.00	23.86	22.53	0.00	81.95	16.39	68.69	29.13	30.19	0.00	62.72	16.78	57.58
1.50	39.59	41.38	0.00	90.27	17.95	45.33	43.35	46.42	0.00	82.41	19.33	44.59
2.00	46.48	49.19	12.87	85.98	16.63	35.78	48.45	51.49	9.21	86.16	18.42	38.02
2.50	51.84	53.27	18.87	100.38	16.92	32.63	53.05	52.79	11.89	91.74	18.00	33.94
3.00	54.48	54.53	22.85	121.16	19.08	35.02	54.23	53.83	15.13	105.75	18.98	35.00
3.25	55.88	56.65	24.02	82.14	13.14	23.52	53.03	52.77	10.93	97.25	18.28	34.47
3.50	56.22	54.54	34.94	83.03	13.00	23.12	53.37	55.44	12.35	97.45	17.20	32.22
3.75	55.64	56.30	32.34	82.19	12.38	22.24	54.08	51.83	18.55	98.59	17.86	33.03
4.00	54.98	52.93	30.05	96.39	13.77	25.04	52.41	52.51	23.36	101.74	16.14	30.80
4.25	60.10	59.40	32.89	98.33	13.35	22.21	56.98	54.82	33.26	104.57	14.16	24.85
4.50	56.09	53.03	40.83	89.28	12.97	23.13	54.34	50.13	26.93	94.09	14.40	26.51
4.75	52.84	52.50	27.92	90.42	14.42	27.29	52.99	51.87	29.62	96.22	14.52	27.40
5.00	52.17	50.76	26.94	86.81	14.27	27.35	51.94	48.73	29.99	97.71	15.15	29.17
5.50	51.04	49.65	23.02	85.70	14.26	27.93	48.76	48.10	24.59	95.00	13.12	26.91
6.00	48.49	45.49	30.45	79.63	11.81	24.36	47.56	46.96	12.65	96.72	14.70	30.90
6.50	45.99	43.82	27.96	77.27	11.81	25.69	44.12	41.46	20.77	80.81	12.35	27.99
8.00	46.90	48.07	24.96	68.79	11.09	23.64	44.37	41.54	6.44	76.82	13.43	30.27
10.00	40.04	39.40	17.75	68.89	10.69	26.70	37.67	37.10	12.78	63.24	11.33	30.09
12.00	37.67	36.37	18.83	64.91	11.19	29.70	36.95	37.23	13.72	74.36	10.93	29.58
24.00	36.31	37.62	15.52	57.99	9.64	26.54	35.13	34.49	19.77	52.40	8.20	23.34
36.00	32.42	29.63	10.97	58.18	10.86	33.50	31.91	32.69	0.00	56.25	10.63	33.32
48.00	29.49	29.16	14.56	55.61	9.20	31.20	27.87	27.44	6.82	41.12	8.26	29.63

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	50 of 68

3.5. Pharmacokinetic Parameters

3.5.1. Individual Data and Descriptive Statistics of the Pharmacokinetic Parameters

The pharmacokinetic analysis was carried out by means of the non-compartmental analysis, using Phoenix® WinNonlin® Version 8.2 and real times, following the administration of levothyroxine 600 µg (3 tablets of 200 µg). Table 8 shows levothyroxine individual values and descriptive statistics used for determining bioequivalence statistics. The uncorrected pharmacokinetic parameters are presented in table A2.4

Table 8. Individual data and descriptive statistics for the levothyroxine pharmacokinetic parameters for adjusted data (C_{max} in ng/mL, AUC_{0-t} in ng*h/mL and $AUC_{0-\infty}$ in ng*h/mL).

Volunteer	Period		Sequence	C _{max}				AUC _{0-t}				AUC _{0-∞}			
	Form			B/A	Ln(B/A)	Form		B/A	Ln(B/A)	Form		B/A	Ln(B/A)		
	A	B				A	B			A	B				
1	2	1	BA	98.33	84.97	0.86	-0.15	2689.21	1962.33	0.73	-0.32	7629.83	3185.87	0.42	-0.87
2	2	1	BA	59.08	59.26	1.00	0.00	1837.68	1370.21	0.75	-0.29	11399.25	2354.71	0.21	-1.58
3	2	1	BA	61.00	56.41	0.92	-0.08	1226.05	1089.98	0.89	-0.12	3779.67	3779.06	1.00	0.00
4	1	2	AB	67.12	63.95	0.95	-0.05	1590.66	1566.01	0.98	-0.02	3376.25	2805.99	0.83	-0.19
5	1	2	AB	53.06	59.02	1.11	0.11	1278.88	1313.99	1.03	0.03	2779.56	4931.11	1.77	0.57
6	2	1	BA	64.49	48.64	0.75	-0.28	1808.01	1158.58	0.64	-0.45	4711.82	3048.40	0.65	-0.44
7	1	2	AB	64.47	69.43	1.08	0.07	1613.07	1922.93	1.19	0.18	4049.63	7788.41	1.92	0.65
8	1	2	AB	64.72	66.18	1.02	0.02	1631.27	1868.76	1.15	0.14	2856.95	4471.12	1.56	0.45
9	1	2	AB	84.71	104.57	1.23	0.21	2039.40	2607.86	1.28	0.25	4687.59	4314.79	0.92	-0.08
10	1	2	AB	81.77	97.25	1.19	0.17	1996.53	2646.91	1.33	0.28	3703.43	6718.92	1.81	0.60
11	1	2	AB	68.86	72.27	1.05	0.05	1819.05	2275.38	1.25	0.22	3550.37	4959.64	1.40	0.33
12	2	1	BA	69.82	69.15	0.99	-0.01	1891.54	1974.42	1.04	0.04	4532.18	3117.89	0.69	-0.37
13	1	2	AB	62.06	51.70	0.83	-0.18	2001.99	1534.42	0.77	-0.27	6086.19	7351.71	1.21	0.19
14	2	1	BA	69.84	68.12	0.98	-0.03	1917.57	2269.15	1.18	0.17	4363.45	5362.42	1.23	0.21
15	2	1	BA	51.95	54.48	1.05	0.05	1200.24	1699.42	1.42	0.35	2732.81	7146.60	2.62	0.96
17	2	1	BA	66.14	68.33	1.03	0.03	1568.88	1626.36	1.04	0.04	1958.82	2041.21	1.04	0.04
18	1	2	AB	67.71	68.11	1.01	0.01	1843.99	1934.69	1.05	0.05	4232.42	5847.55	1.38	0.32
19	2	1	BA	73.11	56.02	0.77	-0.27	2003.56	1500.57	0.75	-0.29	4108.73	3382.13	0.82	-0.19
20	1	2	AB	74.61	60.44	0.81	-0.21	2335.69	1506.84	0.65	-0.44	5650.88	3602.09	0.64	-0.45
22	2	1	BA	50.81	43.65	0.86	-0.15	1094.52	1347.80	1.23	0.21	2115.19	4591.17	2.17	0.77
23	2	1	BA	50.16	73.24	1.46	0.38	1288.89	1856.73	1.44	0.37	2389.96	6212.32	2.60	0.96
24	1	2	AB	75.62	60.54	0.80	-0.22	1586.03	1327.55	0.84	-0.18	2452.72	3747.07	1.53	0.42
25	2	1	BA	59.68	62.69	1.05	0.05	1371.46	1872.58	1.37	0.31	3601.75	3002.55	0.83	-0.18
27	1	2	AB	48.06	52.34	1.09	0.09	1393.96	1342.50	0.96	-0.04	3106.51	1840.81	0.59	-0.52
28	1	2	AB	121.16	105.75	0.87	-0.14	2365.84	1777.47	0.75	-0.29	6969.94	2831.05	0.41	-0.90
29	1	2	AB	65.35	60.17	0.92	-0.08	1614.49	1100.34	0.68	-0.38	2346.45	1261.22	0.54	-0.62
30	2	1	BA	68.88	71.68	1.04	0.04	2047.90	1855.80	0.91	-0.10	7698.37	7971.33	1.04	0.03
31	2	1	BA	49.54	62.01	1.25	0.22	984.41	1681.30	1.71	0.54	1682.68	3464.68	2.06	0.72
33	2	1	BA	86.93	82.18	0.95	-0.06	2777.76	1965.99	0.71	-0.35	9404.14	4083.85	0.43	-0.83
34	1	2	AB	60.92	70.24	1.15	0.14	1423.86	1469.25	1.03	0.03	3357.06	2278.33	0.68	-0.39
35	1	2	AB	59.46	52.07	0.88	-0.13	1828.60	1575.38	0.86	-0.15	5260.60	8928.32	1.70	0.53
36	1	2	AB	74.82	70.08	0.94	-0.07	1468.93	1750.43	1.19	0.18	2996.07	4872.32	1.63	0.49
37	1	2	AB	60.30	68.30	1.13	0.12	1801.46	2017.01	1.12	0.11	4862.37	9642.45	1.98	0.68
39	1	2	AB	100.38	94.09	0.94	-0.06	2746.26	2212.77	0.81	-0.22	6141.94	4801.43	0.78	-0.25
41	1	2	AB	72.78	79.08	1.09	0.08	1795.04	1564.48	0.87	-0.14	4528.22	2357.15	0.52	-0.65
42	2	1	BA	44.51	33.98	0.76	-0.27	1250.47	1221.60	0.98	-0.02	4821.73	8527.56	1.77	0.57
43	2	1	BA	51.13	56.81	1.11	0.11	1529.05	1337.85	0.87	-0.13	3297.62	3246.45	0.98	-0.02
44	2	1	BA	51.87	47.59	0.92	-0.09	1406.46	1262.19	0.90	-0.11	8009.03	3183.88	0.40	-0.92
N				38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00
Geometric Mean				65.66	64.69	0.99	NA	1687.14	1651.82	0.98	NA	4083.25	4088.43	1.00	NA
Arithmetic Mean				67.24	66.44	1.00	-0.01	1738.65	1693.89	1.01	-0.02	4506.11	4554.04	1.18	0.00
Standard Deviation				15.77	15.77	0.15	0.15	438.93	389.50	0.25	0.25	2151.01	2145.52	0.64	0.61
%CV				23.45	23.73	15.13	-1006.61	25.25	22.99	25.03	-1161.73	47.74	47.11	54.46	47802.18
Minimum Value				44.51	33.98	0.75	-0.28	984.41	1089.98	0.64	-0.45	1682.68	1261.22	0.21	-1.58
Median				65.04	65.07	1.00	0.00	1713.16	1653.83	0.98	-0.02	4079.18	3931.45	1.02	0.02
Maximum Value				121.16	105.75	1.46	0.38	2777.76	2646.91	1.71	0.54	11399.25	9642.45	2.62	0.96

NA: Not applicable


 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	51 of 68

Table 9 shows the average results for the levothyroxine pharmacokinetic parameters. There, it can be seen t_{max} values of 3.41 h and 3.51 h, and C_{max} values of 67.24 ng/mL, and 66.44 ng/mL for the reference and test drugs, respectively. Based on these results, it can be inferred that there are no differences in the extent and rate which levothyroxine needs for reaching the circulation.

On the other hand, average AUC_{0-t} was 1738.65 $\mu\text{g}\cdot\text{h/mL}$ and 1693.89 $\text{ng}\cdot\text{h/mL}$ for the reference and test drugs, respectively. $AUC_{0-\infty}$ is only shown for informative purposes, since their values result in a greater extrapolation than 20%. Values were 4506.11 $\text{ng}\cdot\text{h/mL}$ and 4554.04 $\text{ng}\cdot\text{h/mL}$ for the reference and test drugs, respectively. Based on these values, it can be seen that the drug's bioavailability for both formulations does not show differences.

Table 9. Levothyroxine Pharmacokinetic Parameters Results, adjusted data.

Variable	Form							
	Eutirox® approved formulation (A)				Eutirox® test formulation (B)			
	N	Arithmetic Mean	Standard Deviation	%CV	N	Arithmetic Mean	Standard Deviation	%CV
Extrapolated AUC (%)	38.00	56.70	12.83	22.62	38.00	55.87	18.07	32.35
$AUC_{0-\infty}$ (ng·h/mL)	38.00	4506.11	2151.01	47.74	38.00	4554.04	2145.52	47.11
AUC_{0-t} (ng·h/mL)	38.00	1738.65	438.93	25.25	38.00	1693.89	389.50	22.99
Cl/F (mL/h)	38.00	161.15	69.74	43.28	38.00	164.22	83.82	51.04
C_{max} (ng/mL)	38.00	67.24	15.77	23.45	38.00	66.44	15.77	23.73
$t_{1/2}$ (h)	38.00	61.60	32.44	52.67	38.00	65.16	37.04	56.85
Kel (1/h)	38.00	0.01	0.01	46.76	38.00	0.01	0.01	57.13
TMR (h)	38.00	92.27	45.99	49.85	38.00	97.32	54.70	56.21
T_{lag} (h)	38.00	0.11	0.21	196.25	38.00	0.00	0.00	NA
T_{max} (h)	38.00	3.41	0.99	29.07	38.00	3.51	1.17	33.46
Vd/F (L)	38.00	12118.29	3202.28	26.43	38.00	12182.01	2720.22	22.33

NA: Not applicable

Table 10 shows the box and whiskers plots for the parameters used for assessing the levothyroxine absorption rate and bioavailability.


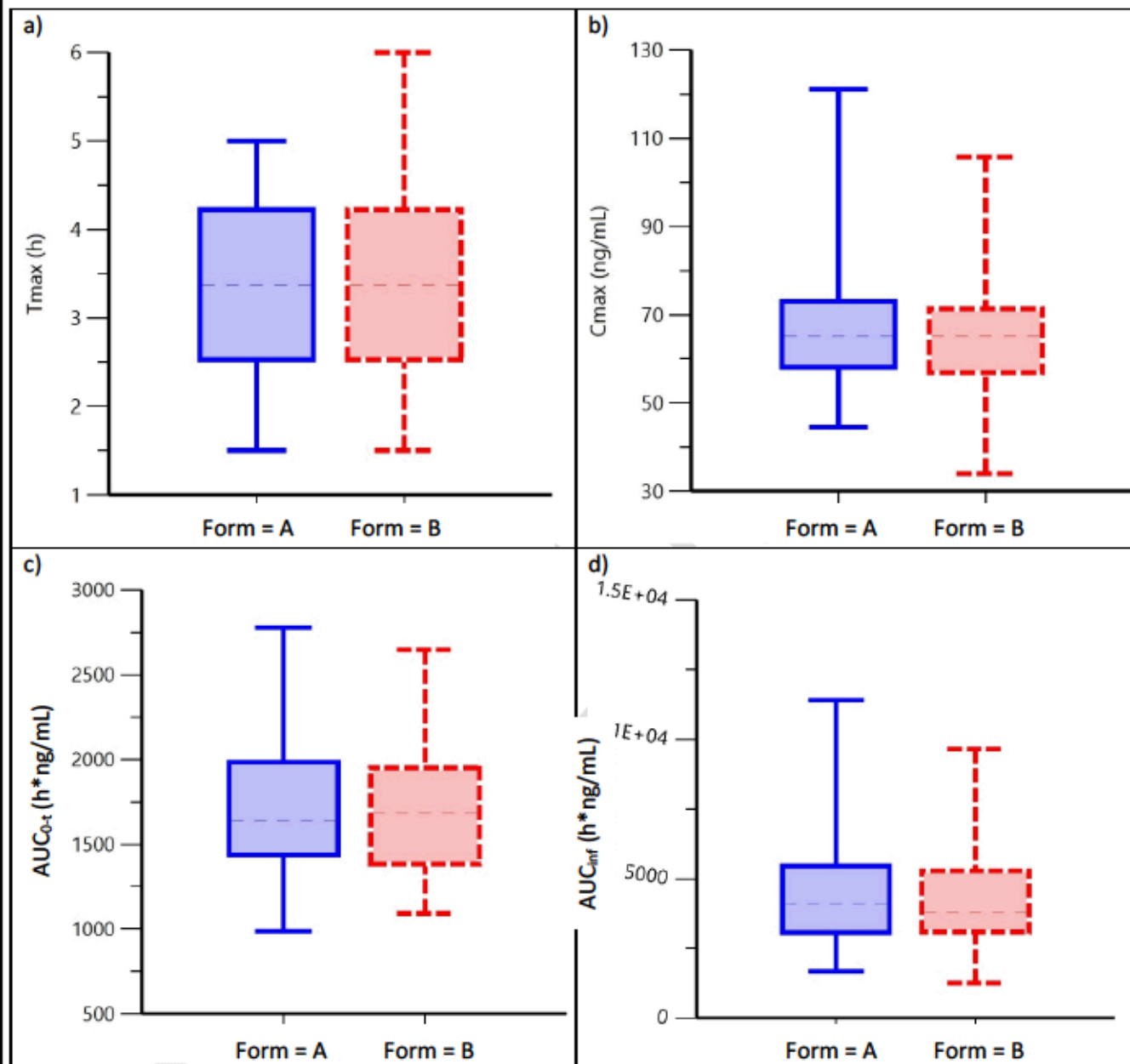

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	52 of 68

Table 10. Box and Whiskers Plot for the Levothyroxine Pharmacokinetic Parameters



Graphically, it is confirmed that there are no differences in the absorption rate or in the bioavailability between both formulations since those representations are very similar to each other.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	53 of 68


4. Variance Analysis (ANOVA)

The analysis of variance was made considering all data obtained in the levothyroxine pharmacokinetic analysis, under the same statistical considerations and the same general linear model previously described for estimating the F statistical value, based on the variance results of the fixed and random factors or effects in each of the pharmacokinetic parameters requested for establishing the bioequivalence. Results of the analysis of variance for the assessed parameters C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ for levothyroxine are shown in Table 11.

Table 11. ANOVA table for the analysis of the levothyroxine logarithmically-transformed pharmacokinetic parameters, for adjusted data (Ln).

Assessed Variable	Source of Variation	Degrees of Freedom	Square Sum	Squared Means	F Value	P Value	Criterion ($P > 0.05$)
$\ln(C_{max})$	Sequence	1	0.08	0.08	0.84	0.36	Pass
$\ln(C_{max})$	Sequence*Volunteer	36	3.28	0.09			Not applicable
$\ln(C_{max})$	Form	1	0.00	0.00	0.36	0.55	Pass
$\ln(C_{max})$	Period	1	1.92×10^{-7}	1.92×10^{-7}	1.69×10^{-5}	1.00	Pass
$\ln(C_{max})$	Error	36	0.41	0.01			Not applicable
$\ln(AUC_{0-t})$	Sequence	1	0.01	0.01	0.15	0.70	Pass
$\ln(AUC_{0-t})$	Sequence*Volunteer	36	3.05	0.08			Not applicable
$\ln(AUC_{0-t})$	Form	1	0.01	0.01	0.29	0.59	Pass
$\ln(AUC_{0-t})$	Period	1	0.07	0.07	2.45	0.13	Pass
$\ln(AUC_{0-t})$	Error	36	1.05	0.03			Not applicable
$\ln(AUC_{0-\infty})$	Sequence	1	0.03	0.03	0.11	0.74	Pass
$\ln(AUC_{0-\infty})$	Sequence*Volunteer	36	8.90	0.25			Not applicable
$\ln(AUC_{0-\infty})$	Form	1	3.06×10^{-5}	3.06×10^{-5}	0.00	0.99	Pass
$\ln(AUC_{0-\infty})$	Period	1	0.50	0.50	2.85	0.10	Pass
$\ln(AUC_{0-\infty})$	Error	36	6.30	0.18			Not applicable

Regarding the analysis of variance for the logarithmically-transformed pharmacokinetic data, no statistical significance was seen in all sources of variations used for the parameters which determine the bioequivalence (C_{max} and AUC_{0-t}). Therefore, the 90 % confidence interval was calculated.

 PPD	ANALYTICAL UNIT	Issue	10-Mar-2020
		Version	1.0
	STATISTICAL DOCUMENT	Page	54 of 68

5. Study Variability

Coefficients of variation obtained in this study for levothyroxine by means of the crossover 2 x 2 design are shown in Table 12.

Table 12. Inter- and Intra-subject Coefficients of Variation Obtained for Levothyroxine adjusted data


Pharmacokinetic Parameter	Inter-subject CV	Intra-subject CV
C_{max}	20.18	10.66
AUC_{0-t}	16.79	17.17
$AUC_{0-\infty}$	19.16	43.74

6. Pharmacokinetic Parameters Outliers Identification

Outliers analysis was made using the intra-subject studentized residuals determination as per the Mexican Official Standard, NOM-177-SSA1-2013, which specifies that the possible outliers are those exceeding the ± 2 studentized-residuals criterion. Table 13 shows the values exceeding this limit, meanwhile figures 79, 80, and 81 show the studentized residual plots vs. the logarithm for the levothyroxine assessed pharmacokinetic parameter.

Table 13. Subjects exceeding the ± 2 levothyroxine studentized residuals criterion.

Pharmacokinetic Parameter	Subject	Studentized Residual Value
$\ln C_{max}$	23	± 2.65
$\ln AUC_{0-t}$	31	± 2.09
$\ln AUC_{0-\infty}$	2	± 2.43

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	55 of 68

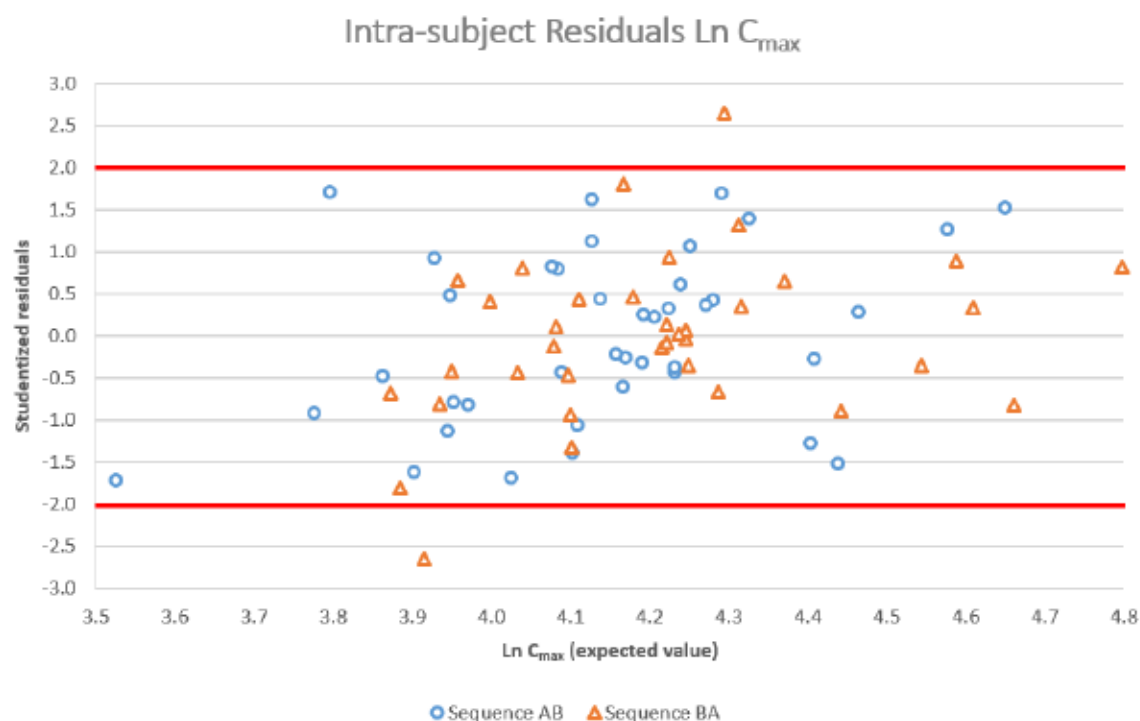


Figure 79. Studentized Residuals Plot for the Levothyroxine Intra-subject Pharmacokinetic Parameter $\ln C_{\max}$.

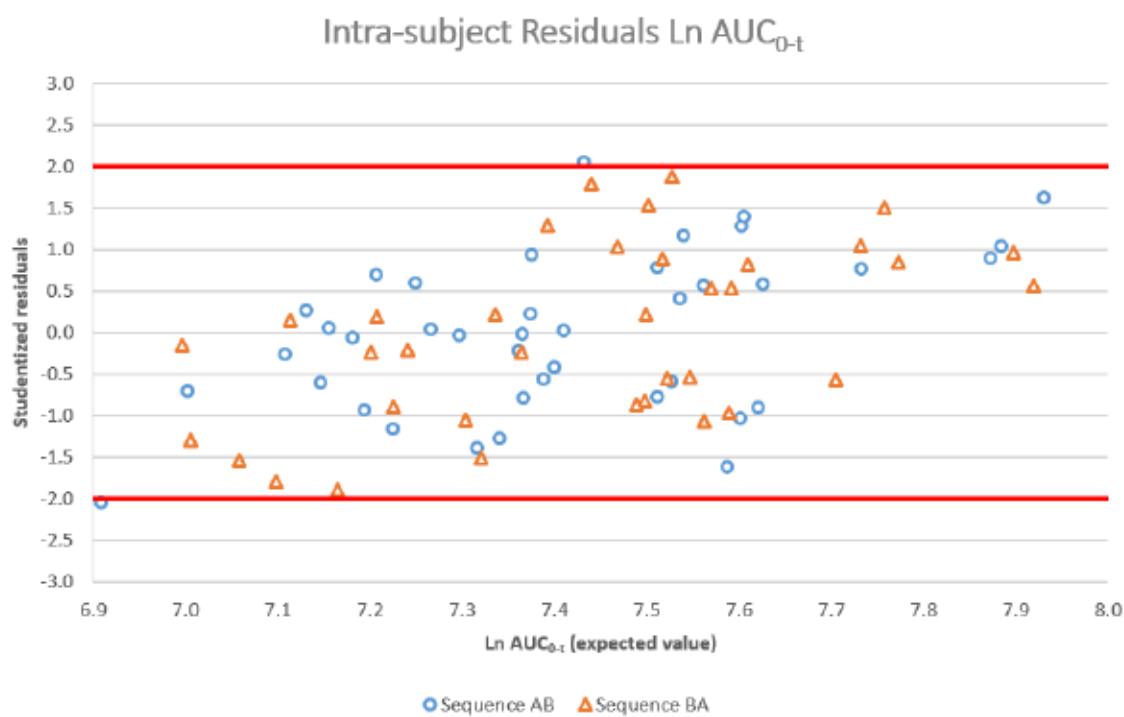



Figure 80. Studentized Residuals Plot for the Levothyroxine Intra-subject Pharmacokinetic Parameter AUC_{0-t} .

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	56 of 68

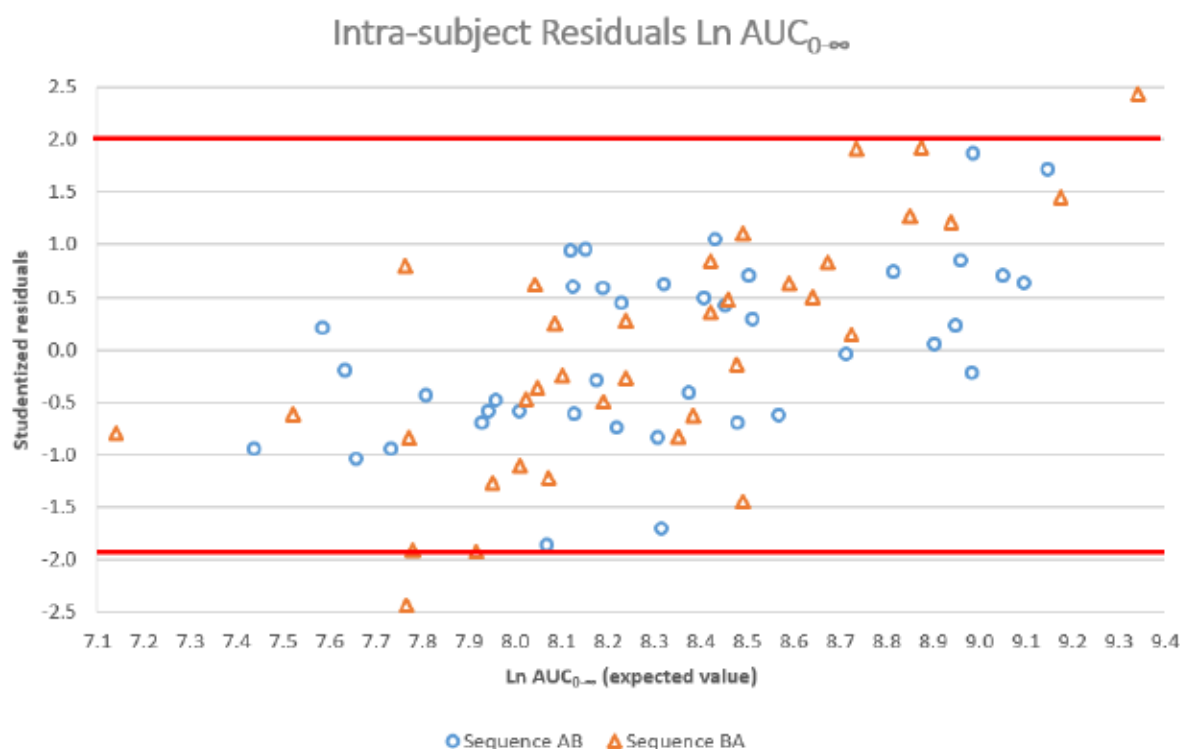



Figure 81. Studentized Residuals Plot for the Levothyroxine Intra-subject Pharmacokinetic Parameter $AUC_{0-\infty}$.

As seen in Table 13 and the figures shown above, subjects 2, 23, and 31 were found as outliers in this study since they exceeded the ± 2 studentized residuals.

As stated in the current national standards, a statistical analysis was made removing subjects 2, 23, and 31. As the results of the confidence intervals do not change, they are not considered influencing-outliers.

As per the current national standards, the Clinical and the Analytical Units jointly with Quality Assurance conducted the appropriate research. The results of this research showed that there were no events that render questionable the results obtained. Therefore, there is no scientific reason to justify the removal of subjects 2, 23, and 31 from the analysis. Therefore, results shown in this report include all subjects who were assessed.

 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	57 of 68

7. Bioequivalence Statistics

Table 14 shows the results of the bioequivalence statistics for the levothyroxine logarithmically-transformed pharmacokinetic data.

Table 14. Statistics of the Levothyroxine Bioequivalence Determination for adjusted value.

Parameter	90 % Confidence Interval		Schuirmann's doubled-side t		Power	Acceptance Criterion	Meets the Criterion
			P < 80 %	P > 125 %			
LnC _{max}	94.55	102.68	0.00	0.00	100.00	(80-125)	YES
LnAUC _{0-t}	91.34	104.26	0.00	0.00	99.98	(80-125)	YES

As established in the Mexican Official Standard, NOM-177-SSA1-2013, the parameters to establish the conclusion about the possible bioequivalence of the products are C_{max} as a rate of absorption indicator and the AUC as the amount absorbed indicator.

The confidence interval for parameters C_{max} and AUC_{0-t} for establishing bioequivalence are within the established acceptance criteria (80 % to 125 %). Therefore, it is shown that there are no statistically significant differences in the absorption rate or in the drug's bioavailability. Even though the AUC_{0-∞} is also within the bioequivalence limits, bioequivalence is established only with the results of C_{max} and AUC_{0-t}.

8. Statistical Plan Deviation

None.

9. Discussion and Conclusion


The 90 % confidence intervals for C_{max} and AUC_{0-t} are contained in the acceptance region for bioequivalence, thus showing that the test formulation has an absorption rate and bioavailability that is equivalent to the one of the reference formulation.

As per the results obtained, it is concluded that the test drug "Eutirox[®], new formulation" is bioequivalent to the reference drug "Eutirox[®], the approved formulation".

10. Annexes

Annex 1. Quality Assurance Report

Annex 2. Statistical information on unadjusted data per baseline levels.

 PPD	ANALYTICAL UNIT																Issue	10-Mar-2020
	STATISTICAL DOCUMENT																Version	1.0
																	Page	58 of 68

Annex 3. Statistical information with all subjects, including a greater than 5% predose concentration.

Table A2.1 Table of individual concentrations corresponding to unadjusted levothyroxine (reference drug [A]). N = 43 subjects.

Form	Volunteer	Time																											
		-0.50	-0.25	0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00		
A	1	51.32	64.16	53.26	47.34	74.32	82.00	89.87	115.60	129.31	133.43	139.27	130.22	152.63	154.58	145.53	146.66	143.06	135.60	126.33	129.01	123.03	115.01	120.74	134.24	106.52	102.69		
A	2	81.52	81.75	83.05	85.21	101.35	115.83	124.86	127.71	128.42	136.55	134.47	133.39	131.35	137.26	135.73	131.66	141.18	127.61	126.72	126.79	128.01	126.24	120.12	116.70	120.24	121.73		
A	3	67.24	59.78	63.57	68.93	108.98	118.62	124.53	108.72	103.61	116.27	99.75	95.87	104.50	107.27	105.89	98.64	94.88	96.45	96.40	103.76	92.79	86.63	90.57	86.16	86.42	83.29		
A	4	77.82	77.88	78.21	80.19	93.71	117.34	133.48	134.48	137.25	130.36	129.67	145.08	127.82	140.38	137.09	125.25	126.62	129.16	119.01	123.52	125.37	115.80	116.95	108.11	107.03	101.07		
A	5	81.33	75.34	76.83	79.14	100.51	110.35	114.52	115.47	130.89	123.34	130.00	124.95	129.61	129.51	130.03	126.29	124.27	126.22	119.11	112.70	111.82	110.51	104.11	102.93	97.25	105.84		
A	6	54.46	57.33	54.72	57.63	59.66	77.05	105.41	119.99	118.56	112.95	113.34	114.36	105.48	113.16	106.90	111.40	108.78	108.75	108.39	110.95	109.41	99.56	98.27	92.30	88.21	84.47		
A	7	67.67	57.02	53.83	62.55	76.01	87.55	89.50	93.95	117.19	107.74	113.89	123.98	115.72	122.98	108.95	112.95	100.80	98.79	102.82	101.27	112.66	92.70	87.22	97.94	88.35	89.99		
A	8	76.72	68.81	67.61	74.08	102.10	115.11	129.39	135.77	128.13	134.38	120.79	129.39	131.45	131.27	128.83	126.25	132.74	125.79	132.44	118.29	122.15	116.15	110.56	103.45	95.93	94.37		
A	9	90.07	85.62	71.38	89.50	93.89	97.98	95.22	101.62	109.01	130.24	136.36	147.11	142.34	159.70	159.21	167.06	162.79	153.70	153.94	144.65	142.75	131.91	121.68	128.59	119.94	121.15		
A	10	81.37	78.12	75.32	72.70	80.13	114.61	130.46	136.57	141.05	149.64	148.31	135.02	153.11	157.35	153.84	160.04	139.45	153.09	141.98	136.69	141.07	133.92	127.26	119.63	109.91	109.09		
A	11	87.13	74.20	77.05	75.73	94.21	107.00	148.32	119.95	131.84	134.97	130.97	135.31	140.88	140.22	144.44	139.12	138.12	138.05	131.25	121.22	119.01	115.98	110.06	119.64	122.81	105.08		
A	12	72.69	71.52	71.11	77.96	98.16	122.07	126.51	134.78	141.60	133.18	135.04	136.97	131.79	137.53	128.60	123.03	124.72	127.30	126.13	119.61	128.87	116.84	114.47	112.03	104.30	101.26		
A	13	68.17	64.00	53.70	69.42	91.53	122.01	108.78	124.35	123.06	123.13	120.50	113.14	103.04	123.08	116.04	116.66	112.62	117.57	114.93	103.88	110.33	99.33	98.19	104.72	106.01	96.85		
A	14	66.40	64.46	67.30	69.39	90.05	109.45	115.05	127.43	120.95	129.65	123.37	125.50	128.21	129.21	122.93	135.90	127.86	121.05	124.71	121.83	124.99	95.93	114.97	106.90	98.05	97.69		
A	15	90.13	88.14	89.46	83.99	94.68	85.71	102.53	114.34	112.09	120.03	132.47	130.51	126.00	130.07	133.38	129.75	141.19	132.04	128.44	123.44	120.72	131.03	126.07	112.29	105.00	114.73		
A	16	83.94	84.37	75.45	89.25	107.94	114.37	116.48	136.92	138.13	147.32	148.33	142.36	137.32	130.90	131.36	140.11	130.18	141.67	136.26	134.26	118.85	122.12	117.61	111.35	101.44	111.14		
A	17	90.72	78.61	82.18	88.62	95.31	98.43	108.80	125.95	149.98	144.25	138.54	134.74	143.14	146.00	129.90	136.14	142.77	134.05	133.04	138.55	138.21	127.73	124.94	120.29	107.72	98.56		
A	18	55.88	56.60	55.98	58.28	90.14	100.60	108.28	114.30	119.96	117.66	117.09	123.86	119.22	117.97	134.85	112.36	111.33	114.29	113.06	104.01	104.99	98.53	101.72	95.30	85.84	86.11		
A	19	61.49	57.91	59.83	64.08	103.32	111.68	109.11	119.26	119.94	117.90	124.72	120.32	109.45	132.85	134.74	112.44	110.92	114.84	102.54	105.61	109.26	99.10	98.98	108.84	94.74	93.74		
A	20	75.47	76.86	73.99	81.76	110.28	144.00	146.54	141.91	150.00	143.23	150.05	143.53	143.56	143.41	139.68	139.00	143.04	142.52	134.90	132.34	136.40	124.74	119.89	124.37	124.86	113.26		
A	21	65.09	61.09	62.88	66.01	90.15	119.37	116.48	124.02	131.63	127.98	125.34	125.89	131.96	128.32	129.01	123.91	121.29	120.48	106.06	112.01	117.89	101.83	98.64	103.30	97.94	95.55		
A	22	73.63	68.17	67.24	65.19	75.16	79.88	83.11	88.55	94.51	93.70	104.63	105.31	99.73	102.57	120.49	97.61	96.62	100.01	100.76	100.39	94.64	101.36	94.47	93.85	92.80	84.24		
A	23	86.59	82.82	81.95	85.82	120.76	131.76	130.09	133.02	131.71	132.03	128.58	133.94	129.48	132.67	128.83	121.14	128.11	124.50	121.61	118.17	120.06	112.58	105.52	109.04	110.66	102.79		
A	24	81.23	79.76	73.25	77.61	101.32	123.26	131.98	153.70	144.82	141.53	149.44	147.95	143.23	145.02	133.19	131.51	127.33	133.34	124.77	119.40	119.70	112.70	113.36	118.07	100.42	97.10		
A	25	70.50	69.32	66.64	60.18	101.03	122.78	116.76	122.70	97.82	112.19	106.21	106.27	110.27	128.50	110.20	134.63	104.56	111.51	112.69	108.85	107.58	98.64	95.63	93.55	95.77	95.40		
A	26	86.68	84.43	90.33	91.62	97.52	114.25	125.07	136.68	128.03	133.73	133.83	129.89	129.68	128.90	122.89	118.13	123.50	130.36	122.33	129.23	138.86	124.62	120.93	123.66	121.56	112.67		
A	27	80.58	78.26	80.40	79.25	97.06	114.25	121.59	122.69	127.81	126.64	124.66	126.35	122.26	127.08	120.57	113.14	116.23	121.86	121.99	119.53	117.47	115.83	110.33	109.58	103.53	103.45		
A	28	55.23	53.72	38.94	55.06	64.88	97.02	111.24	118.04	170.46	114.59	129.32	121.27	117.86	106.81	113.21	102.11	126.61	95.42	103.62	105.32	101.94	100.94	101.29	90.74	105.57	90.47		
A	29	78.49	77.86	79.29	91.23	90.18	110.44	135.51	143.90	117.89	134.41	132.59	120.22	133.59	131.73	128.79	125.34	120.48	121.39	115.51	114.62	127.75	114.76	110.25	119.73	106.76	99.36		
A	30	58.94	51.97	57.95	61.10	80.58	90.20	85.45	108.69	88.78	125.17	111.35	120.01	109.37	134.38	114.11	109.03	107.81	105.38	99.64	96.50	104.52	99.03	98.30	96.57	105.05	93.96		
A	31	77.90	70.91	73.73	78.75	83.48	109.13	109.14	119.30	113.83	115.17	113.51	114.17	112.61	119.20	123.72	122.28	110.27	97.20	104.63	105.89	107.08	91.93	93.01	101.49	85.15	89.19		
A	32	71.01	70.48	75.52	78.92	122.73	125.80	133.37	115.90	111.88	110.41	112.27	116.95	108.88	114.37	109.29	106.88	108.02	111.72	105.59	106.85	107.24	111.29	97.39	102.59	103.19	103.18		
A	33	70.27	66.60	73.34	78.64	107.64	115.33	127.62	146.42	141.58	147.96	152.33	146.97	149.73	157.00	155.63	143.67	151.13	155.63	135.30	143.33	134.14	129.48	134.38	120.80	128.25	125.68		
A	34	96.31	85.91	87.46	88.16	99.06	102.42	112.30	115.50	130.11	138.80	150.81	137.51	138.48	147.39	133.14	134.42	128.36	132.29	126.84	117.85	130.07	121.71	120.29	126.26	112.37	116.33		
A	35	80.06	74.32	75.30	79.74	115.43	135.73	136.03	130.95	130.43	125.37	122.41	122.43	122.61	130.75	120.66	108.04	119.69	122.23	118.35	119.58	123.59	124.62	110.68	116.14	113.08	108.27		
A	36	88.46	84.72	92.32	93.70	138.86	151.02	145.62	140.86	154.16	163.65	150.16	153.67	145.92	147.95	141.26	143.00	140.37	140.48	135.19	134.36	129.85	130.86	124.22	104.35	118.41	119.17		
A	37	79.45	75.66	76.18	75.75	113.46	124.32	137.40	132.15	131.25	134.88	136.69	132.63	129.88	131.70	129.45	125.04	126.53	130.15	130.61	124.54	125.19	115.87	119.11	113.31	110.65	106.46		
A	38	76.83	71.67	78.42	83.69	157.65	165.98	161.69	176.09	162.49	157.84	154.76	157.89	158.87	164.76	162.43	154.43	149.15	161.41	155.34	152.98	144.49	144.60	140.61	127.69	123.18	124.82		
A	40	75.00	71.11	87.64	83.77	97.16	108.84	116.77	151.08	154.63																			


 PPD	ANALYTICAL UNIT																	Issue	10-Mar-2020
	STATISTICAL DOCUMENT																	Version	1.0
																		Page	59 of 68

Table A2.2 Table of individual concentrations corresponding to unadjusted levothyroxine (test drug [B]). N = 43 subjects.

Form	Volunteer	Time																									
		-0.50	-0.25	0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00
B	1	77.32	76.18	77.29	79.72	94.84	108.14	117.40	123.93	131.78	146.37	142.83	161.90	159.57	152.89	151.99	151.58	150.33	135.28	132.14	126.67	135.73	127.72	120.04	116.96	118.70	98.86
B	2	85.65	89.15	85.02	90.38	120.92	136.32	142.12	139.37	144.14	135.56	138.77	133.10	134.53	139.48	135.74	133.69	126.76	128.76	145.86	122.82	119.93	113.80	116.80	115.44	110.37	105.01
B	3	74.50	69.13	67.07	74.80	112.40	126.65	110.21	114.74	106.20	104.54	111.30	109.91	94.63	104.83	118.33	106.64	107.20	94.82	95.67	91.01	76.68	83.01	83.96	90.98	97.80	95.06
B	4	82.49	87.12	80.68	88.73	100.06	122.68	138.14	139.12	147.39	144.15	138.60	137.52	137.32	135.55	131.39	125.56	124.89	126.01	126.69	123.87	125.35	121.30	120.98	113.71	115.32	102.74
B	5	71.80	74.58	71.87	76.35	77.90	82.15	81.96	86.31	87.88	93.30	85.32	99.54	96.11	110.24	114.66	131.78	126.55	120.23	113.16	115.57	110.70	103.13	96.50	102.12	100.37	97.65
B	6	68.72	60.92	65.18	64.38	69.72	80.23	79.48	81.84	80.95	90.42	93.28	98.30	104.86	113.58	110.47	105.75	98.51	103.81	99.02	98.12	94.22	92.97	95.20	90.66	82.82	88.36
B	7	54.86	61.41	58.93	67.13	94.46	100.16	108.05	113.24	127.83	113.44	114.25	100.58	103.65	105.21	108.86	103.67	114.11	110.30	108.81	108.35	101.46	103.75	96.66	99.02	94.72	98.05
B	8	71.37	66.52	66.65	90.67	116.67	129.82	134.36	125.69	126.85	128.78	127.48	121.50	122.13	128.37	121.07	122.62	115.86	122.17	117.98	112.77	108.24	106.73	105.80	99.38	112.81	99.97
B	9	84.53	84.46	87.68	83.60	110.96	129.12	154.59	172.13	179.10	173.35	183.00	184.14	187.29	190.12	179.61	181.77	183.27	180.55	182.27	166.36	159.04	148.79	149.12	127.57	141.81	121.52
B	10	72.63	71.11	69.79	72.61	92.11	119.69	138.98	144.72	151.06	168.43	167.18	151.12	145.51	153.34	156.46	155.51	161.09	141.37	153.77	148.44	147.99	129.14	145.53	123.57	115.98	112.30
B	11	77.30	70.56	74.52	78.86	97.55	133.77	142.00	145.78	141.85	146.40	143.33	136.88	135.84	137.54	131.92	137.56	136.24	130.21	138.51	136.84	127.77	125.41	115.79	124.04	124.42	106.63
B	12	70.94	68.73	69.77	71.55	93.90	110.44	124.37	132.86	124.11	128.00	127.30	127.42	130.72	138.96	125.76	126.01	123.41	118.54	122.17	113.99	122.92	107.96	105.35	118.38	110.32	97.17
B	13	69.05	67.11	64.87	71.27	99.90	116.69	114.44	118.62	116.52	109.52	113.21	103.72	113.04	118.71	113.63	111.00	109.90	109.99	109.77	97.12	107.78	98.18	99.41	86.78	104.90	101.96
B	14	60.84	56.32	58.87	64.82	91.83	111.85	113.68	122.65	112.05	115.07	119.31	120.44	121.53	121.80	121.87	120.35	119.76	126.80	124.51	118.85	121.44	114.12	111.13	98.74	109.62	94.51
B	15	80.35	84.38	73.30	81.22	98.82	112.96	103.62	120.52	126.24	129.53	124.02	124.46	123.96	133.33	123.67	133.82	118.93	117.66	126.49	118.52	132.95	118.76	118.07	111.23	112.40	116.01
B	16	84.99	77.05	90.76	86.67	101.88	117.81	139.30	129.34	129.04	127.74	125.58	123.95	127.43	133.13	130.31	126.11	124.19	129.56	120.51	126.23	122.27	118.94	114.14	127.82	111.96	105.15
B	17	89.07	78.55	72.06	82.78	97.14	108.80	124.40	130.75	132.00	122.13	148.22	146.12	138.86	147.69	143.77	131.29	131.29	131.86	125.30	118.48	135.75	122.74	116.81	114.62	114.84	91.73
B	18	59.73	56.78	57.40	65.24	93.58	105.15	112.79	123.68	126.08	120.71	121.30	119.79	118.29	123.32	115.62	112.48	113.79	111.46	109.38	109.59	110.98	109.59	105.21	95.23	92.69	88.81
B	19	72.61	65.61	69.56	71.76	98.90	111.88	125.27	110.79	121.73	115.91	111.30	108.02	105.61	120.15	116.60	116.45	112.35	114.50	124.69	118.25	110.41	108.08	107.08	98.60	93.10	94.73
B	20	85.42	84.68	85.07	92.13	124.45	138.24	141.11	140.04	145.02	141.68	134.51	134.06	133.26	145.50	133.95	127.40	122.51	121.23	124.53	124.96	128.64	117.33	109.06	114.61	118.48	108.20
B	21	59.65	57.52	63.92	76.24	95.62	119.30	119.55	126.49	126.77	119.65	125.74	122.58	122.96	127.39	122.22	110.35	113.36	114.16	114.48	119.87	124.75	106.76	104.33	100.20	102.22	85.20
B	22	68.84	62.73	67.87	65.27	84.55	100.86	97.47	105.33	109.69	108.94	103.64	106.34	107.20	104.29	102.97	99.22	110.13	102.27	103.97	103.77	96.84	99.35	95.21	95.14	90.70	93.09
B	23	79.86	73.54	79.53	89.28	127.40	148.48	146.23	150.89	137.90	144.25	138.97	137.93	138.88	145.47	139.20	131.91	131.42	127.46	126.44	121.98	118.18	118.15	116.62	117.02	110.53	108.36
B	24	71.89	66.42	70.30	66.96	67.54	69.39	78.87	81.42	86.26	80.47	81.89	88.09	108.99	125.18	124.33	130.07	120.79	115.08	99.27	103.39	106.22	90.95	96.18	103.79	94.42	95.90
B	25	67.95	70.48	68.27	89.15	119.81	129.69	124.26	116.80	125.03	111.16	124.61	131.59	111.88	120.18	109.78	123.62	114.47	126.47	109.91	122.33	113.60	119.75	103.82	116.20	100.79	95.68
B	26	85.21	83.51	83.28	82.65	95.65	109.16	119.14	135.11	138.58	134.03	133.20	137.50	132.08	130.88	130.09	130.22	131.48	129.86	124.73	129.93	133.16	126.23	125.84	120.91	119.69	109.87
B	27	81.93	79.61	79.52	81.58	106.71	119.51	122.59	130.19	124.58	122.95	126.99	125.77	131.49	132.69	122.45	119.21	125.92	120.20	127.14	112.75	121.06	111.11	111.01	109.97	104.54	94.99
B	28	66.97	61.66	59.68	73.55	102.82	94.72	107.26	98.74	168.52	155.87	120.64	154.40	120.93	109.21	132.49	134.03	143.69	112.48	75.42	108.32	88.23	97.09	103.57	104.70	95.27	86.94
B	29	97.34	87.84	87.29	91.29	82.72	76.70	127.77	131.26	132.27	131.44	137.96	135.46	135.17	150.99	148.19	143.18	140.61	140.69	136.39	130.74	135.71	117.00	128.75	125.63	86.25	97.64
B	30	48.27	62.54	60.07	60.99	82.30	103.06	99.13	110.36	99.81	122.50	111.78	128.63	112.50	106.85	106.76	104.07	103.84	100.66	98.92	97.49	94.11	93.29	92.20	95.94	98.34	91.81
B	31	59.76	58.68	57.68	62.51	92.42	105.44	111.58	110.44	120.72	108.24	111.95	109.04	105.12	105.30	106.71	100.94	114.85	105.11	114.56	97.40	99.01	91.39	89.55	94.01	96.74	82.71
B	32	74.57	72.77	73.00	82.92	117.88	129.63	121.07	129.68	130.87	123.49	117.98	135.62	111.94	122.16	121.28	116.37	109.10	111.44	115.81	109.23	112.82	104.36	105.94	109.92	98.12	95.78
B	33	85.82	74.62	76.11	99.07	141.56	161.02	157.87	147.99	148.66	140.65	140.64	141.16	143.42	145.24	145.54	139.16	140.19	131.95	133.43	133.25	131.29	121.27	124.59	122.45	107.39	109.73
B	34	85.60	85.71	87.57	97.29	117.04	136.71	150.13	156.54	144.85	142.16	143.31	144.38	146.08	155.08	143.59	137.64	133.49	127.56	133.97	126.69	122.29	114.37	124.62	115.72	110.54	103.64
B	35	79.92	75.24	77.83	75.58	75.75	93.70	98.58	126.68	129.74	114.37	118.96	126.74	106.00	115.91	122.55	122.51	117.39	113.36	129.33	122.95	114.84	104.42	113.51	114.40	101.69	118.67
B	36	80.90	79.65	83.02	98.85	141.40	146.06	151.27	147.96	126.60	134.04	144.55	128.26	138.90	144.31	135.24	137.31	131.70	131.66	121.30	123.59	127.39	123.36	113.38	111.00	116.32	117.77
B	37	75.84	72.17	70.06	78.77	76.21	98.33	113.56	125.51	133.60	134.37	135.01	137.10	129.76	134.36	124.19	127.55	129.75	140.99	126.73	122.72	119.25					


 PPD	ANALYTICAL UNIT					Issue	10-Mar-2020
						Version	1.0
	STATISTICAL DOCUMENT					Page	60 of 68

Table A2.3. Descriptive statistics of the values of the levothyroxine unadjusted concentration in a biological fluid (N = 43).

Time	Eutirox® approved formulation (A)						Eutirox® test formulation (B)					
	Arithmetic Mean	Median	Minimum Value	Maximum Value	Standard Deviation	%CV	Arithmetic Mean	Median	Minimum Value	Maximum Value	Standard Deviation	%CV
-0.50	74.70	75.58	51.32	96.31	10.92	14.62	74.79	75.57	48.27	97.34	10.76	14.39
-0.25	71.35	71.52	51.97	88.14	9.82	13.76	71.97	72.77	53.78	89.15	9.70	13.48
0.00	71.41	73.34	38.94	92.32	11.63	16.29	72.49	72.06	53.58	90.76	9.69	13.37
0.50	75.36	77.96	47.34	93.70	11.27	14.96	79.29	79.72	60.29	99.07	11.32	14.28
1.00	96.62	97.06	59.66	157.65	18.78	19.44	101.47	98.42	67.54	141.56	18.42	18.16
1.50	112.06	114.25	75.83	165.98	18.88	16.84	115.84	113.55	69.39	161.02	21.28	18.37
2.00	118.83	116.77	82.84	161.69	17.98	15.13	121.49	122.59	75.84	162.04	21.62	17.80
2.50	124.88	124.02	79.51	176.09	17.35	13.90	126.41	126.68	81.42	172.13	21.68	17.15
3.00	127.20	128.42	81.48	170.46	18.67	14.68	127.71	127.83	80.95	179.10	21.19	16.59
3.25	128.76	130.24	89.24	163.65	15.90	12.35	126.26	127.74	80.47	173.35	20.60	16.31
3.50	128.85	129.32	97.75	159.19	15.64	12.14	126.64	125.74	81.89	183.00	20.78	16.41
3.75	128.55	129.39	95.87	163.10	14.98	11.65	127.59	128.26	87.49	184.14	20.45	16.03
4.00	127.59	129.48	98.65	162.15	16.47	12.91	125.51	126.43	86.54	187.29	20.19	16.08
4.25	132.28	130.90	102.57	168.47	16.21	12.25	130.18	130.88	88.43	190.12	19.66	15.10
4.50	128.47	128.83	101.59	165.46	15.95	12.41	127.55	124.19	82.10	179.61	18.68	14.64
4.75	125.43	125.04	97.30	167.06	17.24	13.74	125.76	126.01	84.78	181.77	18.49	14.71
5.00	124.78	124.72	93.84	164.72	17.17	13.76	124.78	122.51	85.15	183.27	18.13	14.53
5.50	123.76	124.50	93.84	161.41	17.16	13.86	122.10	121.23	82.87	180.55	17.38	14.23
6.00	121.22	121.99	91.05	164.27	16.09	13.27	120.67	124.37	75.42	182.27	18.68	15.48
6.50	119.14	119.15	93.42	157.78	15.03	12.62	117.86	118.85	82.30	166.36	16.17	13.72
8.00	119.95	120.06	92.31	157.87	14.79	12.33	118.27	119.93	76.68	159.04	18.07	15.28
10.00	113.14	114.76	82.48	148.44	15.10	13.34	111.35	111.11	78.56	148.79	14.90	13.38
12.00	110.35	110.33	81.44	144.12	14.08	12.76	110.55	111.01	75.99	149.12	15.43	13.96
24.00	108.88	109.58	83.68	128.59	11.95	10.98	108.77	111.23	82.26	127.82	12.50	11.49
36.00	105.08	105.05	85.15	128.25	12.05	11.47	105.08	107.39	75.74	141.81	12.77	12.15
48.00	102.11	101.26	83.29	125.68	11.45	11.22	100.79	98.86	82.69	121.52	10.33	10.25


 PPD	ANALYTICAL UNIT				Issue	10-Mar-2020
					Version	1.0
	STATISTICAL DOCUMENT				Page	61 of 68

Table A2.4. Individual data and descriptive statistics for the levothyroxine pharmacokinetic parameters (C_{max} in ng/mL, AUC_{0-t} in ng*h/mL, and $AUC_{0-\infty}$ in ng*h/mL). Unadjusted data.

Volunteer	Period		Sequence	C _{max}				AUC _{0-t}				AUC _{0-∞}			
	Form			B/A	Ln(B/A)	Form		B/A	Ln(B/A)	Form		B/A	Ln(B/A)		
	A	B				A	B			A	B				
1	2	1	BA	154.58	161.90	1.05	0.05	5385.00	5664.69	1.05	0.05	27555.67	22603.71	0.82	-0.20
2	2	1	BA	141.18	145.86	1.03	0.03	5779.14	5529.30	0.96	-0.04	93377.86	32154.93	0.34	-1.07
3	2	1	BA	124.53	126.65	1.02	0.02	4277.06	4462.98	1.04	0.04	44552.09	36788.29	0.83	-0.19
4	1	2	AB	145.08	147.39	1.02	0.02	5336.10	5576.05	1.04	0.04	33127.36	30266.17	0.91	-0.09
5	1	2	AB	130.89	131.78	1.01	0.01	5015.92	4806.67	0.96	-0.04	23732.87	57135.11	2.41	0.88
6	2	1	BA	119.99	113.58	0.95	-0.05	4473.20	4278.30	0.96	-0.04	27328.49	28813.20	1.05	0.05
7	1	2	AB	123.98	127.83	1.03	0.03	4470.88	4726.66	1.06	0.06	22435.07	38531.61	1.72	0.54
8	1	2	AB	135.77	134.36	0.99	-0.01	5043.45	5144.63	1.02	0.02	25621.50	26220.45	1.02	0.02
9	1	2	AB	167.06	190.12	1.14	0.13	5991.53	6725.22	1.12	0.12	27293.36	20606.86	0.76	-0.28
10	1	2	AB	160.04	168.43	1.05	0.05	5752.82	6068.60	1.05	0.05	22639.84	34231.86	1.51	0.41
11	1	2	AB	148.32	146.40	0.99	-0.01	5637.75	5838.71	1.04	0.04	26441.08	29309.72	1.11	0.10
12	2	1	BA	141.60	138.96	0.98	-0.02	5338.26	5330.46	1.00	0.00	32249.02	17139.15	0.53	-0.63
13	1	2	AB	124.35	118.71	0.95	-0.05	4991.51	4755.50	0.95	-0.05	32366.08	54498.84	1.68	0.52
14	2	1	BA	135.90	126.80	0.93	-0.07	5092.51	5090.77	1.00	0.00	25474.01	23160.87	0.91	-0.10
15	2	1	BA	141.19	133.82	0.95	-0.05	5486.66	5507.99	1.00	0.00	34430.60	56586.85	1.64	0.50
16	2	1	BA	148.33	139.30	0.94	-0.06	5413.91	5636.37	1.04	0.04	22972.97	18563.57	0.81	-0.21
17	1	2	AB	149.98	148.22	0.99	-0.01	5600.98	5479.24	0.98	-0.02	17477.08	19420.11	1.11	0.11
18	2	1	BA	123.86	126.08	1.02	0.02	4541.62	4718.95	1.04	0.04	21671.94	35245.75	1.63	0.49
19	1	2	AB	132.85	125.27	0.94	-0.06	4874.73	4827.43	0.99	-0.01	19071.97	27211.76	1.43	0.36
20	2	1	BA	150.05	145.50	0.97	-0.03	5958.66	5593.17	0.94	-0.06	30288.62	40886.79	1.35	0.30
21	2	1	BA	131.96	127.39	0.97	-0.04	4904.79	4920.17	1.00	0.00	34310.03	18272.51	0.53	-0.63
22	1	2	AB	120.49	110.13	0.91	-0.09	4439.99	4539.05	1.02	0.02	28954.21	40806.98	1.41	0.34
23	2	1	BA	133.94	150.89	1.13	0.12	5312.71	5584.70	1.05	0.05	27710.82	54566.68	1.97	0.68
24	1	2	AB	153.70	130.07	0.85	-0.17	5340.45	4666.15	0.87	-0.13	24452.64	33802.74	1.38	0.32
25	1	2	AB	128.50	131.59	1.02	0.02	4670.87	5185.27	1.11	0.10	29279.92	17005.57	0.58	-0.54
26	1	2	AB	138.86	138.58	1.00	0.00	5830.70	5793.95	0.99	-0.01	34861.83	34957.39	1.00	0.00
27	2	1	BA	127.81	132.69	1.04	0.04	5222.86	5204.65	1.00	0.00	35904.89	20777.14	0.58	-0.55
28	2	1	BA	170.46	168.52	0.99	-0.01	4733.75	4796.02	1.01	0.01	24098.70	16026.55	0.67	-0.41
29	2	1	BA	143.90	150.99	1.05	0.05	5390.91	5379.68	1.00	0.00	18180.48	14997.88	0.82	-0.19
30	1	2	AB	125.17	128.63	1.03	0.03	4751.73	4590.71	0.97	-0.03	35758.50	42327.77	1.18	0.17
31	1	2	AB	123.72	120.72	0.98	-0.02	4558.22	4503.63	0.99	-0.01	26417.08	20488.47	0.78	-0.25
32	1	2	AB	133.37	135.62	1.02	0.02	4979.99	5051.05	1.01	0.01	52815.04	21743.55	0.41	-0.89
33	1	2	AB	157.00	161.02	1.03	0.03	6143.29	5754.78	0.94	-0.07	37077.75	28138.76	0.76	-0.28
34	1	2	AB	150.81	156.54	1.04	0.04	5742.75	5616.20	0.98	-0.02	46512.15	26381.86	0.57	-0.57
35	1	2	AB	136.03	129.74	0.95	-0.05	5504.45	5305.90	0.96	-0.04	42525.83	75099.89	1.77	0.57
36	2	1	BA	163.65	151.27	0.92	-0.08	5745.78	5648.48	0.98	-0.02	25958.30	34447.89	1.33	0.28
37	2	1	BA	137.40	140.99	1.03	0.03	5502.46	5506.30	1.00	0.00	40925.02	63350.40	1.55	0.44
39	2	1	BA	176.09	169.96	0.97	-0.04	6382.19	5858.48	0.92	-0.09	25291.43	27801.24	1.10	0.09
40	2	1	BA	168.47	160.19	0.95	-0.05	6307.53	6170.73	0.98	-0.02	20848.42	25550.79	1.23	0.20
41	2	1	BA	145.51	163.04	1.12	0.11	5292.27	5602.80	1.06	0.06	32314.92	24227.96	0.75	-0.29
42	1	2	AB	103.11	89.15	0.86	-0.15	4063.30	3869.62	0.95	-0.05	35999.62	68147.40	1.89	0.64
43	2	1	BA	125.59	132.44	1.05	0.05	5105.17	4969.59	0.97	-0.03	28249.64	26459.22	0.94	-0.07
44	1	2	AB	116.34	107.26	0.92	-0.08	4501.21	4131.89	0.92	-0.09	79270.70	22946.99	0.29	-1.24
N				43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00
Geometric mean				138.89	137.85	0.99	NA	5200.09	5186.00	1.00	NA	30440.45	29984.99	0.99	NA
Arithmetic mean				139.80	139.17	0.99	-0.01	5229.98	5218.87	1.00	0.00	32507.57	32737.24	1.09	-0.02
Standard deviation				16.16	19.24	0.06	0.06	562.73	587.42	0.05	0.05	14364.09	14856.68	0.48	0.48
CV%				11.56	13.83	6.15	-817.63	10.76	11.26	4.99	-1837.73	44.19	45.38	44.31	-3205.24
Minimum value				103.11	89.15	0.85	-0.17	4063.30	3869.62	0.87	-0.13	17477.08	14997.88	0.29	-1.24
Median				137.40	135.62	0.99	-0.01	5312.71	5305.90	1.00	0.00	28249.64	28138.76	1.02	0.02
Maximum value				176.09	190.12	1.14	0.13	6382.19	6725.22	1.12	0.12	93377.86	75099.89	2.41	0.88

NA: Not applicable

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 PPD	ANALYTICAL UNIT			Issue	10-Mar-2020
				Version	1.0
	STATISTICAL DOCUMENT			Page	62 of 68

Table A2.5. Levothyroxine Pharmacokinetic Parameters Results, unadjusted value.

Variable	Form							
	Eutirox® approved formulation (A)				Eutirox® test formulation (B)			
	N	Arithmetic Mean	Standard Deviation	%CV	N	Arithmetic Mean	Standard Deviation	%CV
Extrapolated AUC (%)	43	81.90	5.81	7.10	43	81.07	7.66	9.44
AUC _{0-∞} (ng*h/mL)	43	32507.57	14364.09	44.19	43	32737.24	14856.68	45.38
AUC _{0-t} (ng*h/mL)	43	5229.98	562.73	10.76	43	5218.87	587.42	11.26
Cl/F (mL/h)	43	20.72	6.06	29.25	43	21.63	8.24	38.10
C _{max} (ng/mL)	43	139.80	16.16	11.56	43	139.17	19.24	13.83
t _{1/2} (h)	43	186.40	96.26	51.64	43	189.10	102.07	53.98
Kel (1/h)	43	0.00	0.00	36.92	43	0.00	0.00	45.83
MRT (h)	43	270.54	138.37	51.15	43	274.33	147.48	53.76
T _{lag} (h)	43	0.00	0.00	NA	43	0.00	0.00	NA
T _{max} (h)	43	3.52	1.19	33.96	43	3.50	1.14	32.58
Vd/F (L)	43	4.88	0.70	14.32	43	4.87	0.66	13.62

NA: Not applicable

Table A2.6. ANOVA table for the analysis of the unadjusted levothyroxine logarithmically-transformed pharmacokinetic parameters (Ln).

Assessed Variable	Source of Variation	Degrees of Freedom	Square Sum	Squared Means	F Value	P Value	Criterion (P > 0.05)
Ln(C _{max})	Sequence	1	0.07	0.07	2.15	0.15	Cumple
Ln(C _{max})	Sequence*Volunteer	41	1.25	0.03			No aplica
Ln(C _{max})	Form	1	1.22 x 10 ⁻³	1.22 x 10 ⁻³	0.64	0.43	Cumple
Ln(C _{max})	Period	1	1.31 x 10 ⁻³	1.31 x 10 ⁻³	0.69	0.41	Cumple
Ln(C _{max})	Error	41	7.86 x 10 ⁻²	1.92 x 10 ⁻³			No aplica
Ln(AUC _{0-t})	Sequence	1	2.69 x 10 ⁻²	2.69 x 10 ⁻²	1.14	0.29	Cumple
Ln(AUC _{0-t})	Sequence*Volunteer	41	0.97	2.36 x 10 ⁻²			No aplica
Ln(AUC _{0-t})	Form	1	1.58 x 10 ⁻⁴	1.58 x 10 ⁻⁴	0.12	0.73	Cumple
Ln(AUC _{0-t})	Period	1	9.64 x 10 ⁻⁵	9.64 x 10 ⁻⁵	0.08	0.78	Cumple
Ln(AUC _{0-t})	Error	41	5.21 x 10 ⁻²	1.27 x 10 ⁻³			No aplica
Ln(AUC _{0-∞})	Sequence	1	0.16	0.16	0.92	0.34	Cumple
Ln(AUC _{0-∞})	Sequence*Volunteer	41	7.00	0.17			No aplica
Ln(AUC _{0-∞})	Form	1	4.89 x 10 ⁻³	4.89 x 10 ⁻³	0.04	0.84	Cumple
Ln(AUC _{0-∞})	Period	1	0.06	0.06	0.55	0.46	Cumple
Ln(AUC _{0-∞})	Error	41	4.84	0.12			No aplica


 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
	STATISTICAL DOCUMENT		Version	1.0
			Page	63 of 68

Table A2.7 shows the results of the bioequivalence statistics for the levothyroxine logarithmically-transformed pharmacokinetic unadjusted data

Table A2.7 Statistics of the Levothyroxine Bioequivalence Determination.

Parameter	90 % Confidence Interval		Schuirmann's doubled-side t		Power (%)	Acceptance Criterion	Meets the Criterion
			P < 80 %	P > 125 %			
LnC _{max}	97.70	100.85	0.00	0.00	100.00	(80-125)	YES
LnAUC _{0-t}	98.45	101.03	0.00	0.00	99.98	(80-125)	YES

Table A3.1 Table of individual concentrations corresponding to adjusted levothyroxine, including predose greater than 5% (reference drug [A]). N = 43 subjects.

Form	Volunteer	Time																											
		0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00				
A	1	0.00	0.00	18.08	25.76	33.62	59.36	73.07	77.18	83.03	73.97	96.39	98.33	89.28	90.42	86.81	79.36	70.08	72.76	66.78	58.76	64.49	57.99	50.27	46.44				
A	2	0.95	3.10	19.25	33.71	42.76	45.60	46.32	54.44	52.37	51.29	49.24	55.16	53.62	49.56	59.08	45.50	44.61	44.62	45.91	44.13	38.01	34.60	38.14	39.62				
A	3	0.04	5.41	45.45	55.09	61.00	45.19	40.08	52.74	36.22	32.34	40.98	43.74	42.37	35.11	31.35	32.92	32.87	40.23	29.26	23.10	27.04	22.63	22.89	19.76				
A	4	0.24	2.22	15.74	39.37	55.52	56.51	59.29	52.39	51.70	67.12	49.86	62.41	59.12	47.28	48.65	51.19	41.04	45.56	47.40	37.83	38.98	30.15	29.06	23.10				
A	5	0.00	1.31	22.68	32.52	36.69	37.64	53.06	45.51	52.17	47.12	51.78	51.68	52.20	48.46	46.44	48.39	41.28	34.87	33.99	32.68	26.28	25.10	19.42	28.01				
A	6	0.00	2.13	4.16	21.55	49.91	64.49	63.06	57.44	57.84	58.86	49.98	57.66	51.39	55.90	53.28	53.25	52.89	55.45	53.91	44.06	42.77	36.80	32.71	28.96				
A	7	0.00	3.04	16.50	28.04	29.99	34.44	57.68	48.23	54.39	64.47	56.21	63.47	49.44	53.45	41.29	40.28	43.31	41.76	53.16	33.20	27.71	38.43	28.84	30.49				
A	8	0.00	3.03	31.05	44.07	58.34	64.72	57.08	63.33	49.74	58.34	60.40	60.22	57.79	55.20	61.69	54.74	61.39	47.24	51.10	45.10	39.51	32.40	24.89	23.33				
A	9	0.00	7.14	11.53	15.62	12.87	19.26	26.65	47.89	54.01	64.75	59.99	77.35	76.86	84.71	80.43	71.34	71.58	62.36	60.40	49.55	39.32	46.23	37.58	38.79				
A	10	0.00	0.00	1.86	36.34	52.20	58.30	62.78	71.37	70.04	56.75	74.84	79.08	75.58	81.77	61.19	74.82	63.72	58.42	62.81	55.65	48.99	41.36	31.64	30.82				
A	11	0.00	0.00	14.75	27.54	68.86	40.49	52.38	55.51	51.51	55.85	61.42	60.76	64.98	59.66	58.66	58.59	51.79	41.77	39.55	36.52	30.60	40.18	43.35	25.62				
A	12	0.00	6.19	26.38	50.30	54.73	63.00	69.82	61.41	63.27	65.19	60.02	65.76	56.83	51.26	52.95	55.53	54.36	47.84	57.10	45.06	42.70	40.25	32.52	29.49				
A	13	0.00	7.13	29.24	59.72	46.49	62.06	60.77	60.84	58.21	50.85	40.75	60.79	53.75	54.37	50.33	55.28	52.64	41.59	48.04	47.04	35.90	42.43	43.72	34.56				
A	14	1.25	3.33	24.00	43.40	49.00	61.37	54.90	63.59	57.32	59.44	62.16	63.16	56.87	69.84	61.81	55.00	58.65	55.78	58.93	29.87	48.92	40.85	32.00	31.63				
A	15	0.22	0.00	5.43	0.00	13.29	25.09	22.85	30.79	43.23	41.27	36.76	40.83	44.14	40.51	51.95	42.80	39.20	34.20	31.48	41.79	36.83	23.05	15.76	25.49				
A	16	0.00	8.00	26.69	33.12	35.23	55.66	56.88	66.06	67.07	61.11	56.07	49.65	49.91	58.86	48.93	60.42	55.01	53.01	37.59	40.86	36.36	30.10	20.19	29.89				
A	17	0.00	4.78	11.47	14.59	24.96	42.11	66.14	60.41	54.70	50.91	59.30	62.16	46.06	52.30	58.93	50.21	49.20	54.71	54.37	43.89	41.10	36.45	23.89	14.73				
A	18	0.00	2.12	33.99	44.44	52.12	58.14	63.81	61.51	60.94	67.71	63.07	61.82	58.70	56.20	55.17	58.14	56.91	47.85	48.84	42.38	45.57	39.15	29.68	29.96				
A	19	0.09	4.33	43.58	51.94	49.37	59.52	60.20	58.16	64.98	60.57	49.71	73.11	55.00	52.70	51.18	55.10	42.80	45.87	49.52	39.35	39.24	50.09	35.00	34.00				
A	20	0.00	6.32	34.84	68.56	71.10	66.47	74.56	67.80	74.61	68.09	68.12	67.57	64.24	63.56	67.00	67.08	59.46	56.90	60.97	49.31	44.45	48.93	49.42	37.82				
A	21	0.00	2.99	27.13	56.35	53.46	61.00	68.61	64.96	62.32	62.87	68.94	65.30	65.99	60.89	58.27	57.45	43.04	48.99	54.87	38.81	35.62	40.28	34.92	32.53				
A	22	0.00	0.00	5.47	10.20	13.43	18.87	24.83	24.02	34.94	35.63	30.05	32.89	50.81	27.92	26.94	30.33	31.08	30.71	24.96	31.68	24.79	24.17	23.12	14.56				
A	23	0.00	2.03	36.97	47.98	46.30	49.23	47.93	48.24	44.80	50.16	45.40	48.89	45.05	37.36	44.33	40.72	37.82	34.38	36.27	28.80	21.73	25.25	26.87	19.00				
A	24	0.00	0.00	23.24	45.18	53.90	75.62	66.74	63.45	71.36	69.87	65.15	66.94	55.11	53.43	49.25	55.26	46.69	41.32	41.62	34.62	35.28	39.99	22.34	19.02				
A	25	0.00	0.00	32.21	53.96	47.94	53.88	29.00	43.37	37.39	37.45	41.45	59.68	41.38	45.81	35.74	42.69	43.87	40.04	38.76	29.82	26.81	24.73	26.95	26.58				
A	26	3.32	4.41	10.30	27.04	37.86	49.47	40.82	46.52	36.61	42.67	34.47	39.69	35.68	30.91	36.29	43.15	35.12	42.01	51.65	37.41	33.72	36.45	34.34	25.45				
A	27	0.65	0.00	17.31	34.50	41.84	42.94	48.06	46.90	44.91	46.60	42.51	47.33	40.83	33.39	36.48	42.11	42.24	39.78	37.72	36.08	30.58	29.83	23.78	23.70				
A	28	0.00	5.77	15.58	47.72	61.94	68.74	121.16	65.30	80.02	71.97	68.57	57.51	63.91	52.81	77.31	46.12	54.33	56.03	52.65	51.64	51.99	41.44	56.27	41.17				
A	29	0.74	12.68	11.63	31.89	56.96	65.35	39.34	55.86	54.04	41.67	55.05	53.18	50.24	46.79	41.93	42.84	36.96	36.07	49.20	36.21	31.70	41.18	28.21	20.81				
A	30	1.66	4.82	24.29	33.51	29.16	52.40	32.50	68.88	55.06	63.72	53.08	58.09	57.83	52.74	51.52	49.09	43.36	40.22	48.23	42.74	42.01	40.28	48.76	37.67				
A	31	0.00	4.57	9.30	34.95	34.96	45.12	39.65	40.99	39.33	39.99	38.43	45.02	49.54	48.10	36.09	23.02	30.45	31.71	32.90	17.75	18.83	27.31	10.97	15.01				
A	32	3.18	6.59	50.40	53.47	61.04	43.57	39.55	38.07	39.94	44.61	36.54	42.04	36.95	34.54	35.68	39.39	33.26	34.52	34.90	39.95	25.06	30.26	30.86	30.84				
A	33	3.27	8.57	37.56	45.26	57.55	76.35	71.51	77.89	82.25	76.90	79.66	86.99	85.56	73.60	61.06	85.56	65.23	73.26	64.06	59.41	64.31	50.72	58.18	55.61				
A	34	0.00	0.00	9.17	12.53	22.41	25.61	40.22	48.91	60.92	47.62	48.59	57.50	43.24	44.53	38.47	42.39	36.95	27.96	40.18	31.81	30.39	36.36	22.47	26.44				
A	35	0.00	3.18	38.87	59.17	59.46	54.39	53.87	48.81	45.85	45.87	46.05	54.19	44.10	31.48	43.13	45.66	41.79	43.02	47.03	48.06	34.11	39.58	36.52	31.71				
A	36	3.49	4.87	51.03	62.19	56.79	52.03	65.33	74.82	61.33	64.84	57.09	59.12	52.43	54.17	51.54	51.65	46.36	45.53	41.02	42.03	35.39	35.52	29.58	30.34				
A	37	0.00	0.00	36.37	47.22	60.30	55.05	54.15	57.78	59.60	55.54	52.78	54.60	52.35	47.95	49.44	53.06	53.52	47.45	48.10	38.77	42.02	36.21	33.56	29.36				
A	39	2.71	7.98	81.95	90.27	85.98	100.38	86.78	82.14	79.05	82.19	83.16	89.05	86.73	78.73	73.45	85.70	79.63	77.27	68.79	68.89	64.91	51.98	47.47	49.11				
A	40	9.72	5.85	19.34	30.92	38.85	73.16	76.71	80.95	81.27	85.18	84.23	90.95	87.54	83.46	86.80	64.95	86.35	79.86	79.95	70.52	66.20	48.16	49.29	34.43				
A	41	0.00	3.33	36.99	51.23	57.14	55.62	64.01	64.35	65.86	59.42	61.18	62.57	72.78	52.99	46.20	40.05	52.40	46.42	48.37	39.45	32.90	46.04	27.53	30.69				
A	42	0.00	2.16	6.44	17.24	24.25	20.91	22.88	30.64	39.15	40.03	40.06	44.51	42.99	38.71	35.24	35.24	32.46	34.83	33.72	23.89	22.85	25.08	27.12	27.15				
A	43	0.00	9.75	0.00	51.13	47.33	44.91	48.87	41.58	43.98	45.90	46.19	48.97	43.90	45.06	44.44	39.67	40.08	35.99	44.86	30.43	31.86	29.09	34.59	23.61				
A	44	1.00	4.89	22.37	35.41	45.79	51.87	48.87	48.92	46.34	44.27	43.36	50.47	44.87	40.22	41.19	38.69	37.78	35.92	30.08	30.31	30.37	27.85	26.68	26.28				
Arithmetic Mean		0.76	3.81	24.20	39.66	46.34	52.39	54.72	56.28	56.36	56.07	55.10	59.79	55.98	52.95	52.39	51.27	48.73	46.65	47.46	40.66	37.87	36.39	32.59	29.62				
Standard Deviation		1.75	3.98	16.08	17.36	16.00	16.33	18.63	13.46	13.52	12.62	14.49	14.14	13.92	15.08	14.89	13.83	12.98	12.44	11.90	11.07	11.57	9.34	10.70	8.70				
NCV		231.17	80.71	66.46	43.78	34.52	31.17	34.04	23.91	23.99	22.87	26.30	23.65	24.86	28.48	28.47	26.98	26.64	26.66	25.06	27.24	30.56	25.68	18.83	29.39				


 PPD	ANALYTICAL UNIT															Issue	10-Mar-2020
																Version	1.0
	STATISTICAL DOCUMENT															Page	64 of 68

Table A3.2 Table of individual concentrations corresponding to levothyroxine, including predose greater than 5% (reference drug). N = 43 subjects.

Form	Volunteer	Time																							
		0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.50	6.00	6.50	8.00	10.00	12.00	24.00	36.00	48.00
B	1	0.36	2.79	17.91	31.20	40.46	46.99	54.85	69.43	65.89	84.97	82.64	75.96	75.05	74.65	73.40	58.34	55.21	49.74	58.80	50.79	43.11	40.03	41.77	21.93
B	2	0.00	3.77	34.31	49.71	55.52	52.76	57.53	48.95	52.17	46.50	47.92	52.87	49.14	47.08	40.16	42.16	59.26	36.21	33.32	27.19	30.20	28.83	23.76	18.41
B	3	0.00	4.56	42.17	56.41	39.98	44.50	35.97	34.31	41.07	39.67	24.39	34.59	48.09	36.40	36.96	24.59	25.43	20.77	6.44	12.78	13.72	20.74	27.56	24.82
B	4	0.00	5.29	16.63	39.25	54.71	55.69	63.95	60.72	55.17	54.09	53.89	52.11	47.96	42.13	41.46	42.58	43.26	40.44	41.92	37.87	37.55	30.28	31.89	19.31
B	5	0.00	3.60	5.15	9.40	9.21	13.56	15.13	20.55	12.57	26.79	23.36	37.49	41.91	59.02	53.80	47.48	40.41	42.82	37.95	30.38	23.75	29.37	27.62	24.90
B	6	0.24	0.00	4.78	15.29	14.54	16.90	16.01	25.48	28.34	33.35	39.92	48.64	45.53	40.81	33.57	38.87	34.07	33.18	29.28	28.03	30.25	25.72	17.88	23.41
B	7	0.53	8.73	36.06	41.76	49.65	54.84	69.43	55.04	55.85	42.18	45.25	46.82	50.46	45.27	55.71	51.90	50.42	49.95	43.06	45.35	38.26	40.62	36.32	39.65
B	8	0.00	22.49	48.49	61.64	66.18	57.51	58.67	60.60	59.30	53.33	53.95	60.19	52.90	54.45	47.68	53.99	49.81	44.60	40.06	38.55	37.62	31.20	44.63	31.79
B	9	2.13	0.00	25.40	43.56	69.04	86.57	93.54	87.80	97.45	98.59	101.74	104.57	94.06	96.22	97.71	95.00	96.72	80.81	73.49	63.24	63.56	42.01	56.25	35.96
B	10	0.00	1.43	20.93	48.51	67.80	73.54	79.88	97.25	96.00	79.94	74.34	82.17	85.29	84.34	89.85	70.20	82.59	77.27	76.82	57.96	74.36	52.40	44.80	41.12
B	11	0.39	4.73	23.43	59.64	67.87	71.66	67.73	72.27	69.20	62.75	61.72	63.41	57.79	63.43	62.11	56.08	64.38	62.71	53.65	51.28	41.67	49.91	50.30	32.51
B	12	0.00	1.73	24.09	40.62	54.56	63.04	54.30	58.19	57.49	57.61	60.91	69.15	55.95	56.19	53.60	48.72	52.36	44.18	53.11	38.15	35.54	48.57	40.50	27.35
B	13	0.00	4.26	32.89	49.68	47.43	51.61	49.51	42.51	46.20	36.71	46.03	51.70	46.62	43.99	42.89	43.98	42.76	30.11	40.77	31.17	32.40	19.77	37.89	34.95
B	14	0.20	6.14	33.16	53.17	55.00	63.97	53.37	56.39	60.64	61.77	62.86	63.12	63.19	61.68	61.09	68.12	65.83	60.17	62.76	55.44	52.45	40.06	50.94	35.83
B	15	0.00	1.87	19.48	33.62	24.27	41.18	46.90	50.19	44.68	45.12	44.01	53.99	44.32	54.48	39.59	38.31	47.15	39.17	53.60	39.42	38.73	31.88	33.06	36.67
B	16	6.49	2.41	17.61	33.54	55.03	45.07	44.78	43.47	41.31	39.68	43.17	48.86	46.04	41.85	39.92	45.29	36.25	41.96	38.01	34.67	29.87	43.55	27.70	20.88
B	17	0.00	2.89	17.25	28.91	44.51	50.85	52.11	42.23	68.33	66.23	58.97	67.80	63.88	51.40	51.40	51.97	45.41	38.59	55.86	42.85	36.91	34.72	34.95	11.84
B	18	0.00	7.27	35.61	47.18	54.82	65.71	68.11	62.74	63.33	61.82	60.32	65.35	57.65	54.51	55.82	53.49	51.41	51.62	53.01	51.62	47.24	37.26	34.72	30.84
B	19	0.30	2.50	29.64	42.62	56.02	41.53	52.48	46.66	42.04	38.77	36.36	50.90	47.34	47.19	43.10	45.24	55.43	49.00	41.15	38.82	37.83	29.34	23.85	25.47
B	20	0.01	7.07	39.40	53.19	56.06	54.98	59.97	56.63	49.46	49.00	48.20	60.44	48.90	42.34	37.45	36.18	39.47	39.90	43.58	32.28	24.00	29.55	33.42	23.14
B	21	3.56	15.88	35.26	58.93	59.18	66.13	66.40	59.28	65.38	62.22	62.60	67.03	61.85	49.99	53.00	53.79	54.12	59.51	64.38	46.40	43.97	39.84	41.86	24.83
B	22	1.39	0.00	18.07	34.38	30.99	38.85	43.21	42.46	37.15	39.86	40.72	37.81	36.49	32.74	43.65	35.78	37.49	37.29	30.36	32.87	28.72	28.66	24.22	26.61
B	23	1.89	11.64	49.76	70.84	68.59	73.24	60.25	66.61	61.33	60.29	61.24	67.83	61.56	54.26	53.77	49.82	48.79	44.34	40.53	40.50	38.97	39.37	32.88	30.72
B	24	0.76	0.00	0.00	0.00	9.34	11.89	16.72	10.93	12.35	18.55	39.45	55.64	54.80	60.54	51.26	45.55	29.73	33.85	36.69	21.42	26.65	34.25	24.89	26.37
B	25	0.00	20.25	50.91	60.79	55.35	47.89	56.13	42.26	55.71	62.69	42.97	51.28	40.88	54.72	45.57	57.57	41.01	53.43	44.70	50.85	34.92	47.30	31.89	26.78
B	26	0.00	0.00	11.65	25.16	35.14	51.11	54.58	50.03	49.19	53.50	48.08	46.87	46.09	46.22	47.47	45.86	40.73	45.93	49.16	42.23	41.84	36.91	35.69	25.87
B	27	0.00	1.22	26.36	39.15	42.23	49.84	44.22	42.60	46.63	45.42	51.14	52.34	42.09	38.86	45.57	39.84	46.78	32.39	40.71	30.76	30.65	29.61	24.19	14.63
B	28	0.00	10.78	40.05	31.95	44.49	35.97	105.75	93.10	57.87	91.63	58.16	46.44	69.72	71.26	80.92	49.71	12.65	45.55	25.46	34.32	40.80	41.93	32.50	24.17
B	29	0.00	0.46	0.00	0.00	36.95	40.43	41.45	40.61	47.14	44.64	44.35	60.17	57.37	52.35	49.79	49.87	45.56	39.91	44.89	26.18	37.92	34.80	0.00	6.82
B	30	3.11	3.63	25.34	46.10	42.17	53.40	36.85	65.54	54.82	71.68	55.55	49.89	49.80	47.11	46.88	43.70	41.96	40.53	37.15	36.33	35.24	38.98	41.39	34.86
B	31	0.00	3.80	33.71	46.73	52.87	51.74	62.01	49.53	53.25	50.33	46.42	46.59	48.00	42.24	56.14	46.41	55.85	38.69	40.30	32.69	30.85	35.30	38.03	24.01
B	32	0.00	9.47	44.44	56.18	47.62	56.23	57.42	50.04	44.53	62.17	38.50	48.71	47.84	42.93	35.65	38.00	42.37	35.78	39.37	30.91	32.49	36.47	24.68	22.33
B	33	0.00	20.22	62.72	82.18	79.02	69.15	69.81	61.80	61.79	62.31	64.57	66.39	66.69	60.32	61.34	53.11	54.58	54.40	52.44	42.43	45.74	43.60	28.55	30.88
B	34	1.28	10.99	30.74	50.42	63.83	70.24	58.56	55.87	57.01	58.08	59.78	68.78	57.30	51.35	47.19	41.26	47.67	40.39	36.00	28.07	38.33	29.43	24.24	17.34
B	35	0.17	0.00	0.00	16.04	20.92	49.01	52.07	36.70	41.30	49.07	28.33	38.25	44.89	44.85	39.72	35.70	51.67	45.29	37.17	26.76	35.85	36.73	24.02	41.01
B	36	1.83	17.66	60.21	64.87	70.08	66.77	45.41	52.85	63.36	47.07	57.71	63.12	54.05	56.11	50.51	50.47	40.10	42.39	46.20	42.17	32.18	29.81	35.13	36.58
B	37	0.00	6.08	3.52	25.64	40.87	52.82	60.91	61.67	62.32	64.41	57.07	61.67	51.50	54.86	57.06	68.30	54.04	50.03	46.56	45.74	43.97	43.70	37.54	39.90
B	39	0.00	21.11	58.94	82.41	86.16	91.74	86.69	73.80	73.91	84.89	84.48	70.66	94.09	85.59	77.05	60.60	52.98	58.79	62.34	55.82	45.68	48.10	33.44	35.15
B	40	0.00	0.00	16.31	31.43	43.30	58.76	65.02	68.52	74.09	71.22	70.39	78.08	75.35	70.39	72.83	71.95	65.40	65.58	65.92	59.63	58.56	42.80	37.96	38.58
B	41	0.00	14.77	39.58	62.91	57.36	79.08	49.75	52.69	57.46	38.34	54.72	63.73	47.79	41.76	36.95	59.50	40.42	34.98	63.09	26.06	40.04	32.28	25.61	17.70
B	42	0.00	5.13	20.63	29.26	20.68	31.73	33.98	30.70	33.13	32.32	31.38	33.26	26.93	29.62	29.99	27.70	27.90	27.14	31.69	23.39	20.83	27.09	24.76	27.53
B	43	0.98	5.77	41.87	50.89	50.10	56.81	46.08	50.09	47.69	54.80	50.80	48.40	41.95	40.31	46.32	40.53	37.32	32.31	36.35	33.93	29.34	22.89	21.13	30.42
B	44	0.00	5.77	37.85	47.59	41.39	37.75	41.29	37.34	38.76	39.51	3													


 PPD	ANALYTICAL UNIT					Issue	10-Mar-2020
						Version	1.0
	STATISTICAL DOCUMENT					Page	65 of 68

Table A3.3. Descriptive statistics of the values of the levothyroxine concentration in a biological fluid, including predose greater than 5% (N = 43).

Time	Eutirox® Approved formulation (A)						Eutirox® test formulation (B)					
	Arithmetic Mean	Median	Minimum value	Maximum value	Standard Deviation	CV%	Arithmetic Mean	Median	Minimum value	Maximum value	Standard Deviation	CV%
0.00	0.76	0.00	0.00	9.72	1.75	231.17	0.60	0.00	0.00	6.49	1.26	211.29
0.50	3.81	3.33	0.00	12.68	3.08	80.71	6.47	4.56	0.00	22.49	6.44	99.62
1.00	24.20	22.68	0.00	81.95	16.08	66.46	28.66	29.64	0.00	62.72	16.39	57.18
1.50	39.66	39.37	0.00	90.27	17.36	43.78	43.09	46.10	0.00	82.41	18.77	43.57
2.00	46.34	49.00	12.87	85.98	16.00	34.52	48.40	50.10	9.21	86.16	17.54	36.23
2.50	52.39	53.88	18.87	100.38	16.33	31.17	53.33	52.82	11.89	91.74	17.09	32.05
3.00	54.72	54.90	22.85	121.16	18.63	34.04	54.62	54.58	15.13	105.75	18.05	33.05
3.25	56.28	57.44	24.02	82.14	13.46	23.91	53.17	52.69	10.93	97.25	17.42	32.76
3.50	56.36	54.70	34.94	83.03	13.52	23.99	53.55	55.17	12.35	97.45	16.73	31.24
3.75	56.07	56.75	32.34	85.18	12.82	22.87	54.51	53.50	18.55	98.59	17.20	31.56
4.00	55.10	53.08	30.05	96.39	14.49	26.30	52.43	51.14	23.36	101.74	15.71	29.97
4.25	59.79	59.12	32.89	98.33	14.14	23.65	57.09	53.99	33.26	104.57	13.97	24.48
4.50	55.98	52.43	35.68	89.28	13.92	24.86	54.47	49.80	26.93	94.09	14.10	25.89
4.75	52.95	52.70	27.92	90.42	15.08	28.48	52.68	51.35	29.62	96.22	14.12	26.81
5.00	52.29	50.33	26.94	86.81	14.89	28.47	51.69	47.68	29.99	97.71	14.93	28.88
5.50	51.27	50.21	23.02	85.70	13.83	26.98	49.01	47.48	24.59	95.00	12.97	26.47
6.00	48.73	44.61	30.45	86.35	12.98	26.64	47.59	46.78	12.65	96.72	14.27	29.99
6.50	46.65	44.62	27.96	79.86	12.44	26.66	44.77	42.39	20.77	80.81	12.34	27.57
8.00	47.46	48.10	24.96	79.95	11.90	25.06	45.18	41.92	6.44	76.82	13.45	29.77
10.00	40.66	39.35	17.75	70.52	11.07	27.24	38.26	37.87	12.78	63.24	11.31	29.56
12.00	37.87	35.90	18.83	66.20	11.57	30.56	37.47	37.55	13.72	74.36	10.93	29.18
24.00	36.39	36.80	15.52	57.99	9.34	25.68	35.68	35.30	19.77	52.40	7.92	22.18
36.00	32.59	30.86	10.97	58.18	10.70	32.83	32.10	32.88	0.00	56.25	10.24	31.89
48.00	29.62	29.49	14.56	55.61	8.70	29.39	27.71	26.78	6.82	41.12	8.06	29.09


 PPD	ANALYTICAL UNIT				Issue	10-Mar-2020
					Version	1.0
	STATISTICAL DOCUMENT				Page	66 of 68

Table A3.4. Individual data and descriptive statistics for the levothyroxine pharmacokinetic parameters (C_{max} in ng/mL, AUC_{0-t} in ng*h/mL, and $AUC_{0-\infty}$ in ng*h/mL). Including predose greater than 5%

Volunteer	Period		Sequence	C _{max}				AUC _{0-t}				AUC _{0-∞}			
	Form			B/A	Ln(B/A)	Form		B/A	Ln(B/A)	Form		B/A	Ln(B/A)		
	A	B				A	B			A	B				
1	2	1	BA	98.33	84.97	0.86	-0.15	2689.21	1962.33	0.73	-0.32	7629.83	3185.87	0.42	-0.87
2	2	1	BA	59.08	59.26	1.00	0.00	1837.68	1370.21	0.75	-0.29	11399.25	2354.71	0.21	-1.58
3	2	1	BA	61.00	56.41	0.92	-0.08	1225.73	1095.22	0.89	-0.11	3777.54	3797.19	1.01	0.01
4	1	2	AB	67.12	63.95	0.95	-0.05	1591.53	1566.01	0.98	-0.02	3378.30	2805.99	0.83	-0.19
5	1	2	AB	53.06	59.02	1.11	0.11	1280.47	1327.98	1.04	0.04	2783.29	5019.26	1.80	0.59
6	2	1	BA	64.49	48.64	0.75	-0.28	1808.01	1158.58	0.64	-0.45	4711.82	3048.40	0.65	-0.44
7	1	2	AB	64.47	69.43	1.08	0.07	1612.86	1922.93	1.19	0.18	4049.42	7788.41	1.92	0.65
8	1	2	AB	64.72	66.18	1.02	0.02	1636.89	1868.76	1.14	0.13	2868.45	4471.12	1.56	0.44
9	1	2	AB	84.71	104.57	1.23	0.21	2045.76	2607.86	1.27	0.24	4703.01	4314.79	0.92	-0.09
10	1	2	AB	81.77	97.25	1.19	0.17	1996.53	2646.91	1.33	0.28	3703.43	6718.92	1.81	0.60
11	1	2	AB	68.86	72.27	1.05	0.05	1819.09	2275.38	1.25	0.22	3550.70	4959.64	1.40	0.33
12	2	1	BA	69.82	69.15	0.99	-0.01	1891.63	1974.48	1.04	0.04	4532.57	3117.95	0.69	-0.37
13	1	2	AB	62.06	51.70	0.83	-0.18	2001.92	1534.42	0.77	-0.27	6086.38	7351.71	1.21	0.19
14	2	1	BA	69.84	68.12	0.98	-0.03	2004.14	2284.89	1.14	0.13	4664.28	5395.53	1.16	0.15
15	2	1	BA	51.95	54.48	1.05	0.05	1200.24	1699.47	1.42	0.35	2732.81	7145.54	2.61	0.96
16	2	1	BA	67.07	55.03	0.82	-0.20	1510.80	1584.61	1.05	0.05	2995.80	2265.70	0.76	-0.28
17	1	2	AB	66.14	68.33	1.03	0.03	1568.88	1626.36	1.04	0.04	1958.82	2041.21	1.04	0.04
18	2	1	BA	67.71	68.11	1.01	0.01	1843.99	1934.81	1.05	0.05	4232.42	5847.67	1.38	0.32
19	1	2	AB	73.11	56.02	0.77	-0.27	2003.61	1500.69	0.75	-0.29	4107.73	3381.13	0.82	-0.19
20	2	1	BA	74.61	60.44	0.81	-0.21	2335.65	1506.84	0.65	-0.44	5651.05	3602.09	0.64	-0.45
21	2	1	BA	68.94	67.03	0.97	-0.03	1878.60	2016.17	1.07	0.07	5532.19	3558.37	0.64	-0.44
22	1	2	AB	50.81	43.65	0.86	-0.15	1094.52	1350.77	1.23	0.21	2115.19	4602.71	2.18	0.78
23	2	1	BA	50.16	73.24	1.46	0.38	1288.89	1856.73	1.44	0.37	2389.96	6212.32	2.60	0.96
24	1	2	AB	75.62	60.54	0.80	-0.22	1586.03	1327.55	0.84	-0.18	2452.72	3747.07	1.53	0.42
25	1	2	AB	59.68	62.69	1.05	0.05	1371.46	1872.81	1.37	0.31	3601.75	3002.78	0.83	-0.18
26	1	2	AB	51.65	54.58	1.06	0.06	1641.62	1759.85	1.07	0.07	3342.39	3811.39	1.14	0.13
27	2	1	BA	48.06	52.34	1.09	0.09	1397.92	1342.50	0.96	-0.04	3116.06	1840.81	0.59	-0.53
28	2	1	BA	121.16	105.75	0.87	-0.14	2365.84	1777.07	0.75	-0.29	6969.94	2829.90	0.41	-0.90
29	2	1	BA	65.35	60.17	0.92	-0.08	1614.56	1100.34	0.68	-0.38	2345.54	1261.22	0.54	-0.62
30	1	2	AB	68.88	71.68	1.04	0.04	2052.91	1856.34	0.90	-0.10	7712.38	7998.73	1.04	0.04
31	1	2	AB	49.54	62.01	1.25	0.22	984.41	1681.30	1.71	0.54	1682.68	3464.68	2.06	0.72
32	1	2	AB	61.04	62.17	1.02	0.02	1508.72	1521.89	1.01	0.01	6168.89	2613.22	0.42	-0.86
33	1	2	AB	86.93	82.18	0.95	-0.06	2777.76	1970.60	0.71	-0.34	9404.14	4094.94	0.44	-0.83
34	1	2	AB	60.92	70.24	1.15	0.14	1423.86	1468.97	1.03	0.03	3357.06	2278.05	0.68	-0.39
35	1	2	AB	59.46	52.07	0.88	-0.13	1829.52	1581.34	0.86	-0.15	5265.86	8982.58	1.71	0.53
36	2	1	BA	74.82	70.08	0.94	-0.07	1468.93	1750.43	1.19	0.18	2996.07	4872.32	1.63	0.49
37	2	1	BA	60.30	68.30	1.13	0.12	1801.46	2017.01	1.12	0.11	4862.37	9642.45	1.98	0.68
39	2	1	BA	100.38	94.09	0.94	-0.06	2748.65	2212.77	0.81	-0.22	6147.33	4801.43	0.78	-0.25
40	2	1	BA	90.55	78.08	0.86	-0.15	2560.22	2227.62	0.87	-0.14	4307.50	4618.20	1.07	0.07
41	2	1	BA	72.78	79.08	1.09	0.08	1795.04	1564.48	0.87	-0.14	4528.22	2357.15	0.52	-0.65
42	1	2	AB	44.51	33.98	0.76	-0.27	1250.47	1223.34	0.98	-0.02	4821.73	8541.54	1.77	0.57
43	2	1	BA	51.13	56.81	1.11	0.11	1529.05	1337.85	0.87	-0.13	3297.62	3246.45	0.98	-0.02
44	1	2	AB	51.87	47.59	0.92	-0.09	1426.32	1293.80	0.91	-0.10	8140.54	3276.84	0.40	-0.91
N				43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00
Geometric Mean				65.78	64.47	0.98	NA	1700.84	1670.95	0.98	NA	4117.37	3989.61	0.97	NA
Arithmetic Mean				67.31	66.09	0.99	-0.02	1751.20	1710.70	1.01	-0.02	4513.37	4424.84	1.13	-0.03
Standard Deviation				15.45	15.13	0.15	0.14	435.41	378.25	0.24	0.23	2068.32	2074.66	0.62	0.59
%CV				22.95	22.90	14.72	-719.49	24.86	22.11	23.54	-1306.44	45.83	46.89	54.81	-1869.16
Minimum Value				44.51	33.98	0.75	-0.28	984.41	1095.22	0.64	-0.45	1682.68	1261.22	0.21	-1.58
Median				65.35	63.95	0.99	-0.01	1641.62	1681.30	1.01	0.01	4107.73	3797.19	1.01	0.01
Maximum Value				121.16	105.75	1.46	0.38	2777.76	2646.91	1.71	0.54	11399.25	9642.45	2.61	0.96

NA: Not applicable

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 PPD	ANALYTICAL UNIT			Issue	10-Mar-2020
				Version	1.0
	STATISTICAL DOCUMENT			Page	67 of 68

Table A3.5. Levothyroxine Pharmacokinetic Parameters Results, including predose greater than 5%.

Variable	Form							
	Eutirox® approved formulation (A)				Eutirox® test formulation (B)			
	N	Arithmetic Mean	Standard Deviation	%CV	N	Arithmetic Mean	Standard Deviation	%CV
Extrapolated AUC (%)	43.00	56.71	12.80	22.56	43.00	54.51	17.63	32.35
AUC _{0-∞} (ng*h/mL)	43.00	4513.37	2068.32	45.83	43.00	4424.84	2074.66	46.89
AUC _{0-t} (ng*h/mL)	43.00	1751.20	435.42	24.86	43.00	1710.70	378.25	22.11
Cl/F (mL/h)	43.00	158.97	67.19	42.26	43.00	166.99	80.99	48.50
C _{max} (ng/mL)	43.00	67.31	15.45	22.95	43.00	66.09	15.13	22.90
t _{1/2} (h)	43.00	61.57	32.13	52.18	43.00	62.32	36.07	57.88
Kel (1/h)	43.00	0.01	0.01	46.06	43.00	0.01	0.01	54.74
TMR (h)	43.00	92.33	45.56	49.35	43.00	93.19	53.14	57.02
T _{lag} (h)	43.00	0.09	0.20	211.64	43.00	0.02	0.11	458.13
T _{max} (h)	43.00	3.52	1.20	33.97	43.00	3.50	1.14	32.58
Vd/F (mL)	43.00	12013.60	3144.99	26.18	43.00	11950.47	2697.91	22.58

Table A3.6. ANOVA table for the analysis of the levothyroxine logarithmically-transformed pharmacokinetic parameters (Ln), including predose greater than 5%.

Assessed Variable	Source of Variation	Degrees of Freedom	Square Sum	Squared Means	F Value	P Value	Criterion (P > 0.05)
Ln(C _{max})	Sequence	1	0.13	0.13	1.58	0.22	Pass
Ln(C _{max})	Sequence*Volunteer	41	3.46	8.43 x 10 ⁻²			Not applicable
Ln(C _{max})	Form	1	8.61 x 10 ⁻³	8.61 x 10 ⁻³	0.82	0.37	Pass
Ln(C _{max})	Period	1	2.28 x 10 ⁻³	2.28 x 10 ⁻³	0.22	0.64	Pass
Ln(C _{max})	Error	41	0.43	1.05 x 10 ⁻²			Not applicable
Ln(AUC _{0-t})	Sequence	1	4.79 x 10 ⁻²	4.79 x 10 ⁻²	0.59	0.45	Pass
Ln(AUC _{0-t})	Sequence*Volunteer	41	3.34	0.08			Not applicable
Ln(AUC _{0-t})	Form	1	6.76 x 10 ⁻³	6.76 x 10 ⁻³	0.26	0.61	Pass
Ln(AUC _{0-t})	Period	1	7.01 x 10 ⁻²	7.01 x 10 ⁻²	2.72	0.11	Pass
Ln(AUC _{0-t})	Error	41	1.06	2.58 x 10 ⁻²			Not applicable
Ln(AUC _{0-∞})	Sequence	1	3.38 x 10 ⁻²	3.38 x 10 ⁻²	0.15	0.70	Pass
Ln(AUC _{0-∞})	Sequence*Volunteer	41	9.41	0.23			Not applicable
Ln(AUC _{0-∞})	Form	1	2.14 x 10 ⁻²	2.14 x 10 ⁻²	0.13	0.72	Pass
Ln(AUC _{0-∞})	Period	1	0.45	0.45	2.68	0.11	Pass
Ln(AUC _{0-∞})	Error	41	6.84	0.17			Not applicable


 PPD	ANALYTICAL UNIT		Issue	10-Mar-2020
			Version	1.0
	STATISTICAL DOCUMENT		Page	68 of 68

Table A3.7 shows the results of the bioequivalence statistics for the levothyroxine logarithmically-transformed pharmacokinetic data, including predose greater than 5%.

Table A3.7 Statistics of the Levothyroxine Bioequivalence Determination.

Parameter	90 % Confidence Interval		Schuirmann's doubled-side t		Power (%)	Acceptance Criterion	Meets the Criterion
			P < 80 %	P > 125 %			
LnC _{max}	94.40	101.72	0.00	0.00	100.00	(80-125)	YES
LnAUC _{0-t}	92.55	104.00	0.00	0.00	99.99	(80-125)	YES

11. References

- Chow S. C. y Liu J. P. (2009). Design and Analysis of Bioavailability and Bioequivalence Studies Third edition. USA: CRC Press.
- Mexican Official Standard NOM-177-SSA1-2013. Which establishes the tests and procedures to prove that a drug is interchangeable. The requirements for third parties performing interchangeability tests should fulfill. The requirements for conducting biocomparability studies. Requirements that third parties, investigational sites, or hospital institutions performing interchangeability tests must adhere to.

12. History of Changes

DATE OF CHANGE	CHANGE DESCRIPTION	LEVEL
	New Document	1.0