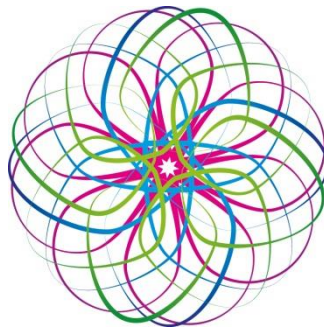




CHDR
Centre for Human Drug Research

Statistical appendix: Analysis of pharmacokinetic parameters

CHDR1939

Randomized, double-blind, placebo-controlled, two way crossover, single centre study evaluating the acute and chronic effect of clonazepam on cognitive tests and patient-reported outcome measures in patients with ARID1B-related intellectual disability

PROTOCOL MANAGEMENT

CHDR protocol ID	CHDR1939
Short title	Clonazepam in ARID1B Evaluation (CARE study)
Sponsor protocol ID	
File name	CHDR1939_FPK_2022-10-05.docx
Date	2022-10-05

Investigator site

Responsible investigator	R. (Rob) Zuiker, MD, PhD
Co-investigator(s)	G. (Gijs) Santen, MD, PhD, K. (Koshar) Safai Pour, MD, C. (Cecile) Berends. MSc
Pharmacometrician	D. van Asten, BSc
Study location	Centre for Human Drug Research (CHDR) Zernikedreef 8 2333 CL Leiden The Netherlands
	Telephone +31 71 5246400
	Telefax +31 71 5246499
	Emergency (24h/day) +31 71 5246444

Sponsor

Company name

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Non-compartmental analysis information

All PK parameter calculations were based on actual sampling time. For calculation of PK parameters, all BLQ concentrations that were between the first and last non-BLQ values were dropped (treated as 'missing'). For calculation of AUClast and $t_{1/2}$, additionally all values that were BLQ after the last non-BLQ value were dropped (treated as missing). If data points for concentrations were missing, the AUC parameters were derived by interpolating with regard to the 2 neighboring non-missing concentrations. AUC was calculated using the log-linear trapezoidal rule.

If the same maximum concentrations were observed at 2 or more time points, the earliest time point will be used as t_{max} .

The half-life was calculated as $t_{1/2} = \ln(2)/\lambda_z$, where λ_z is the terminal elimination rate constant determined by unweighted least squares regression of the terminal part of each individual log/linear concentration/time profile. The following rules were applied to determine the terminal elimination phase:

- The slope of the regression line must be negative ($\lambda_z > 0$).
- Sample at t_{max} cannot be included.
- At least 3 data points should be used
- $R^2 > 0.85$

In general, the more data points are used in the estimation, the better. The number of data points were selected automatically to achieve the largest adjusted R^2 value. If two adjusted R^2 values (based on different number of data points) deviated with less than 0.0001, then the fit based on the most data points was selected. An half-life estimate was not excluded based on the range of the data included in the regression as compared to the estimated half-life (the span-ratio). The average span-ratio was 1.01.

Reporting of drug concentration data

The concentrations are summarized (n, mean, SD, %CV, median, Min and Max values) by treatment and time, and are also presented graphically as mean over time, with standard deviation as error bars. For graphical and summary purposes of drug concentrations, values below the limit of quantification (BLQ) are set to zero. The SD and CV% are not reported if the mean is 0. Individual concentrations versus time are plotted for each treatment using both a linear and logarithmic y-axis. Individual profiles for each subject are provided on a linear and logarithmic y-axis. The individual concentrations are listed by treatment, subject and time.

Reporting of PK parameters

The individual PK parameters (except t_{max}) are summarized (n, mean, SD, %CV, geometric mean, geometric %CV, median, Min and Max) per treatment group and a selection of the PK parameters are presented graphically as boxplots. For t_{max} , the n, median, Min and Max statistics are reported. Boxplots present the median (horizontal solid line), the 25%-75% distribution (IQR), with 1.5x the IQR as whiskers. Circles present the observations. The individual calculated PK parameters are listed by treatment, subject and time.

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Comments from bioanalysis

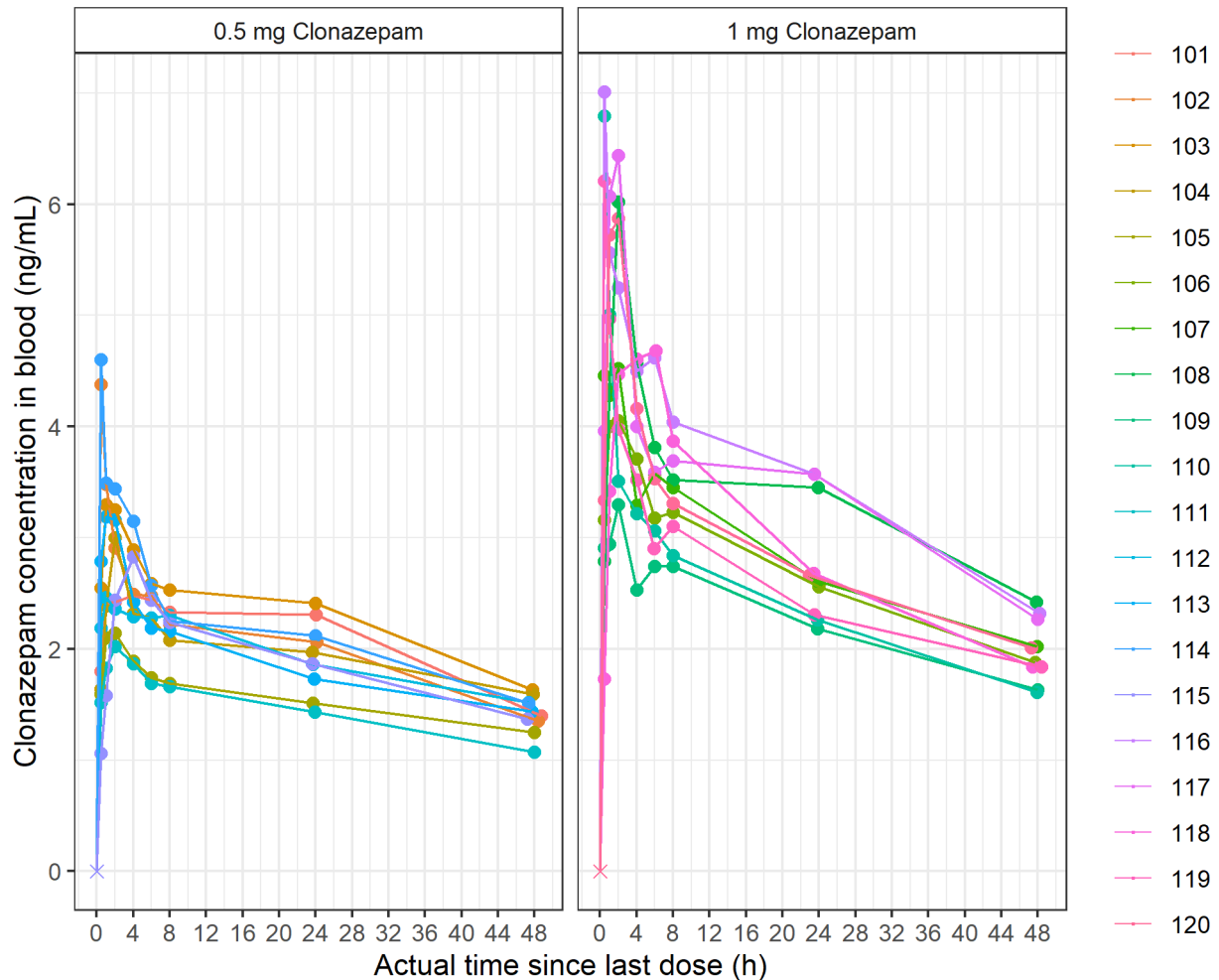
The lower limit of quantification (LLOQ) for the concentration of clonazepam in blood and saliva were <2ng/mL and <0.5 ng/mL, respectively. Concentrations reported below these values are best estimates and were used for summary and parameter calculation in this analysis.

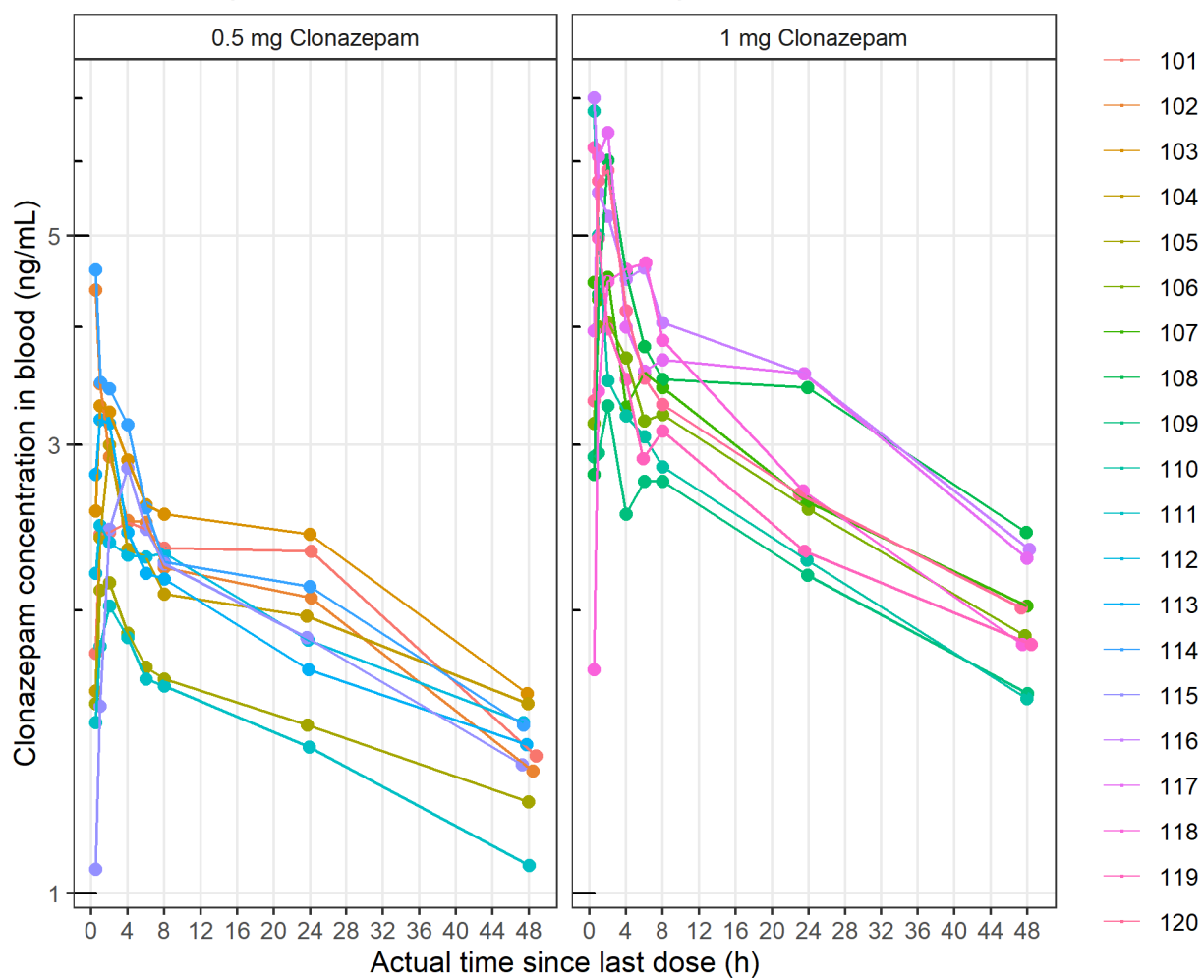
Drug Concentration Tables and Figures

Individual Plots

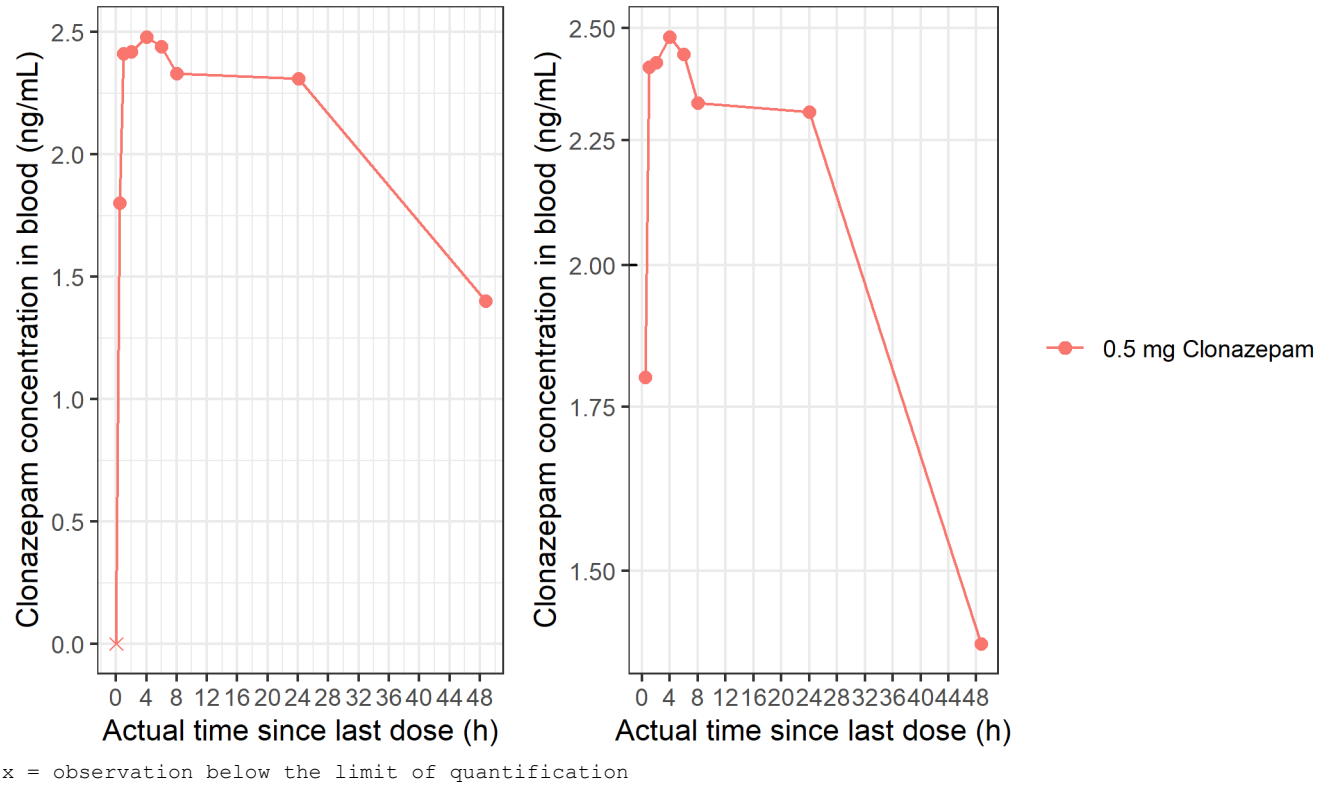
Individual profiles of Clonazepam concentration in Plasma (ng/mL) (linear y-axis)

Individual pharmacokinetics of Clonazepam in Plasma

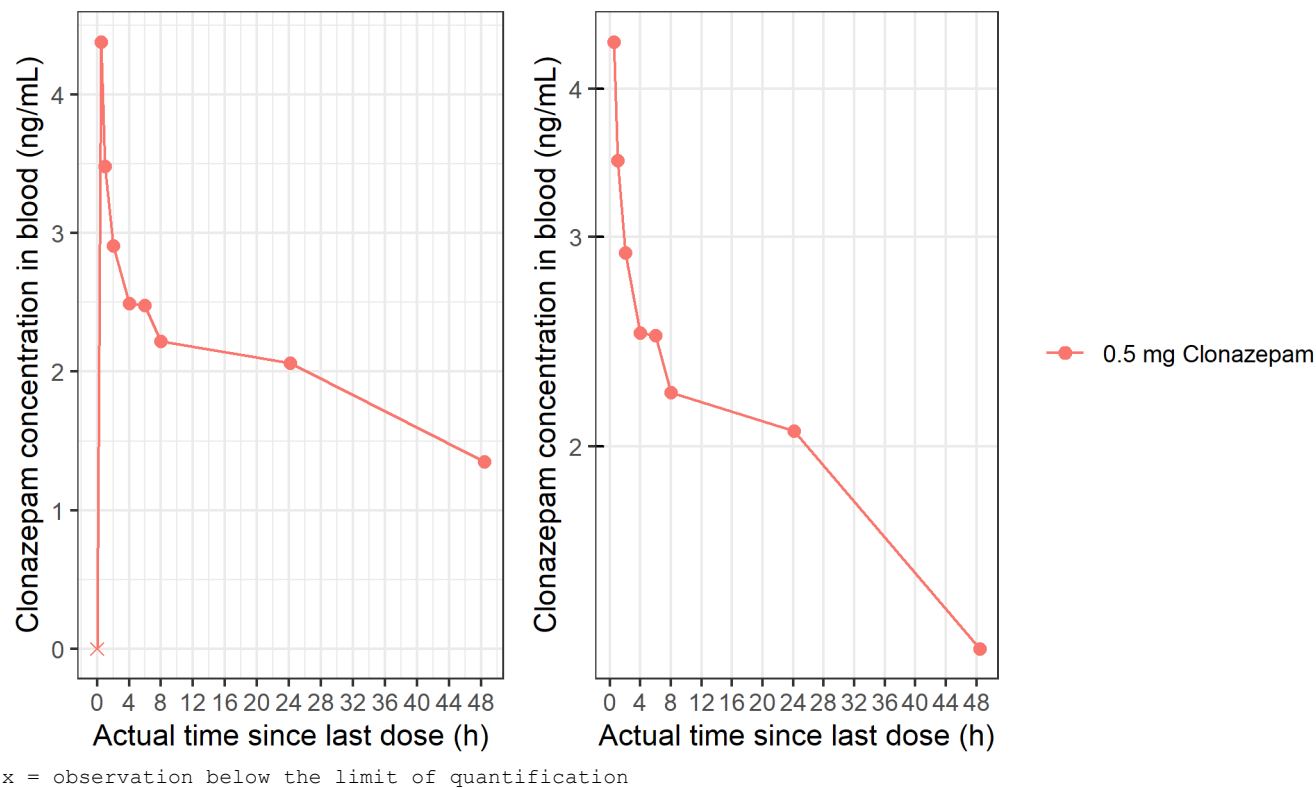


Individual profiles of Clonazepam concentration in Plasma (ng/mL) (log y-axis)**Individual pharmacokinetics of Clonazepam in Plasma**

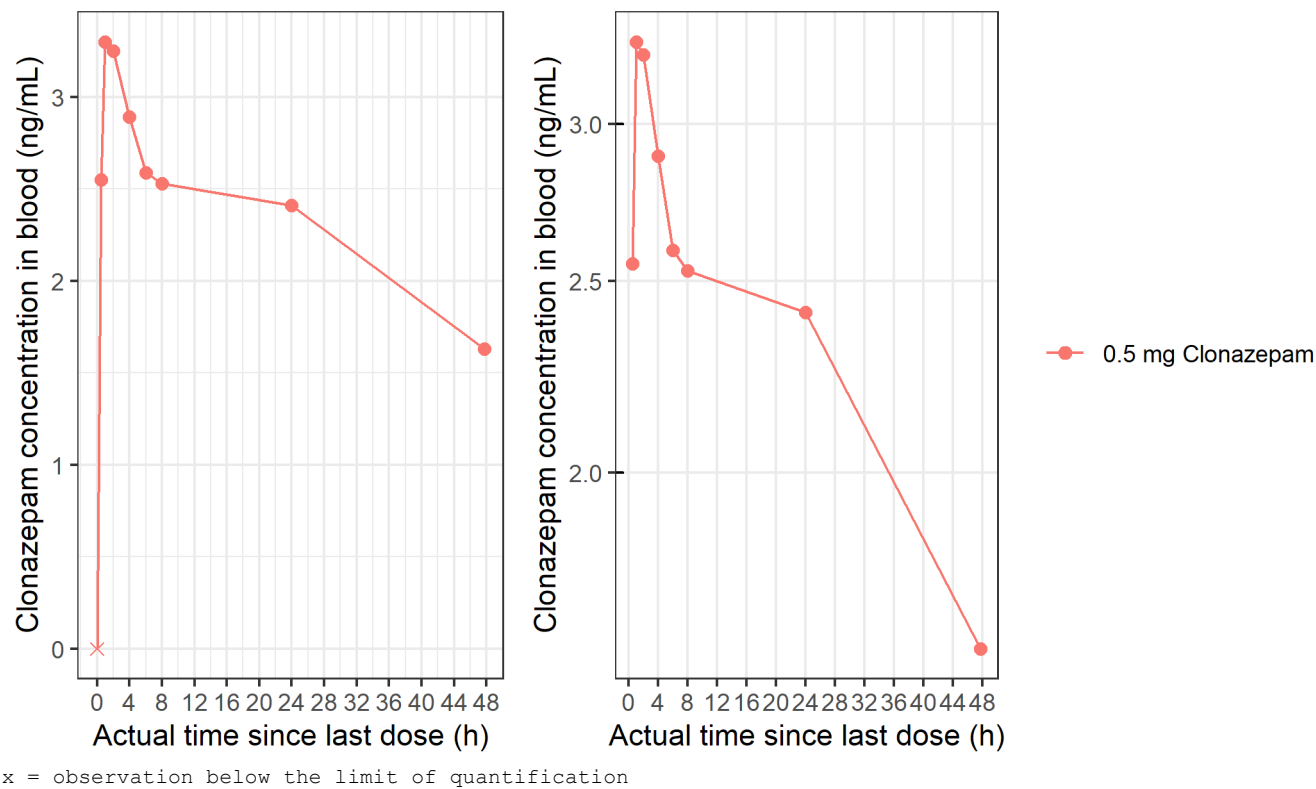
Subject 101 - Clonazepam concentration in Plasma (ng/mL)



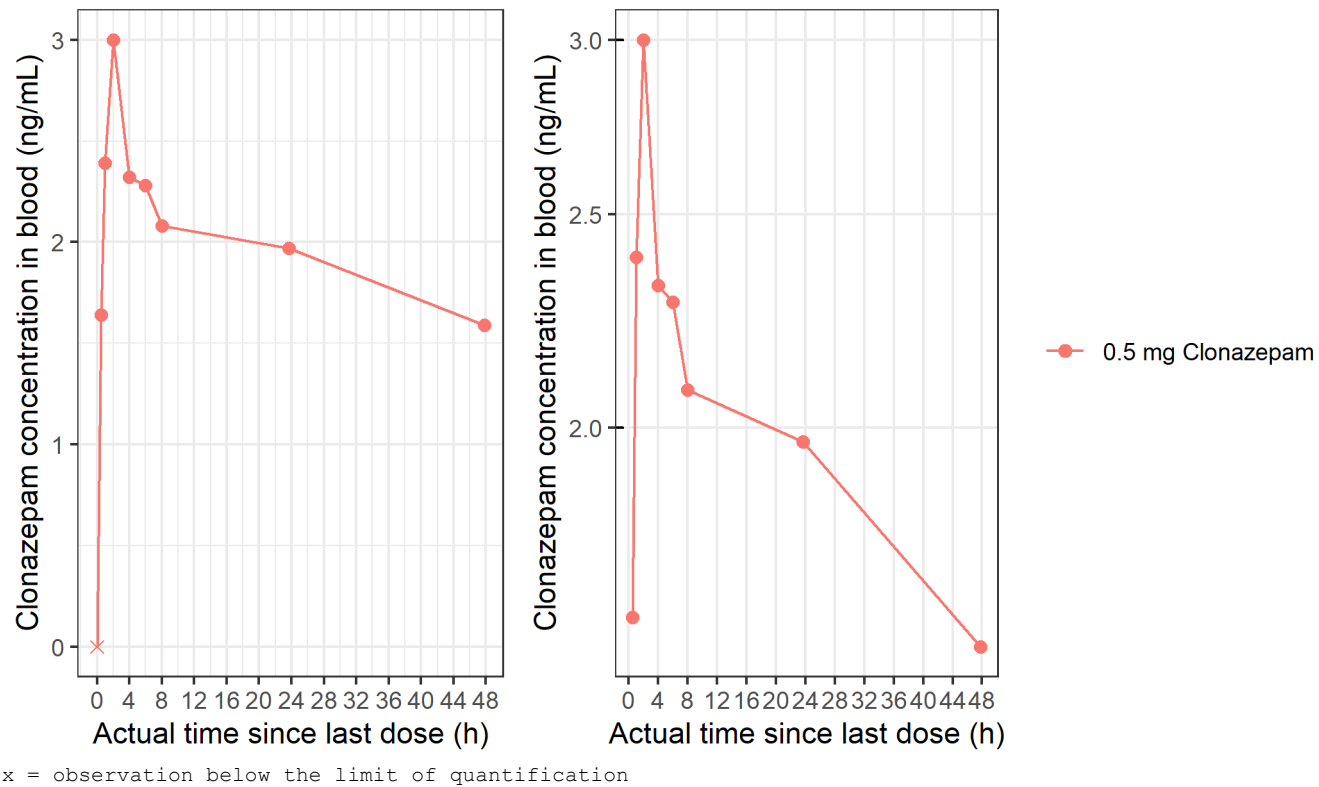
Subject 102 - Clonazepam concentration in Plasma (ng/mL)



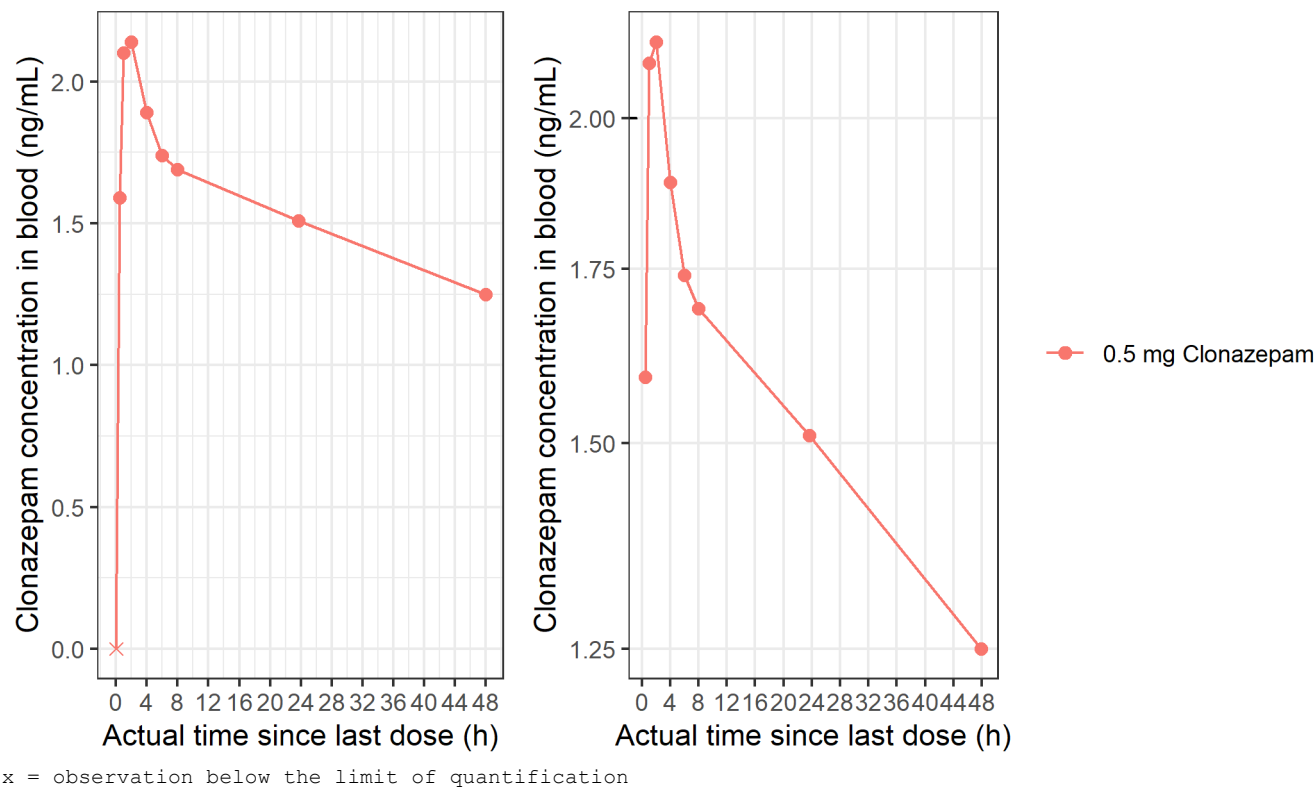
Subject 103 - Clonazepam concentration in Plasma (ng/mL)



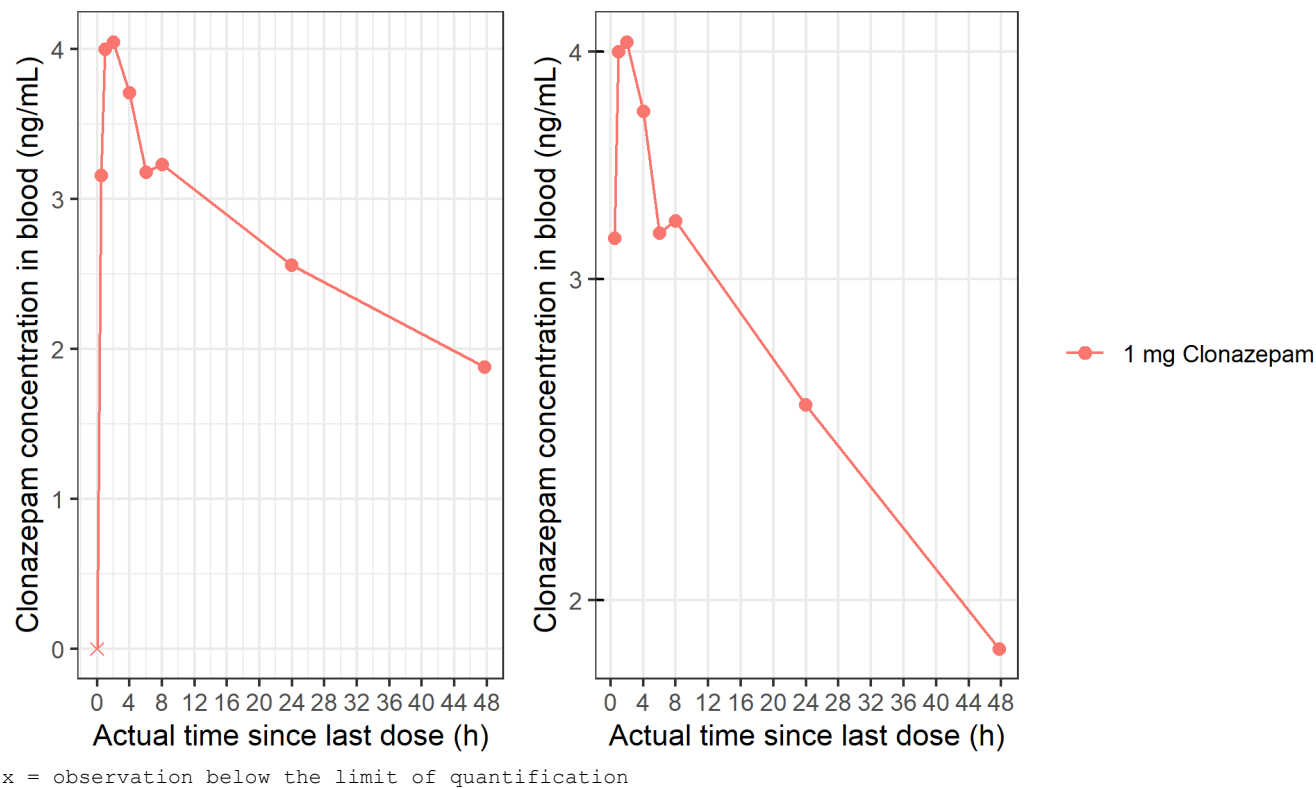
Subject 104 - Clonazepam concentration in Plasma (ng/mL)



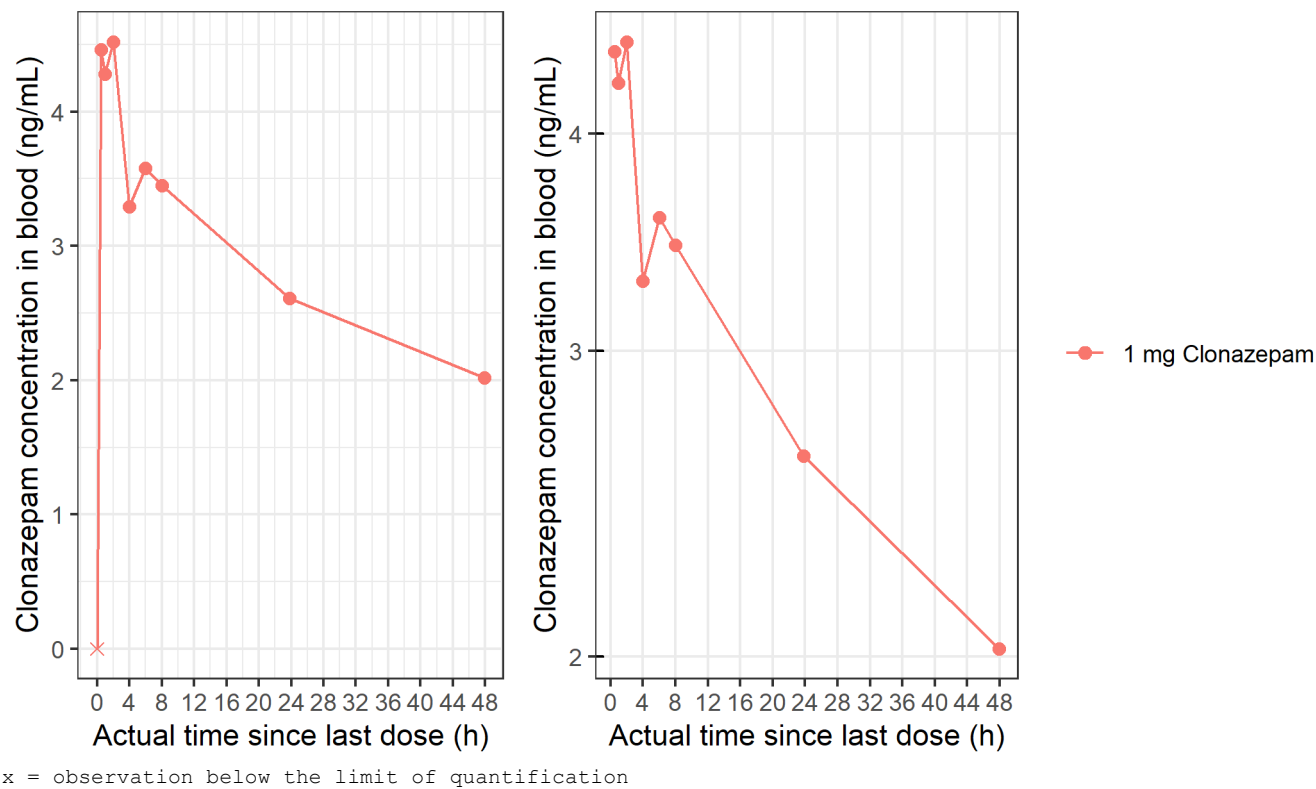
Subject 105 - Clonazepam concentration in Plasma (ng/mL)



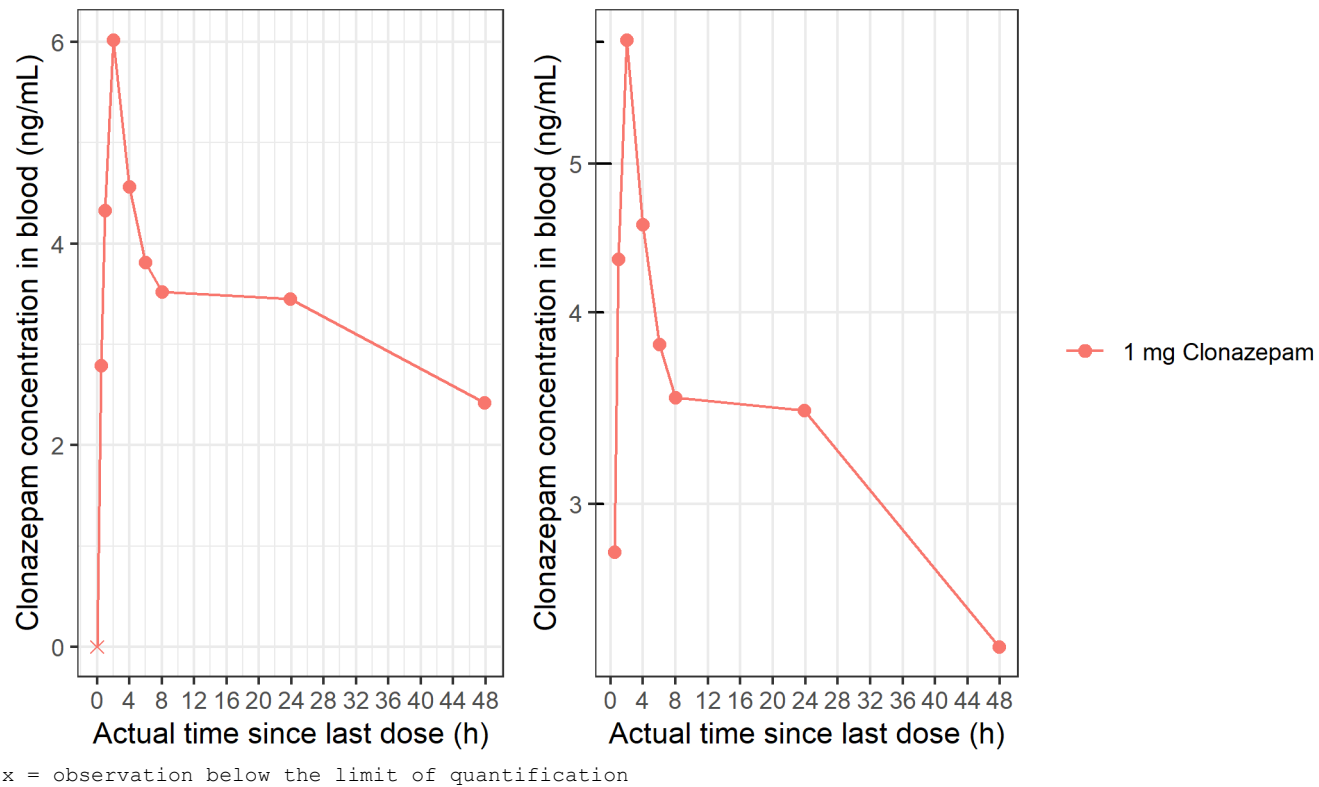
Subject 106 - Clonazepam concentration in Plasma (ng/mL)



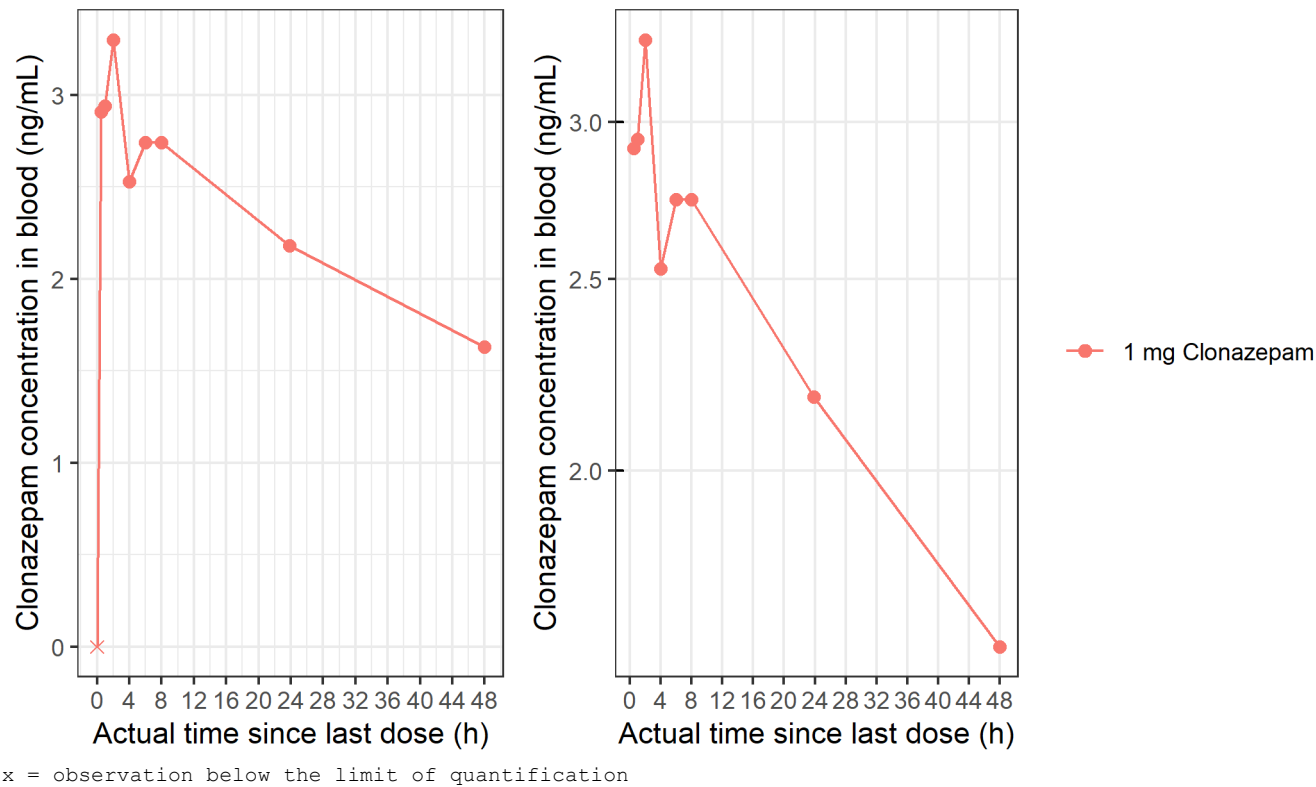
Subject 107 - Clonazepam concentration in Plasma (ng/mL)



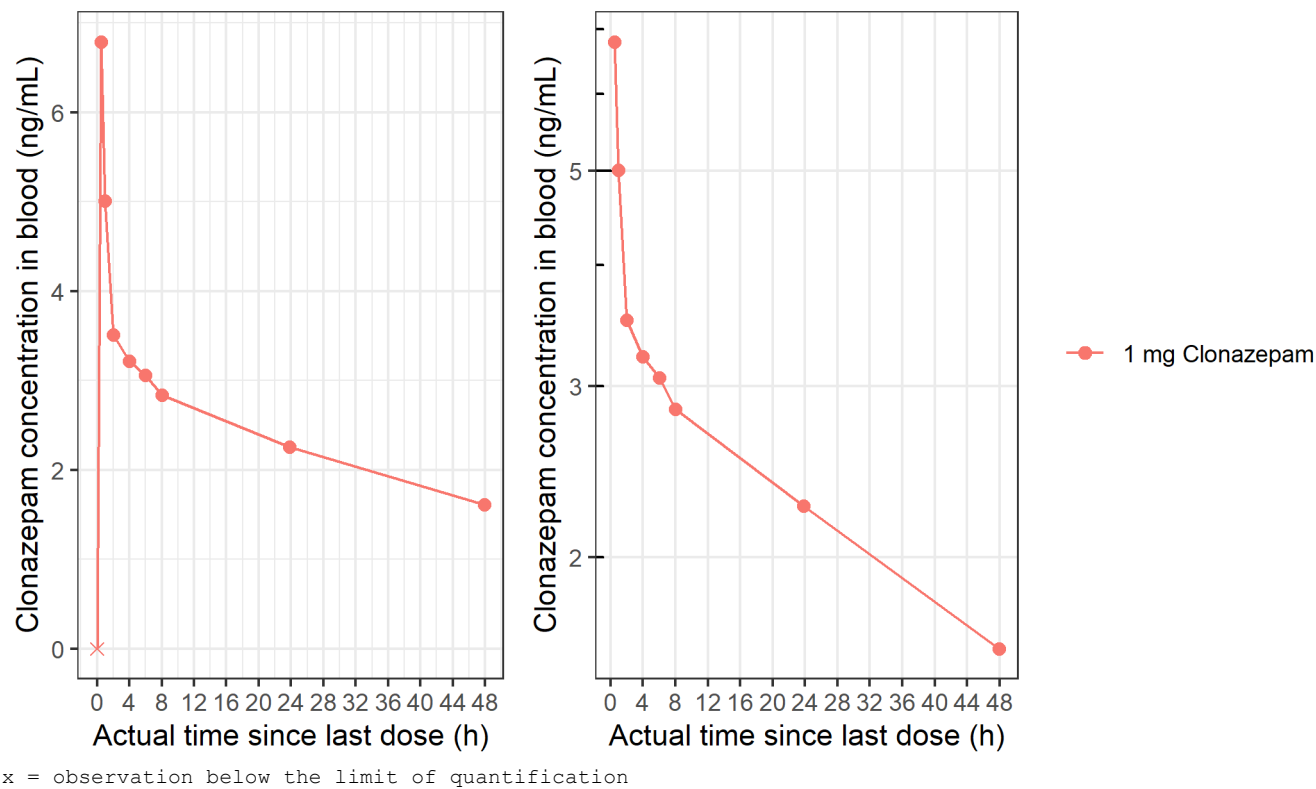
Subject 108 - Clonazepam concentration in Plasma (ng/mL)



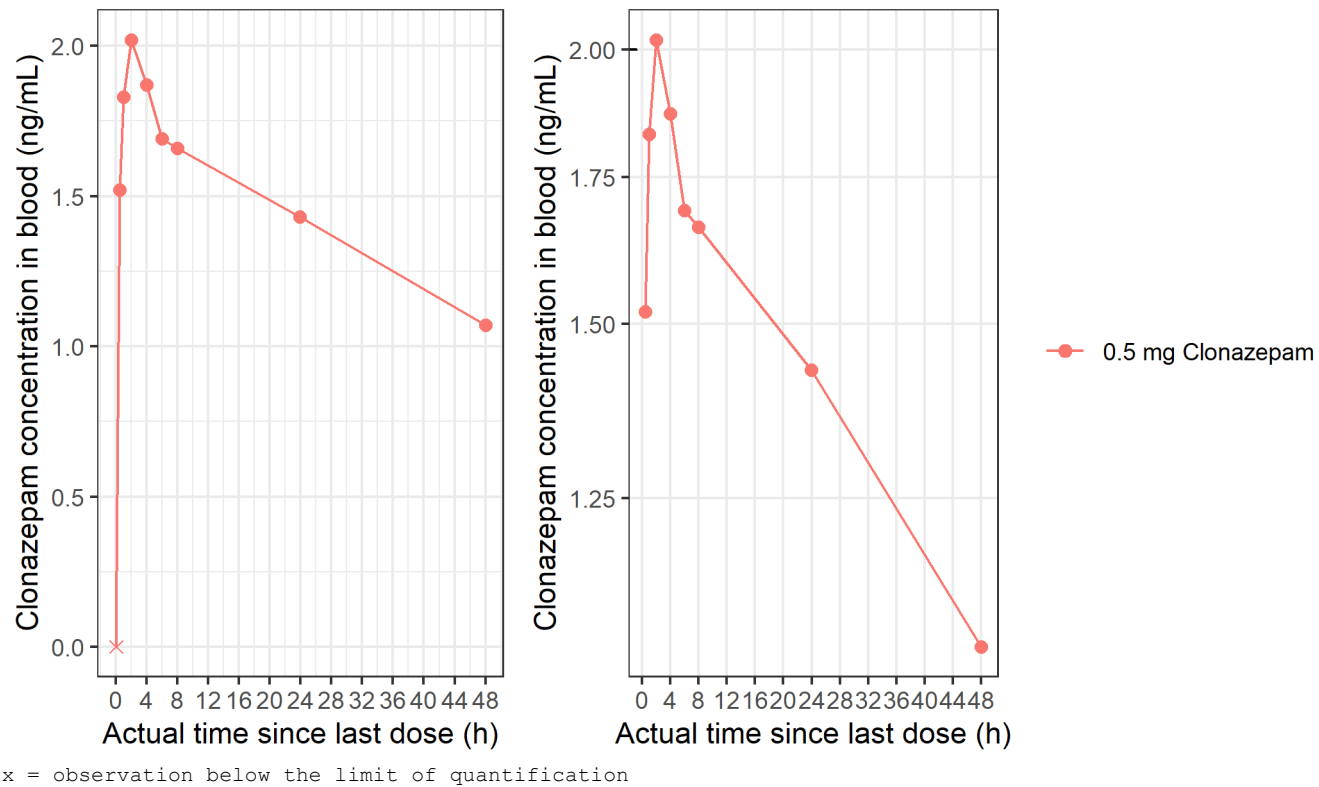
Subject 109 - Clonazepam concentration in Plasma (ng/mL)



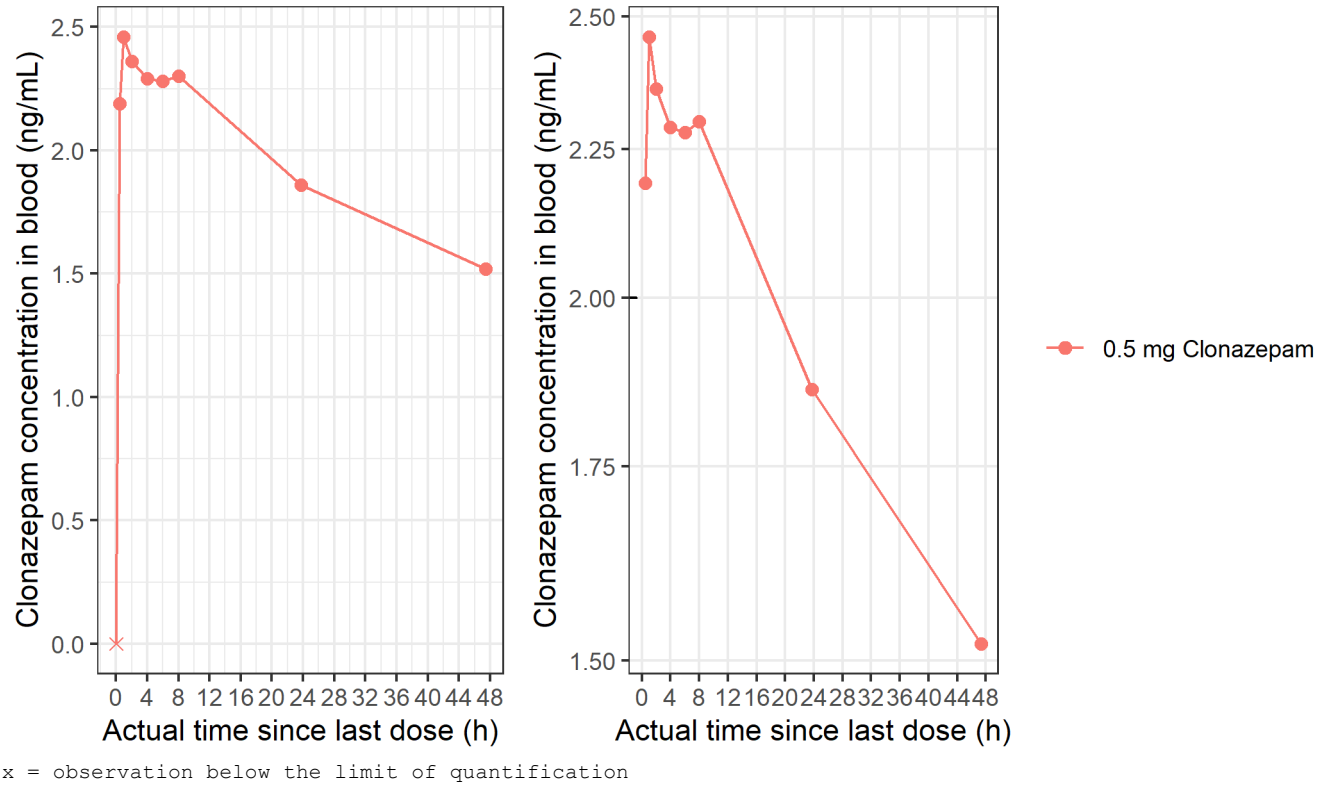
Subject 110 - Clonazepam concentration in Plasma (ng/mL)



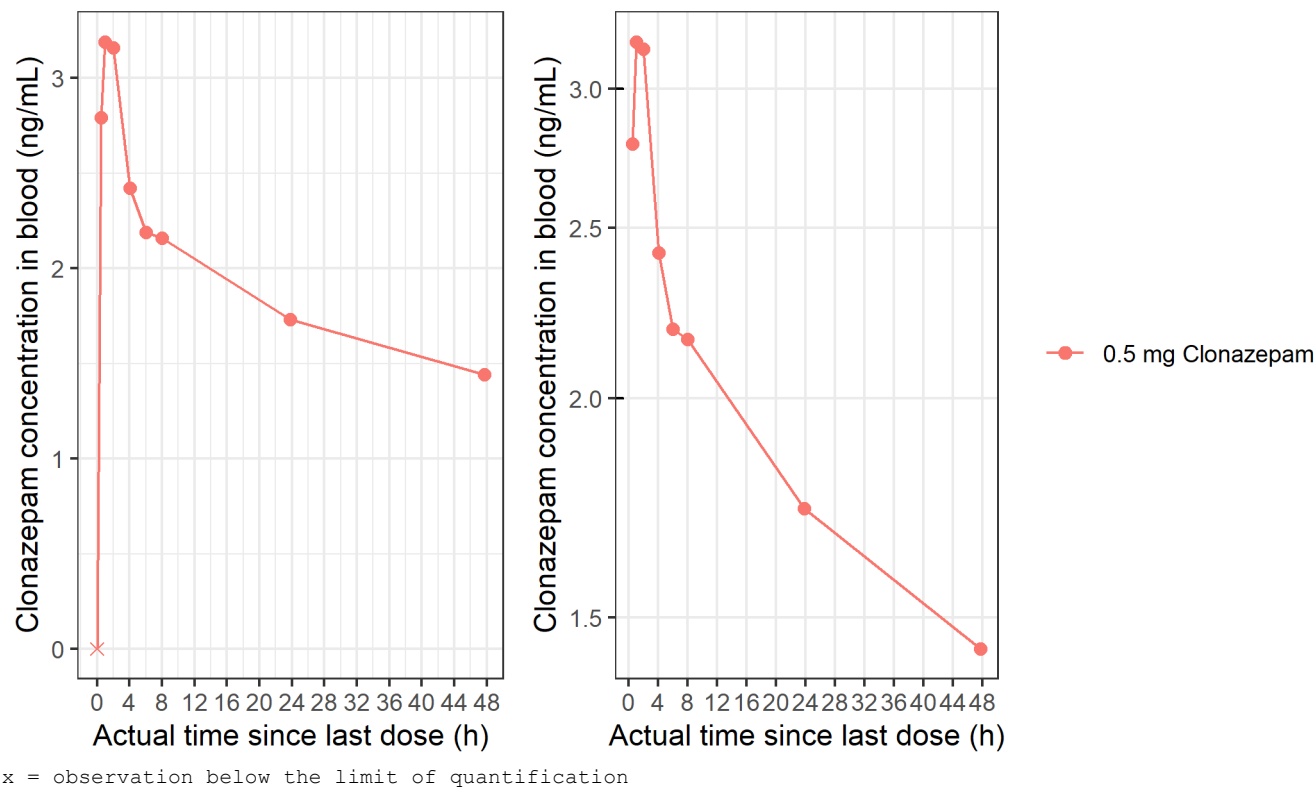
Subject 111 - Clonazepam concentration in Plasma (ng/mL)



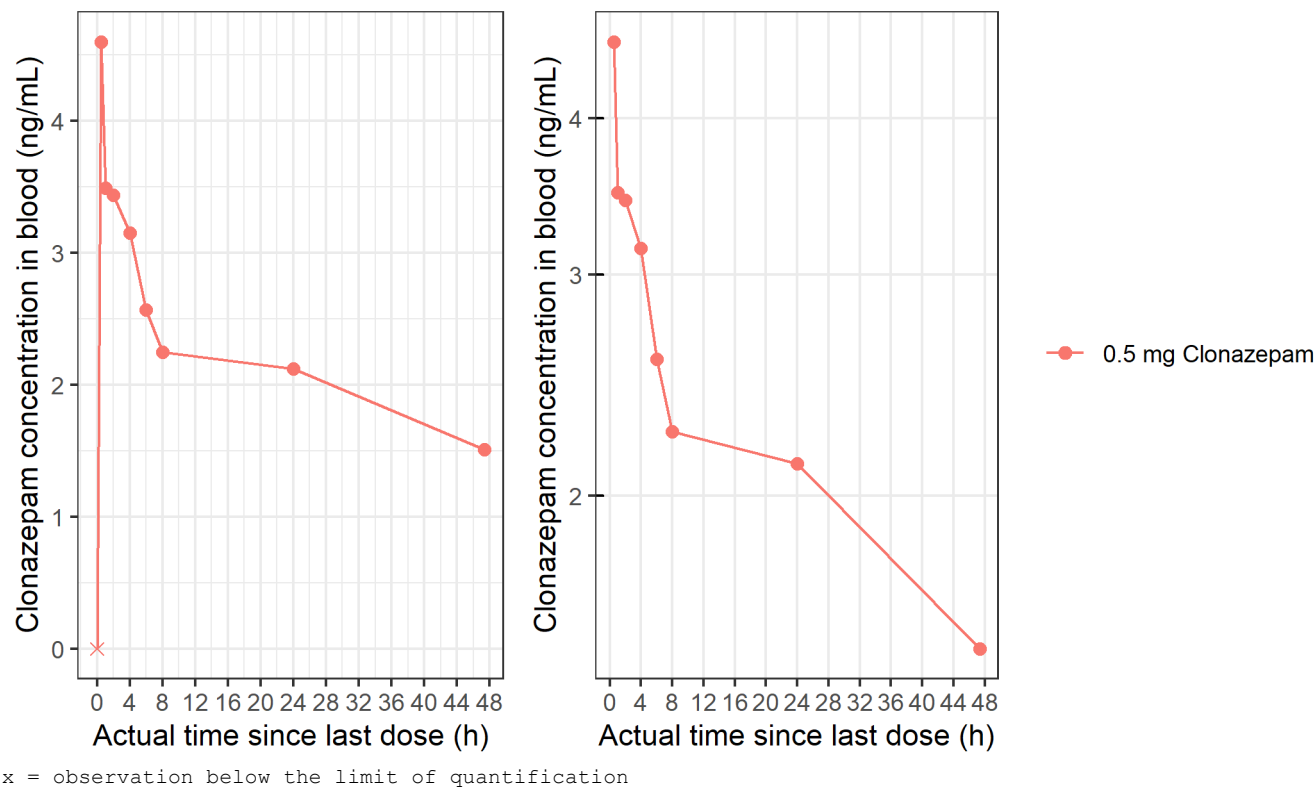
Subject 112 - Clonazepam concentration in Plasma (ng/mL)



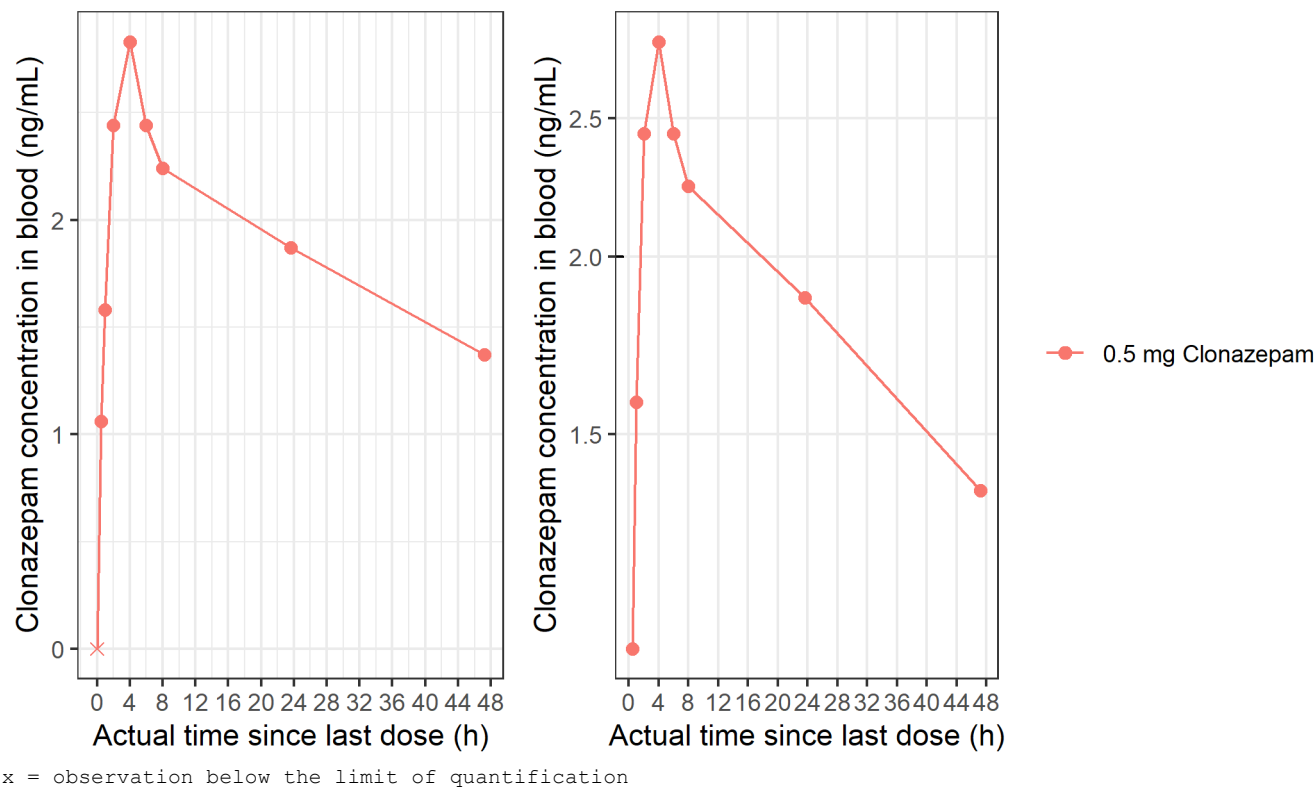
Subject 113 - Clonazepam concentration in Plasma (ng/mL)



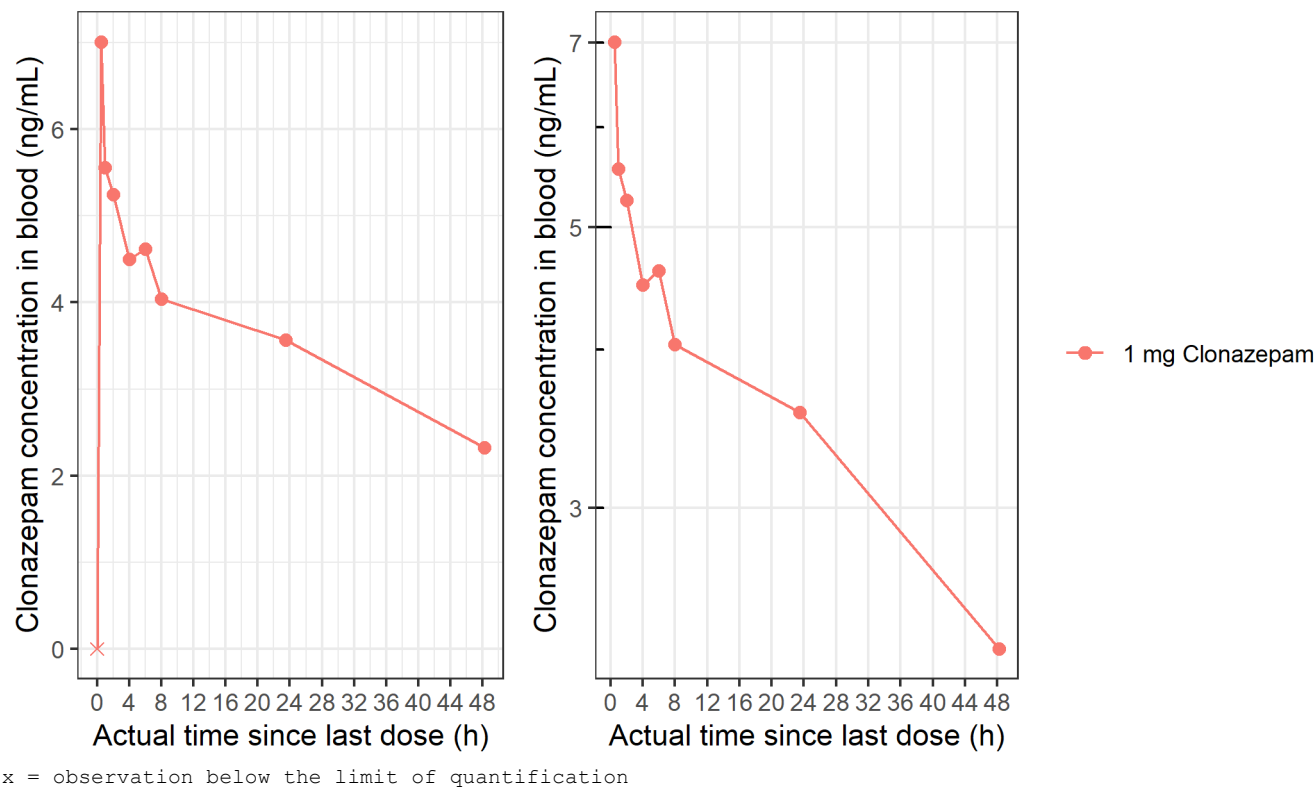
Subject 114 - Clonazepam concentration in Plasma (ng/mL)



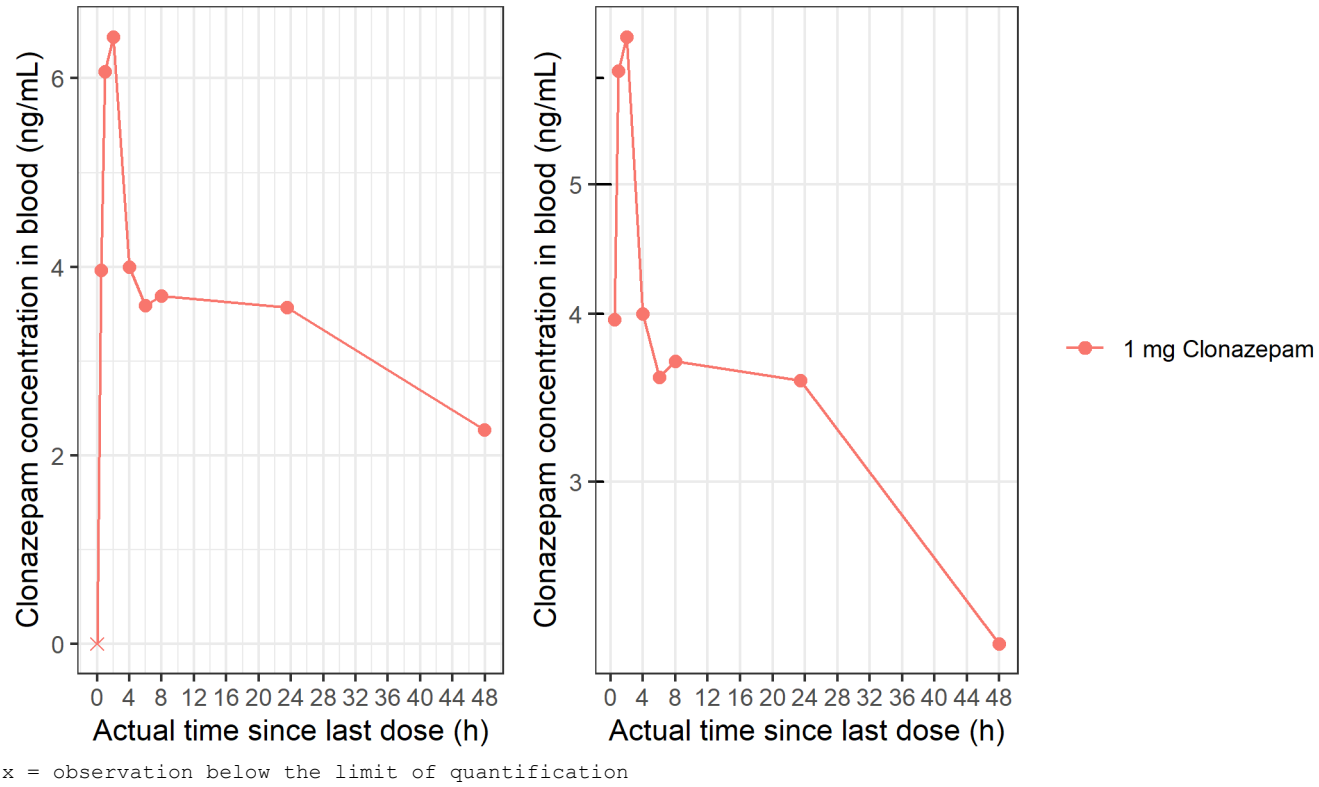
Subject 115 - Clonazepam concentration in Plasma (ng/mL)



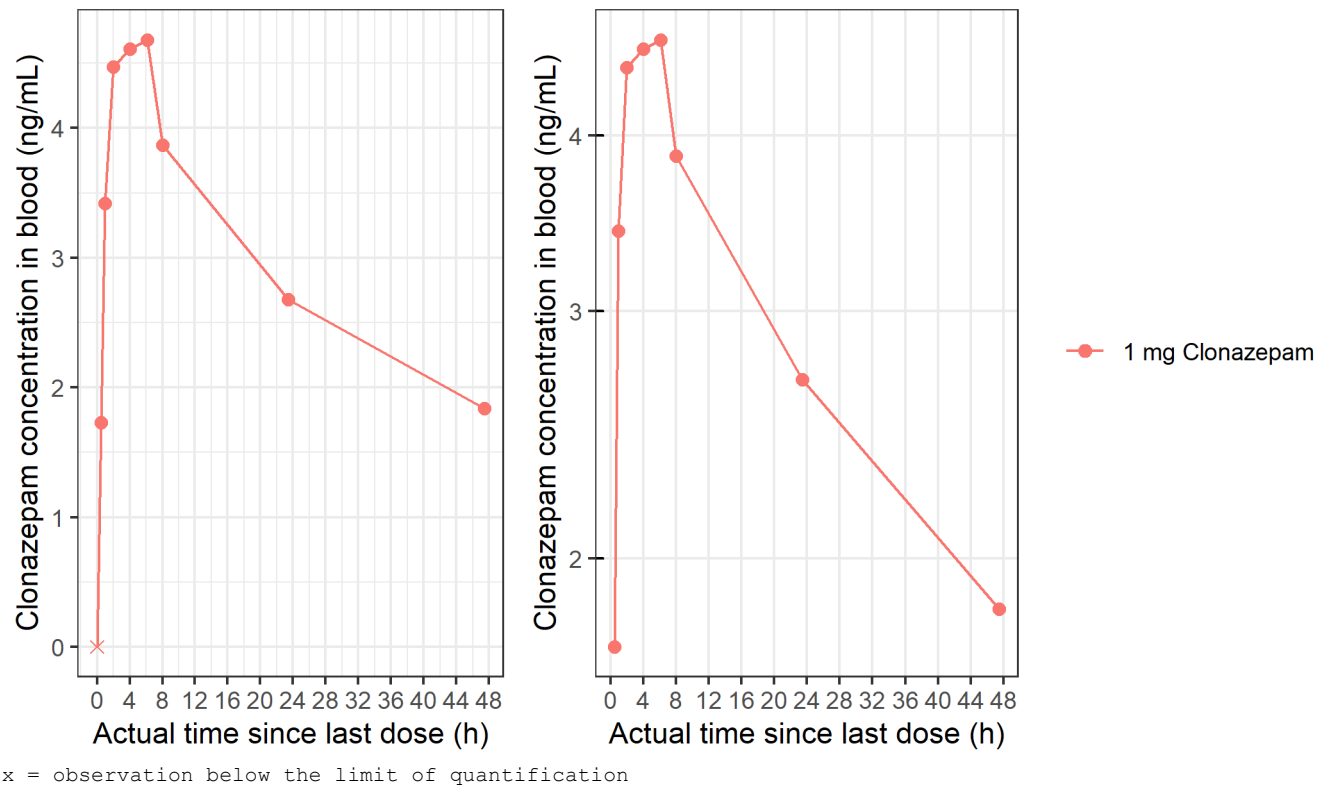
Subject 116 - Clonazepam concentration in Plasma (ng/mL)



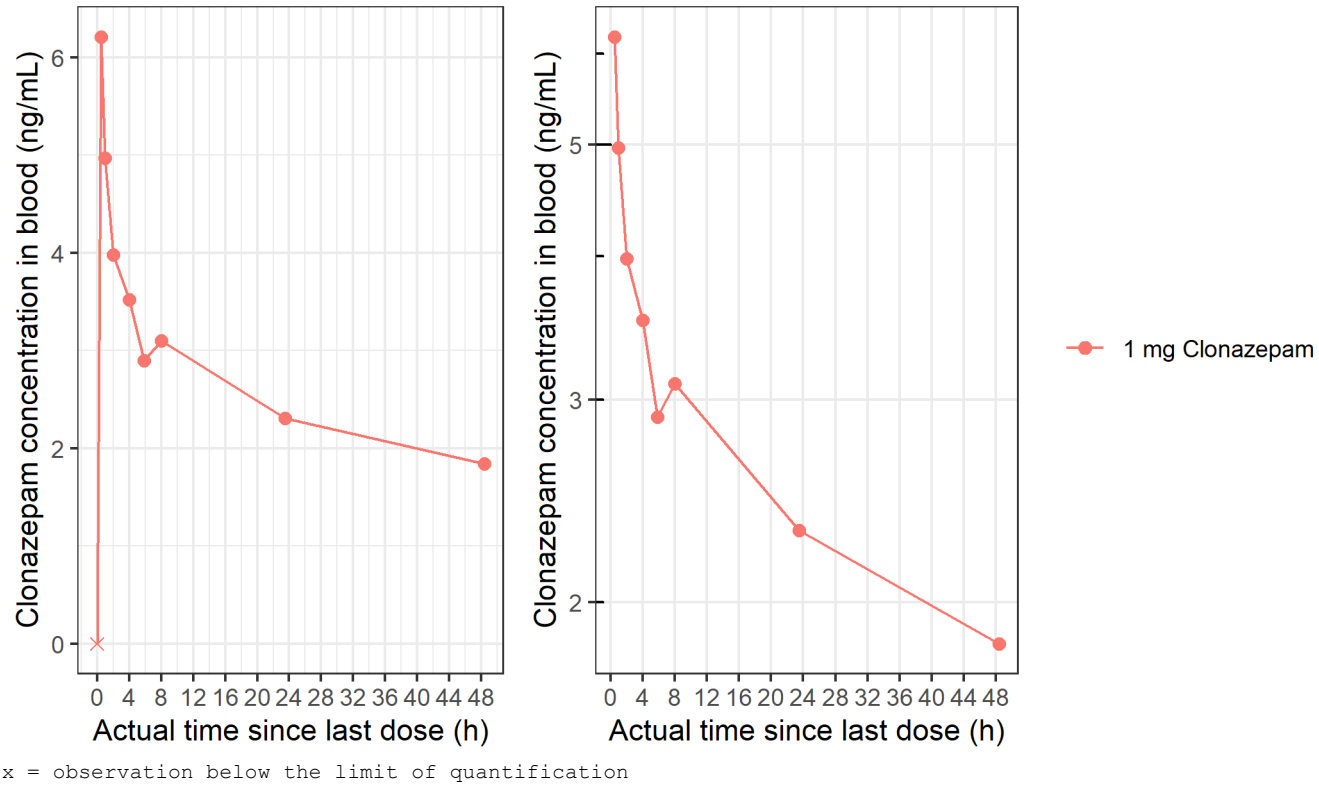
Subject 117 - Clonazepam concentration in Plasma (ng/mL)



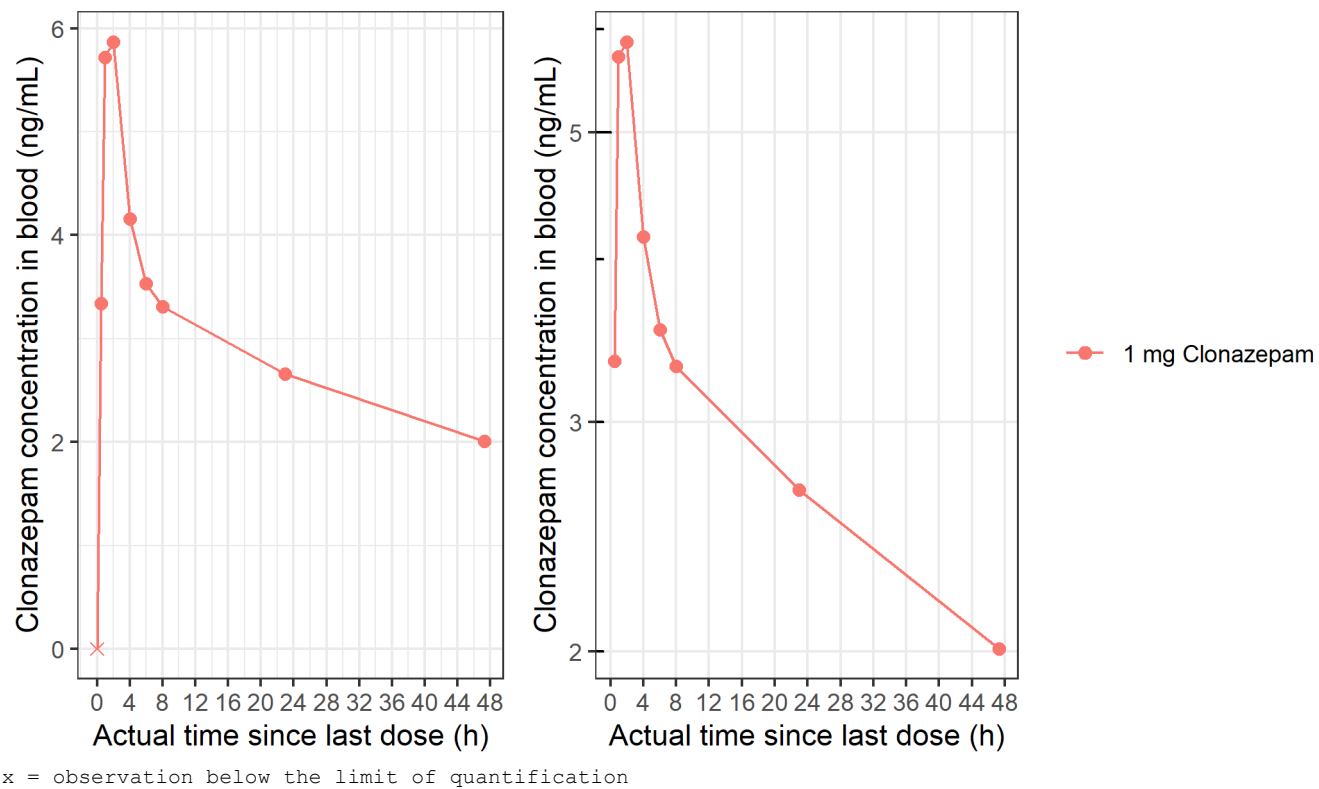
Subject 118 - Clonazepam concentration in Plasma (ng/mL)



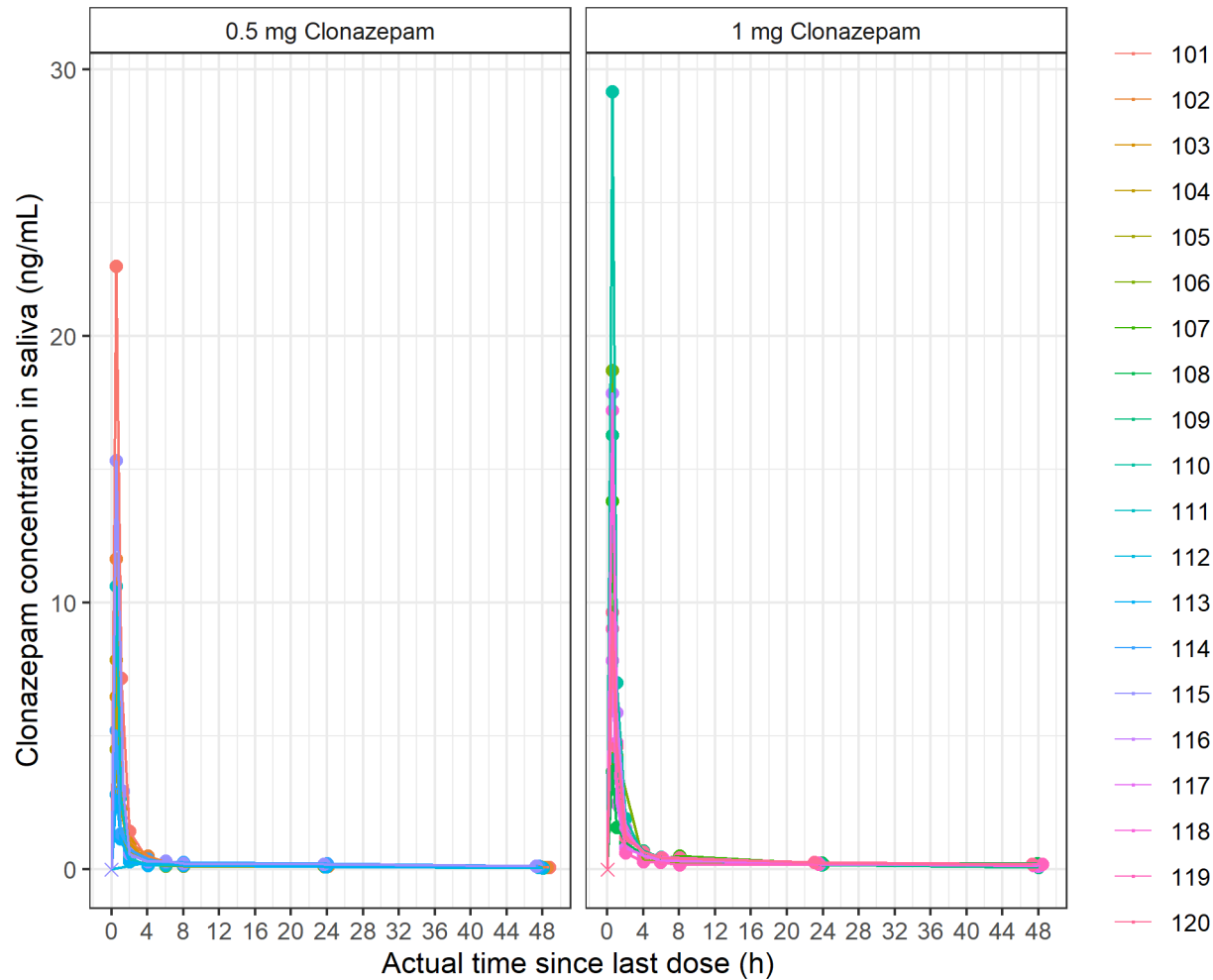
Subject 119 - Clonazepam concentration in Plasma (ng/mL)



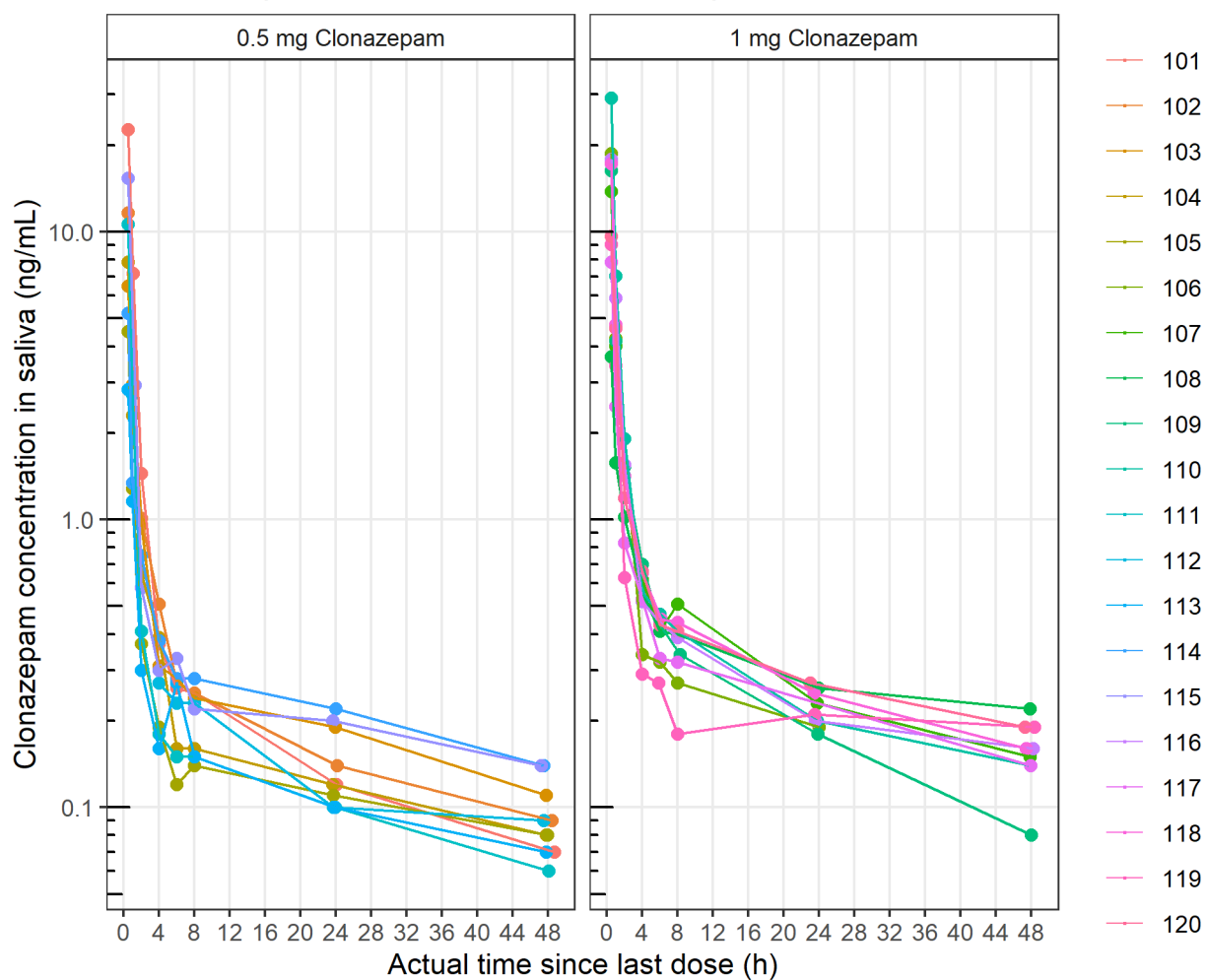
Subject 120 - Clonazepam concentration in Plasma (ng/mL)



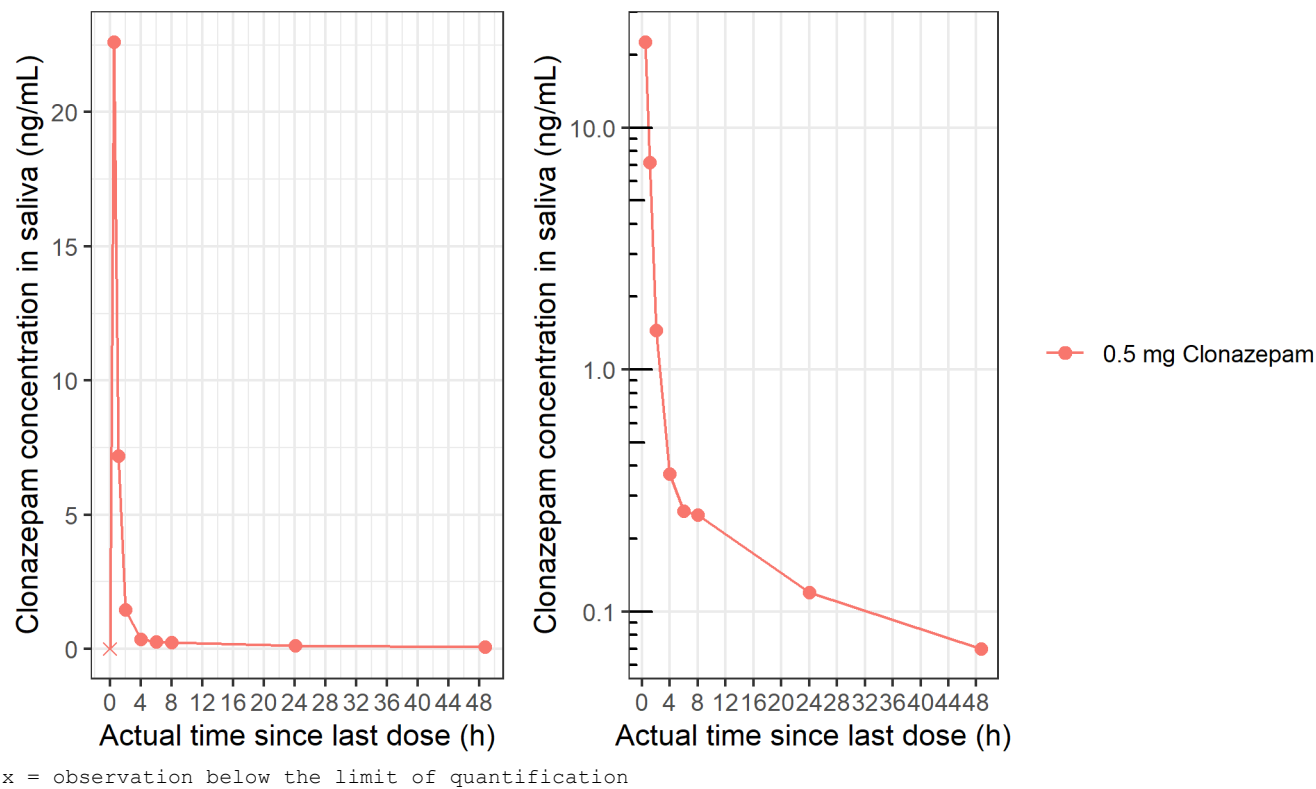
Individual profiles of Clonazepam concentration in Saliva (ng/mL) (linear y-axis)
Individual pharmacokinetics of Clonazepam in Saliva



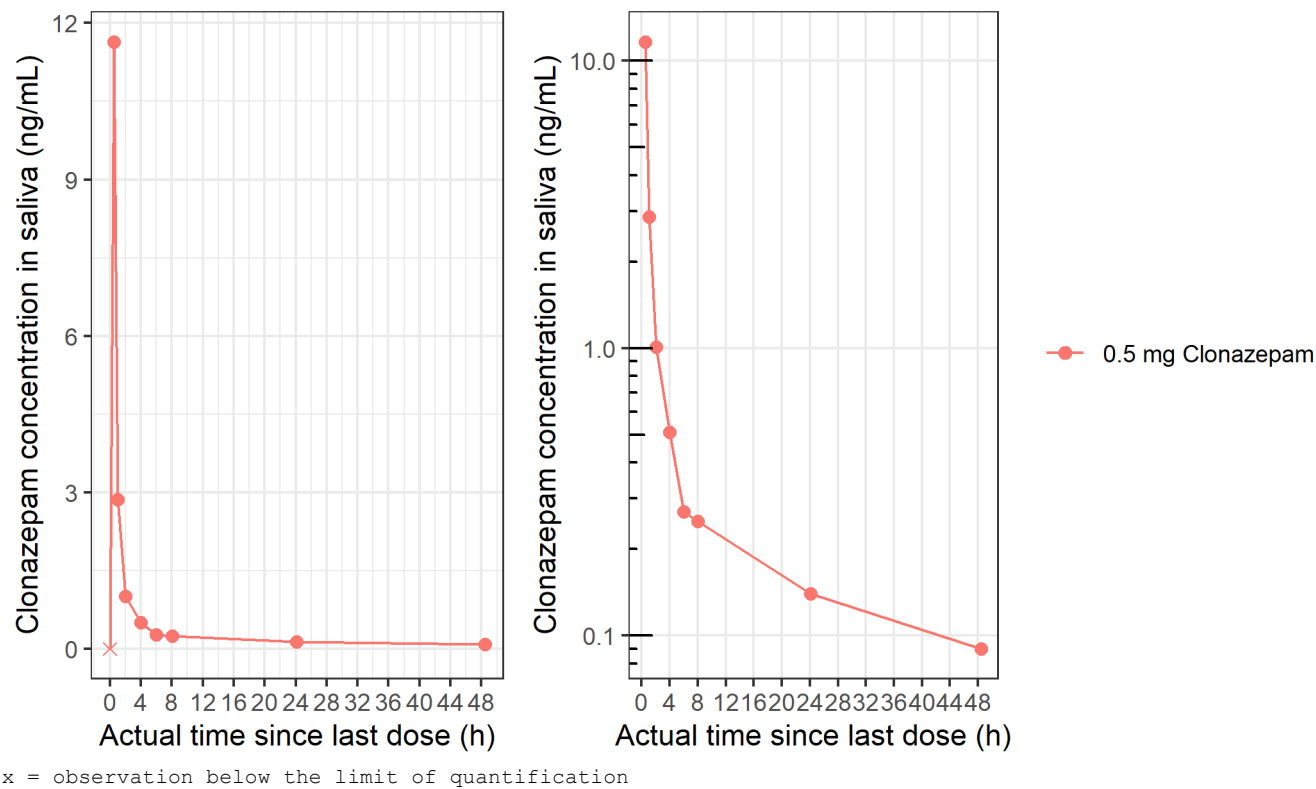
x = observation below the limit of quantification

Individual profiles of Clonazepam concentration in Saliva (ng/mL) (log y-axis)**Individual pharmacokinetics of Clonazepam in Saliva**

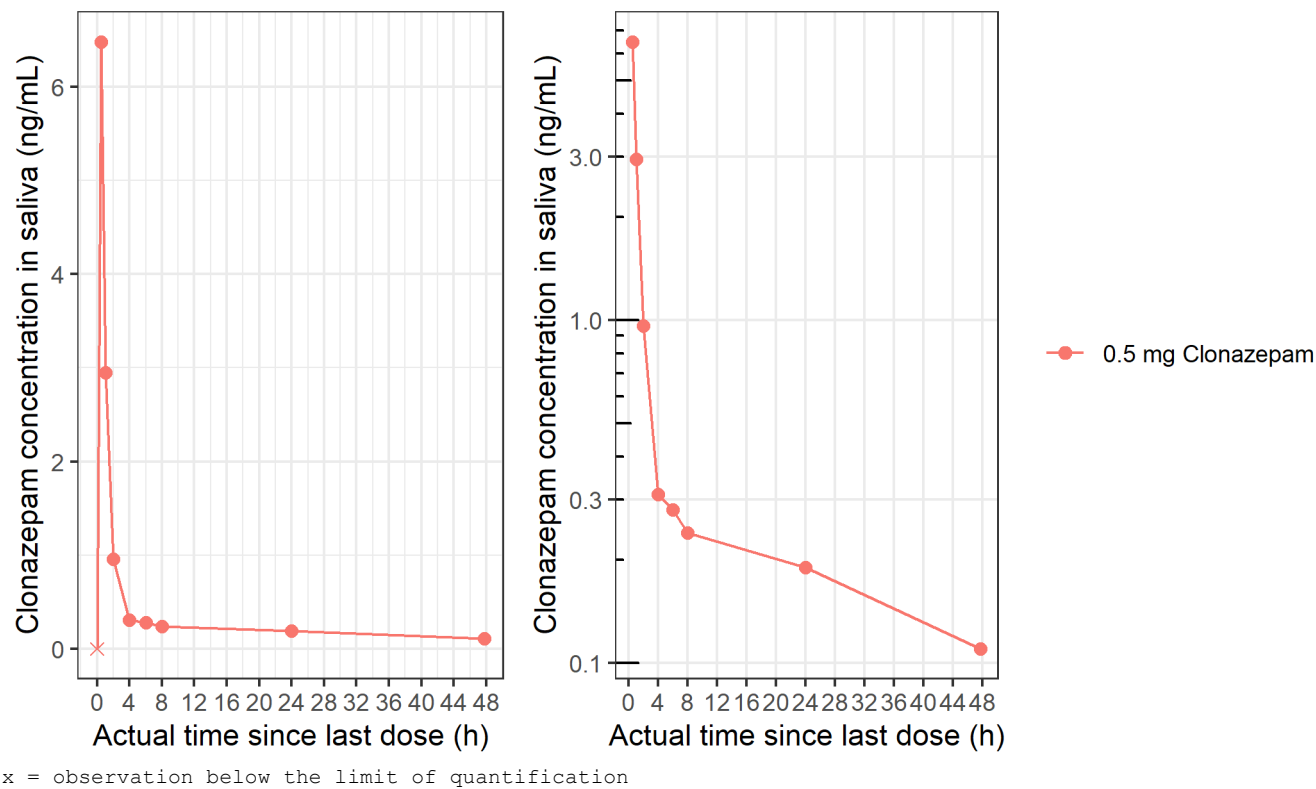
Subject 101 - Clonazepam concentration in Saliva (ng/mL)



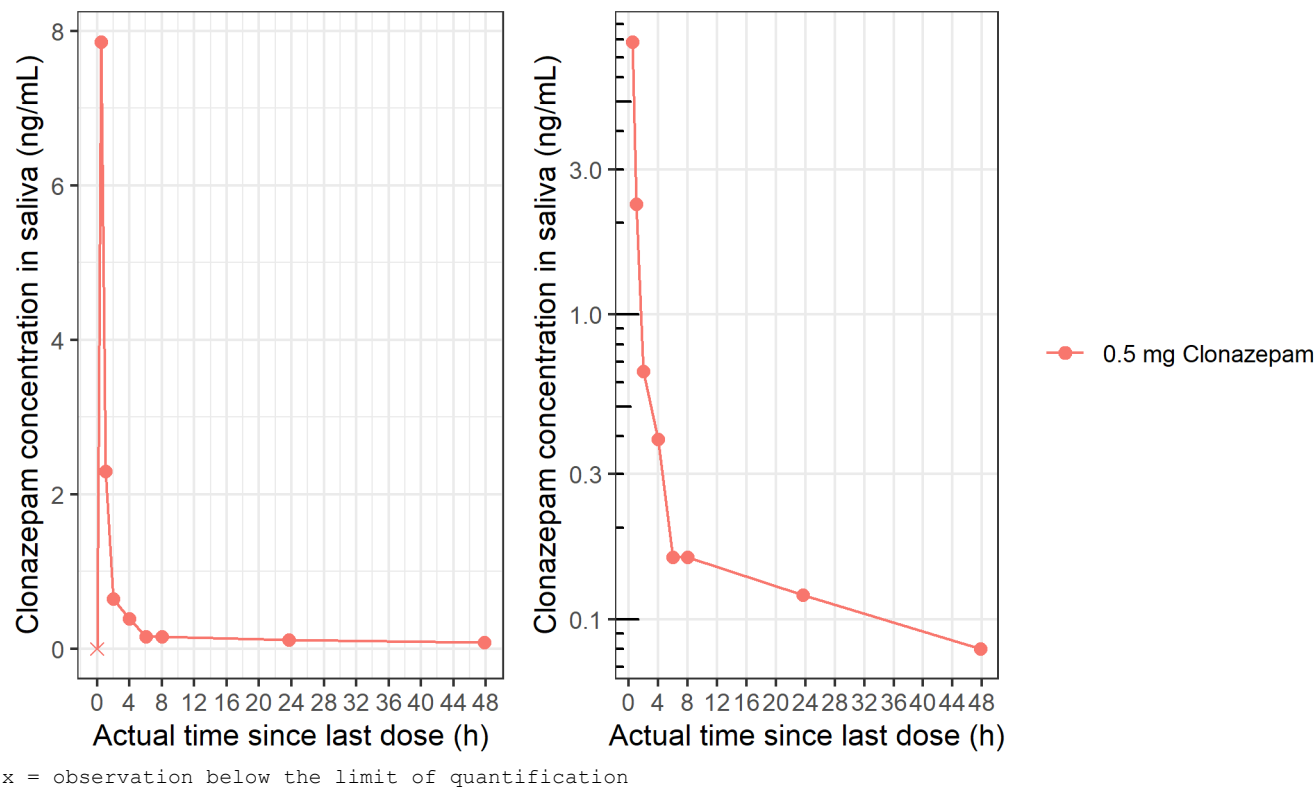
Subject 102 - Clonazepam concentration in Saliva (ng/mL)



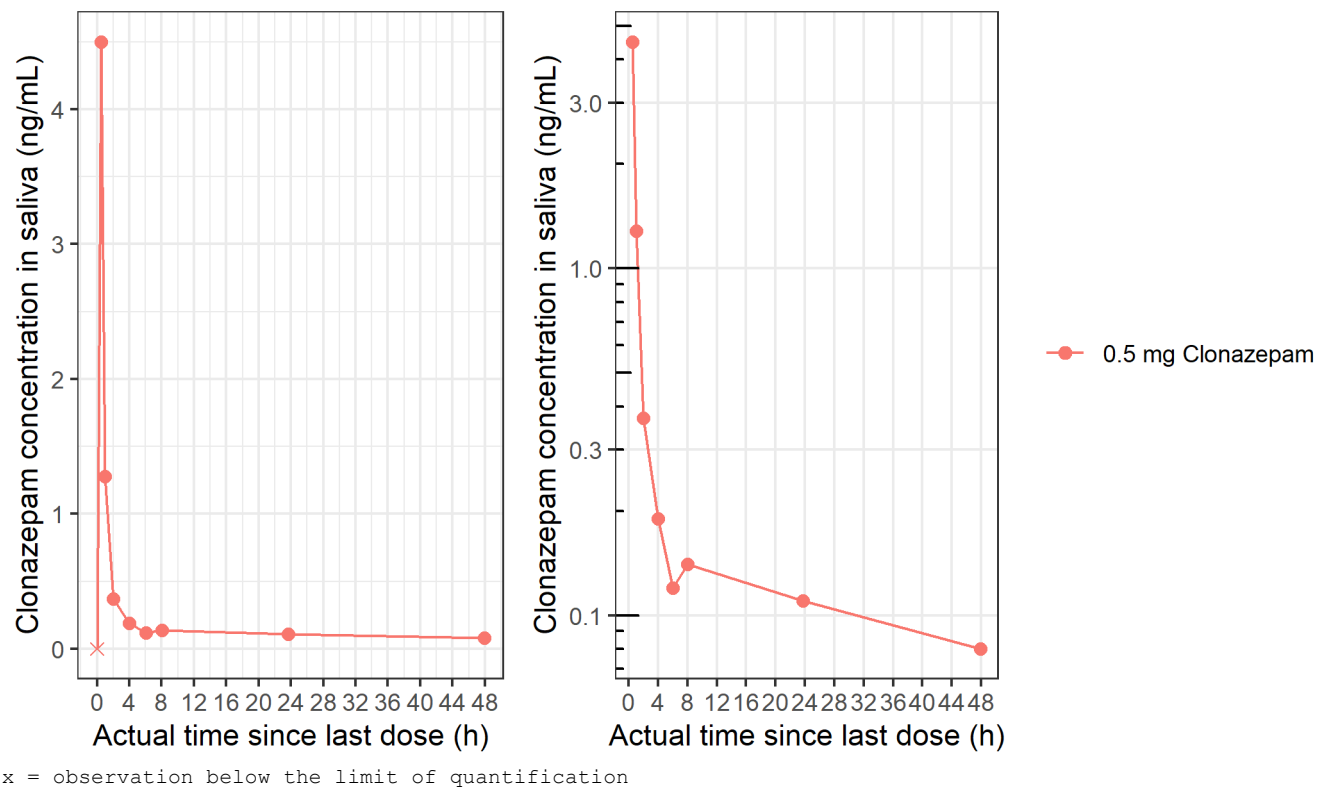
Subject 103 - Clonazepam concentration in Saliva (ng/mL)



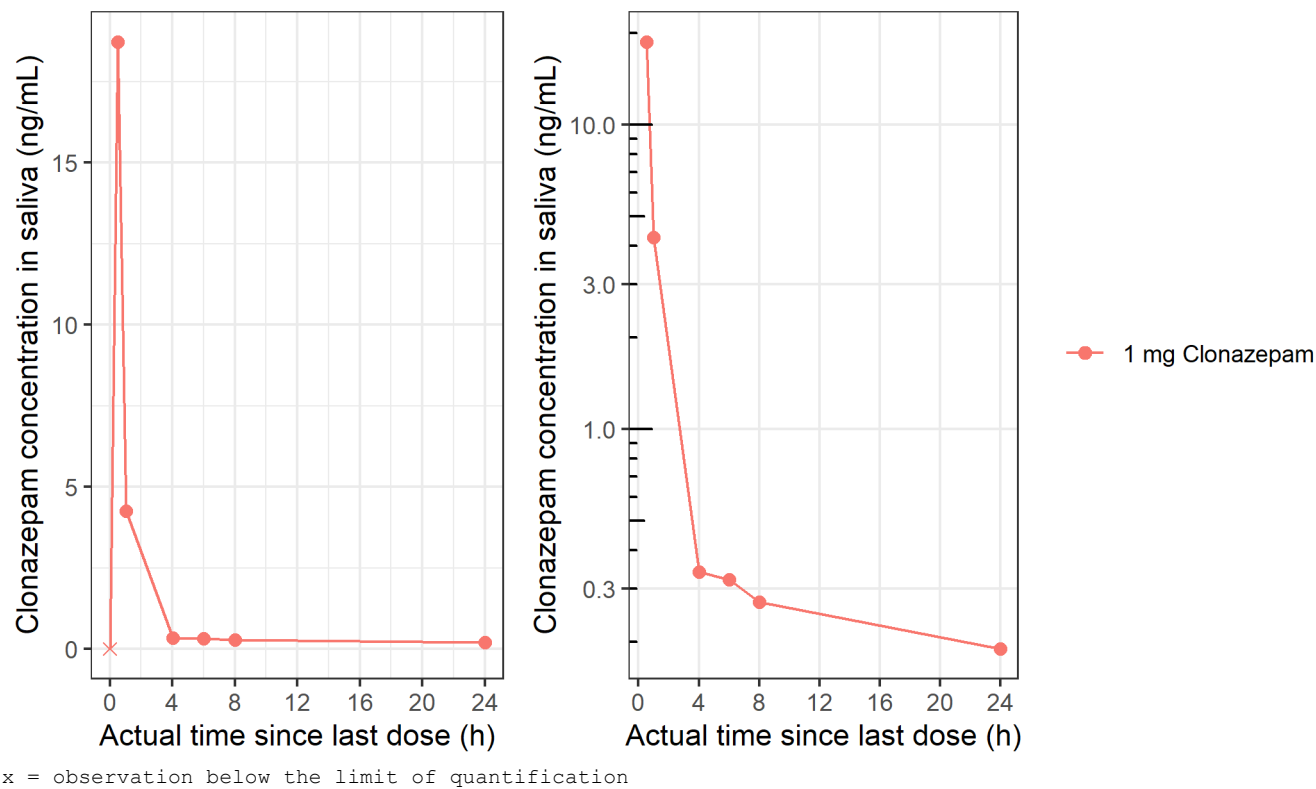
Subject 104 - Clonazepam concentration in Saliva (ng/mL)



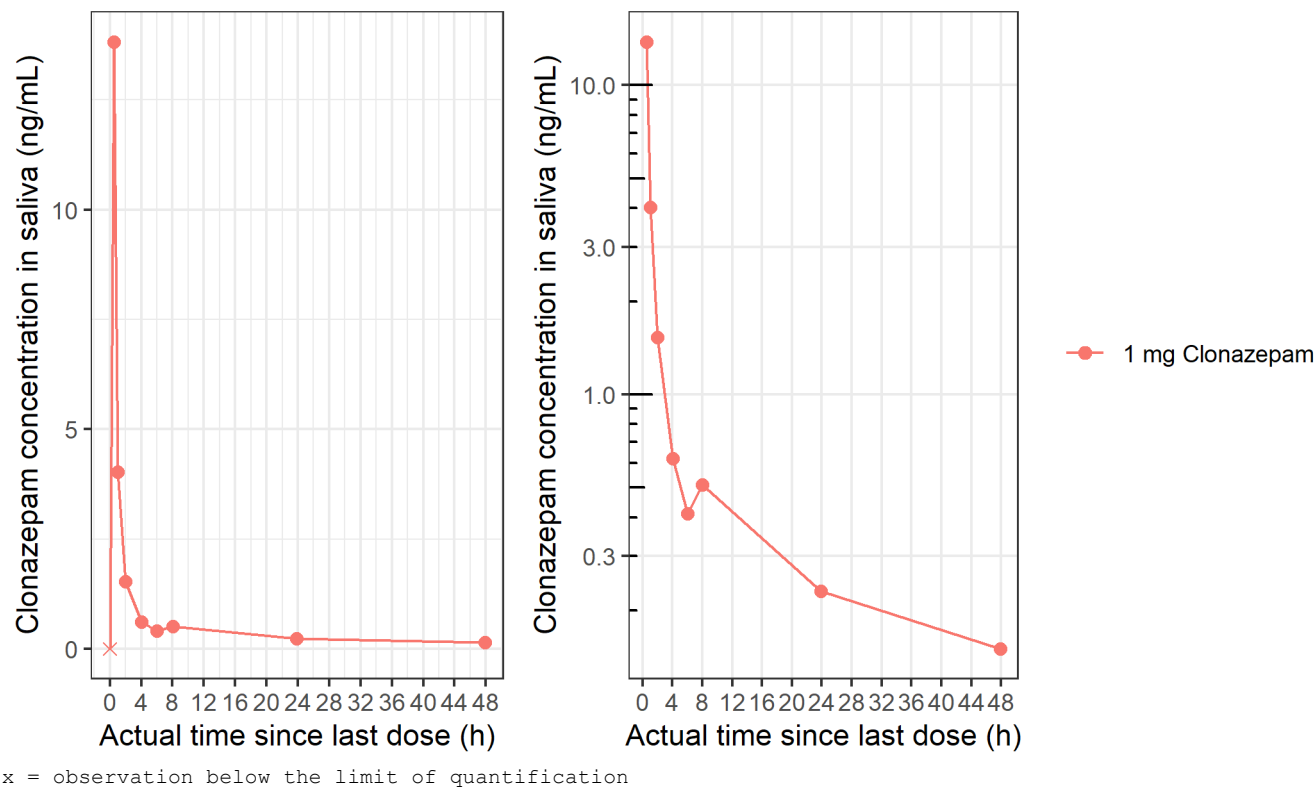
Subject 105 - Clonazepam concentration in Saliva (ng/mL)



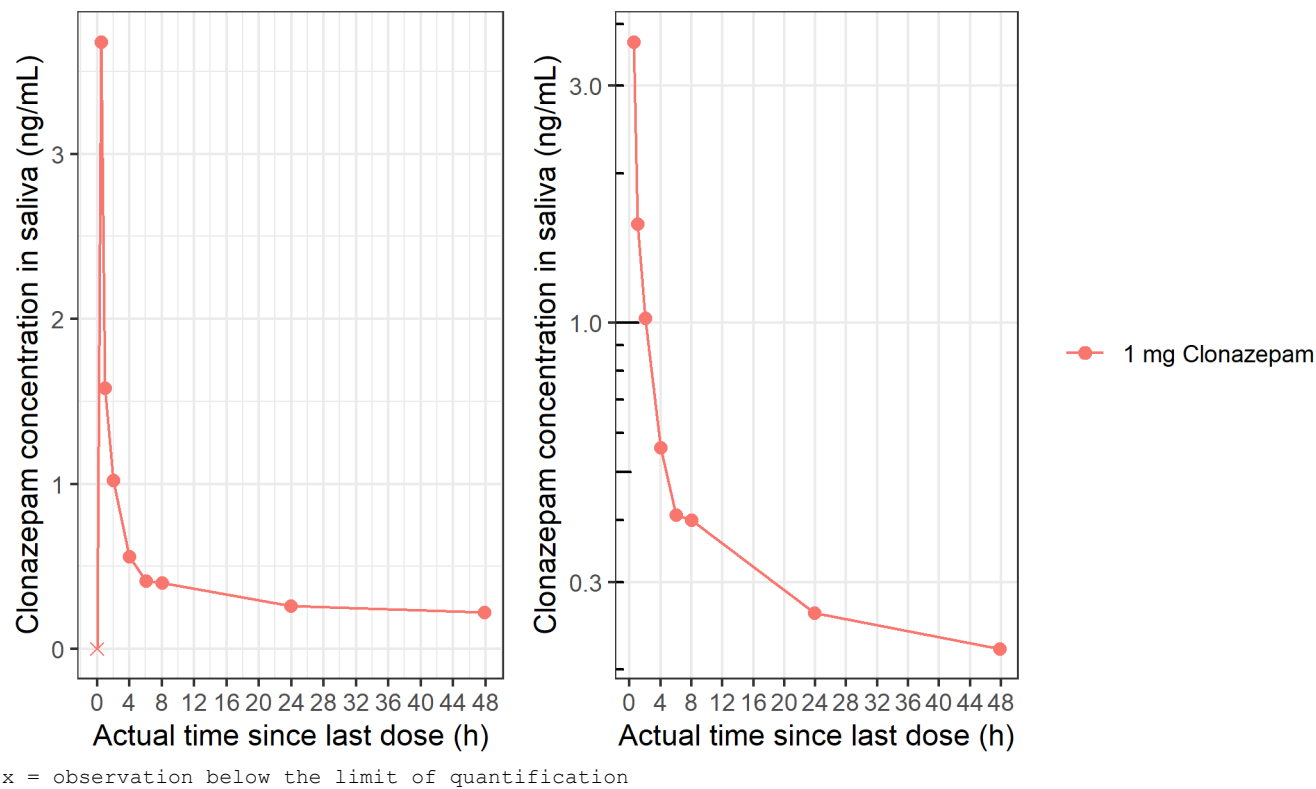
Subject 106 - Clonazepam concentration in Saliva (ng/mL)



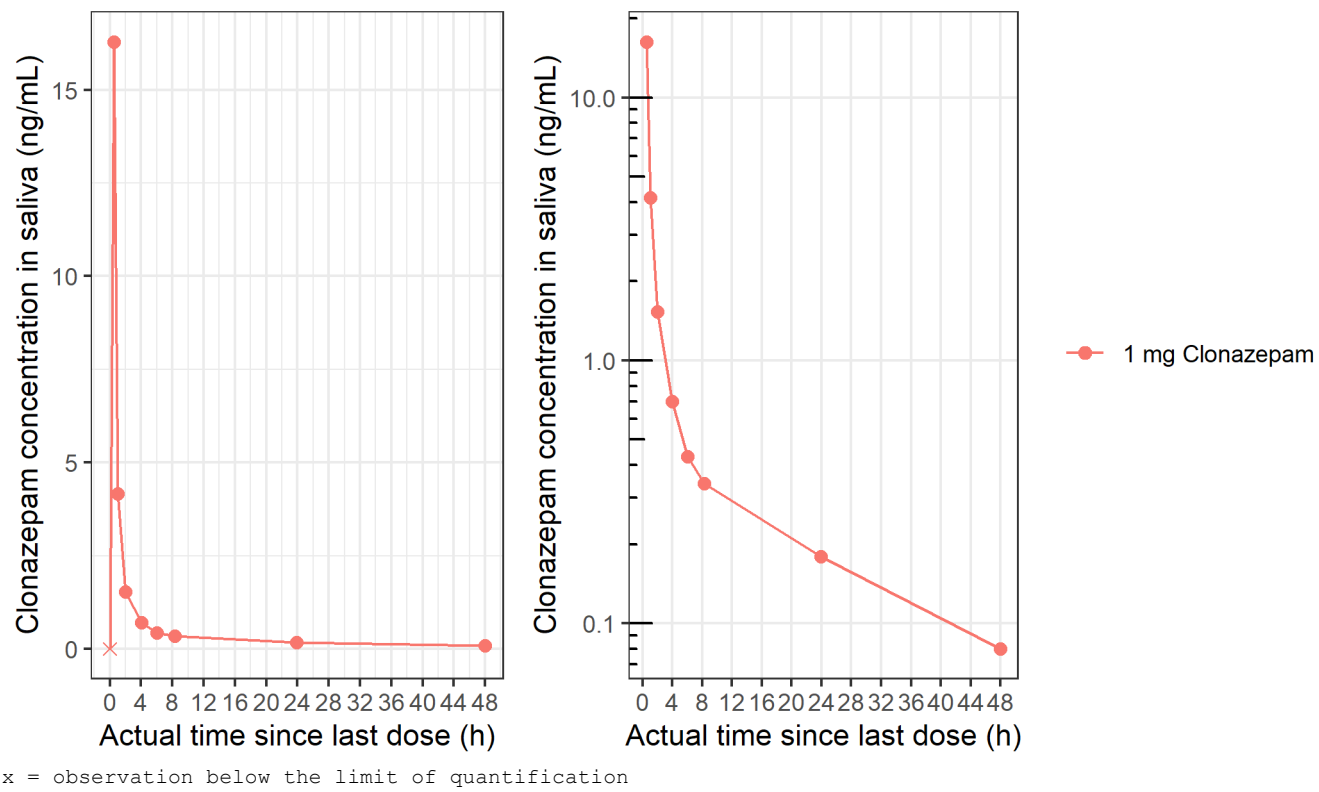
Subject 107 - Clonazepam concentration in Saliva (ng/mL)



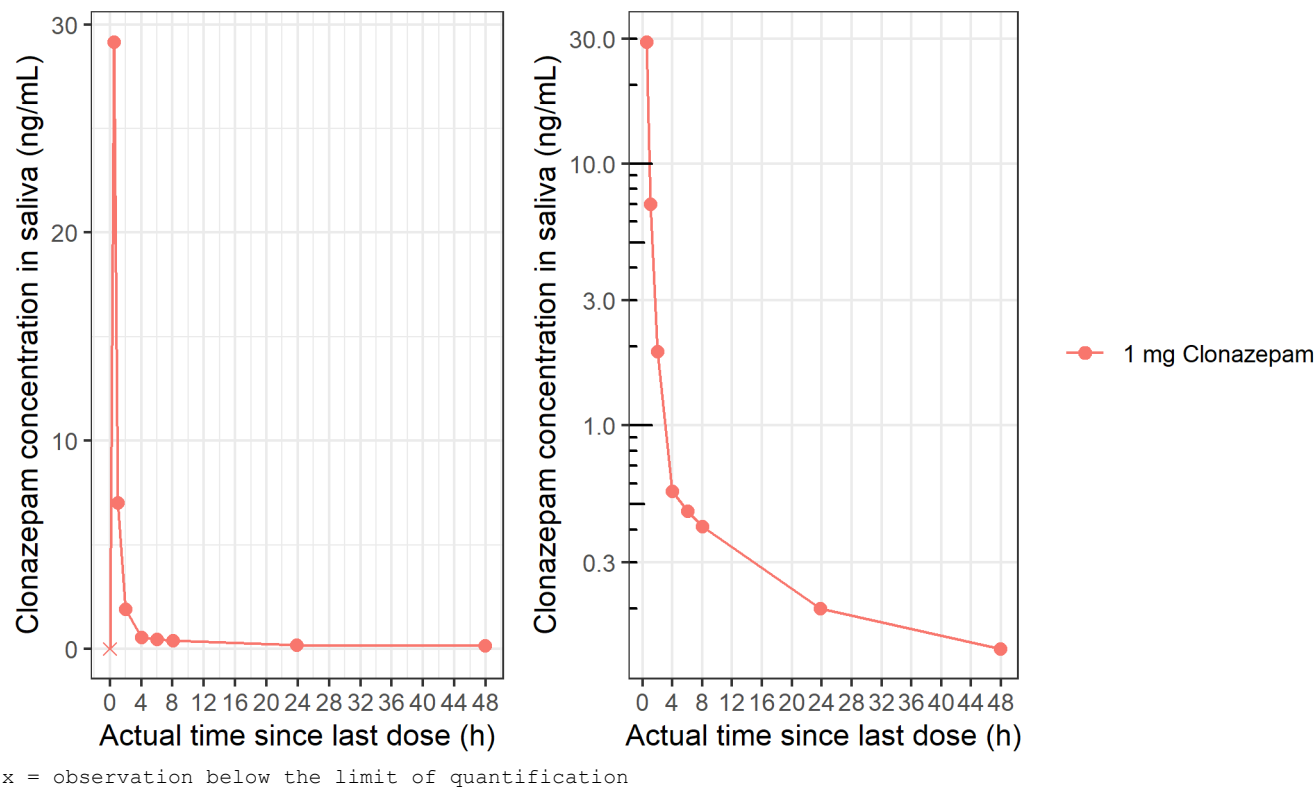
Subject 108 - Clonazepam concentration in Saliva (ng/mL)



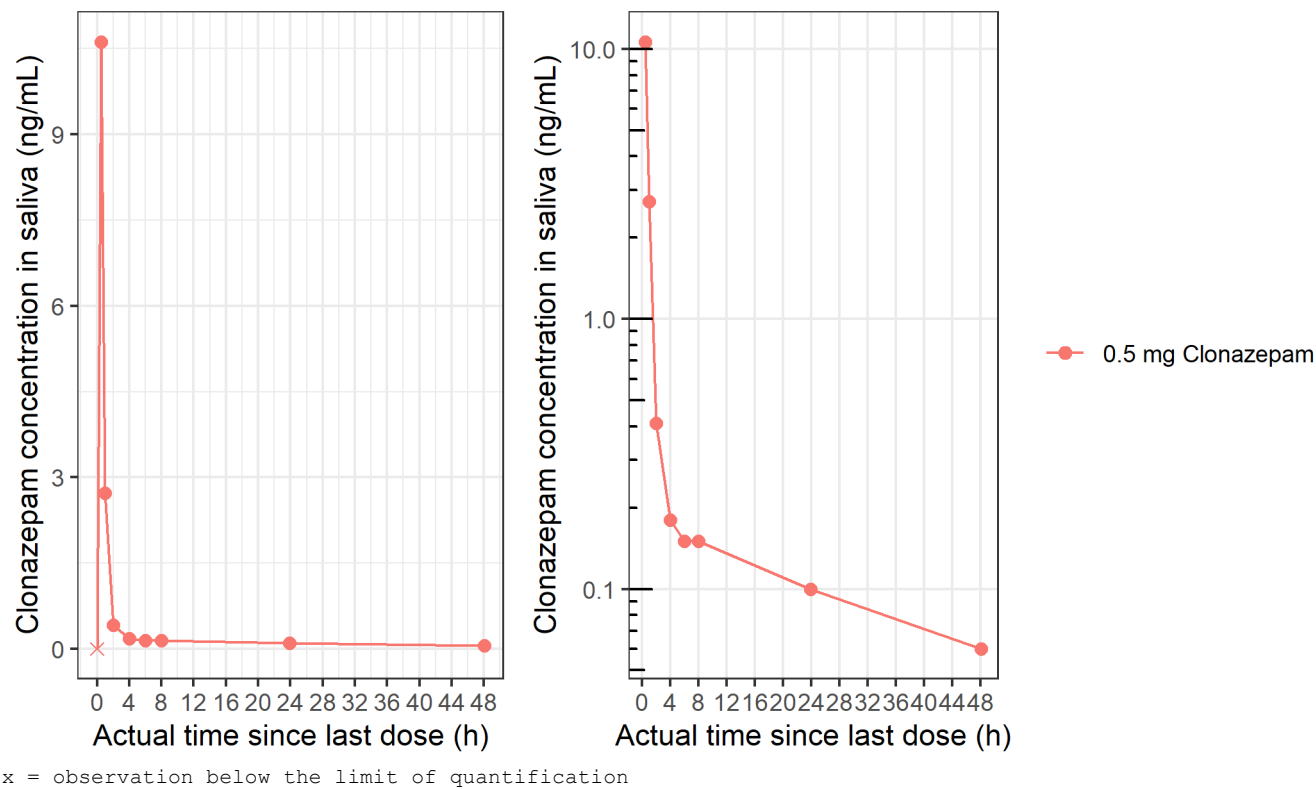
Subject 109 - Clonazepam concentration in Saliva (ng/mL)



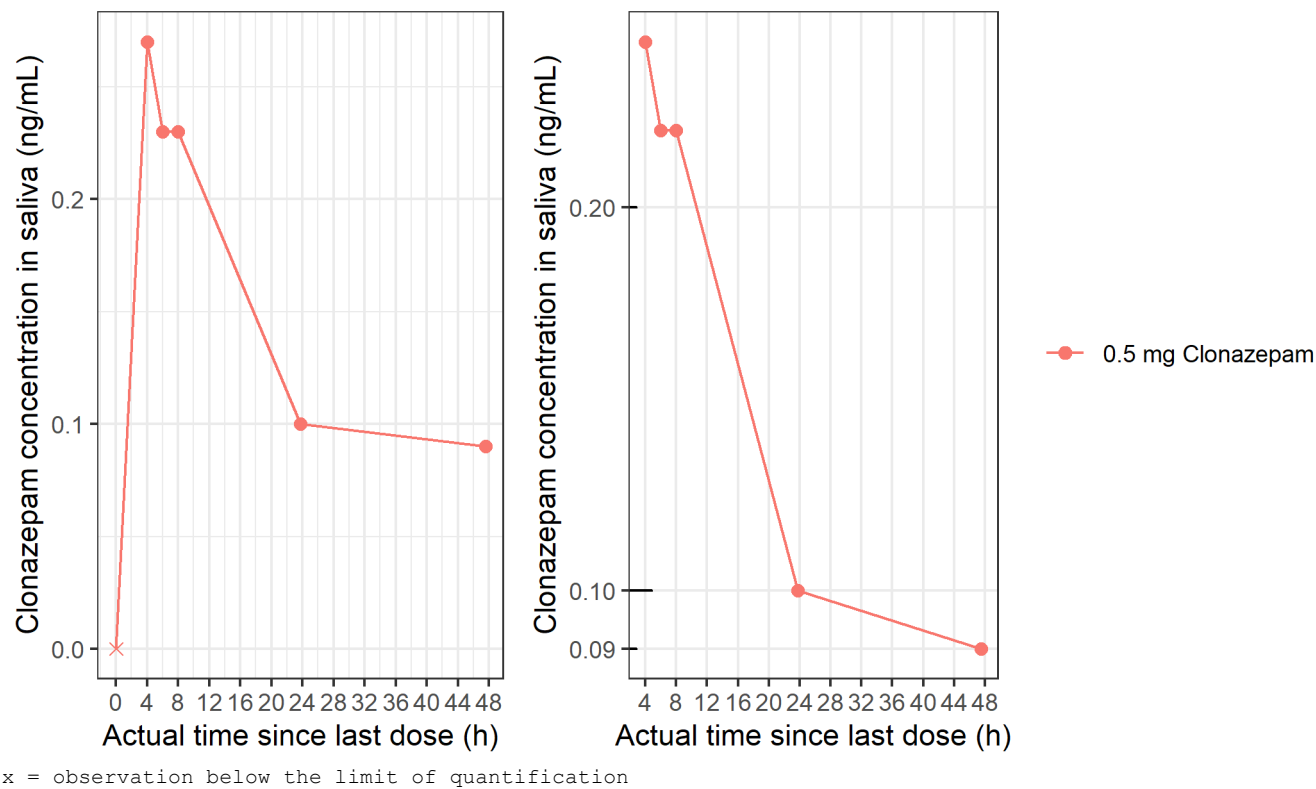
Subject 110 - Clonazepam concentration in Saliva (ng/mL)



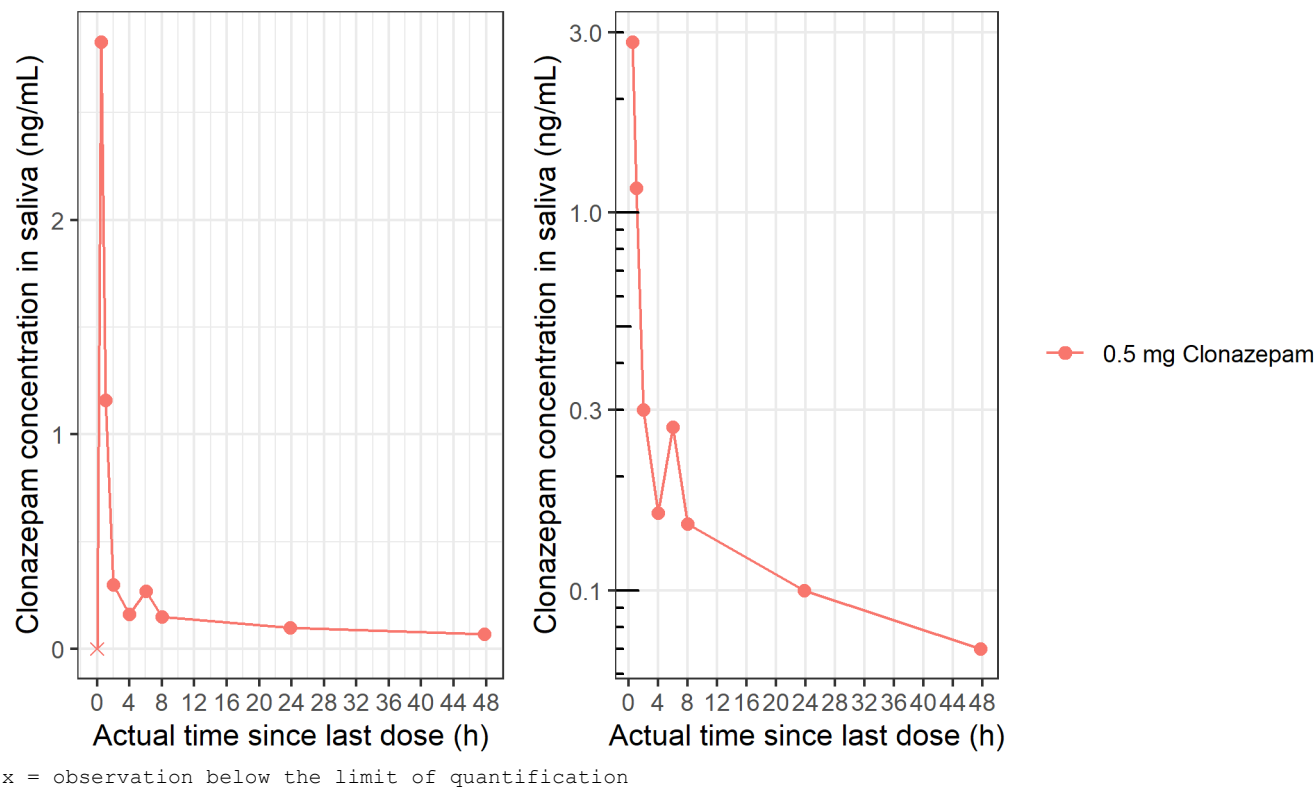
Subject 111 - Clonazepam concentration in Saliva (ng/mL)



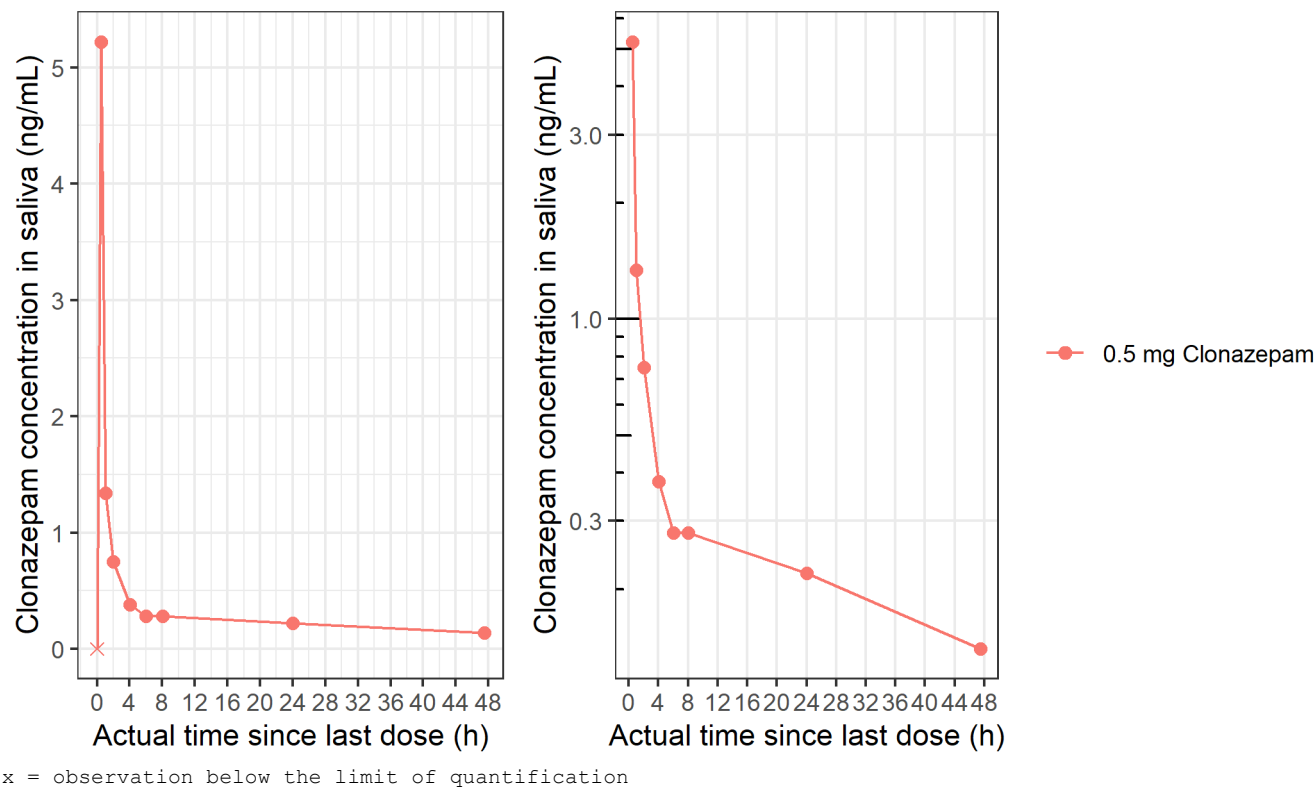
Subject 112 - Clonazepam concentration in Saliva (ng/mL)



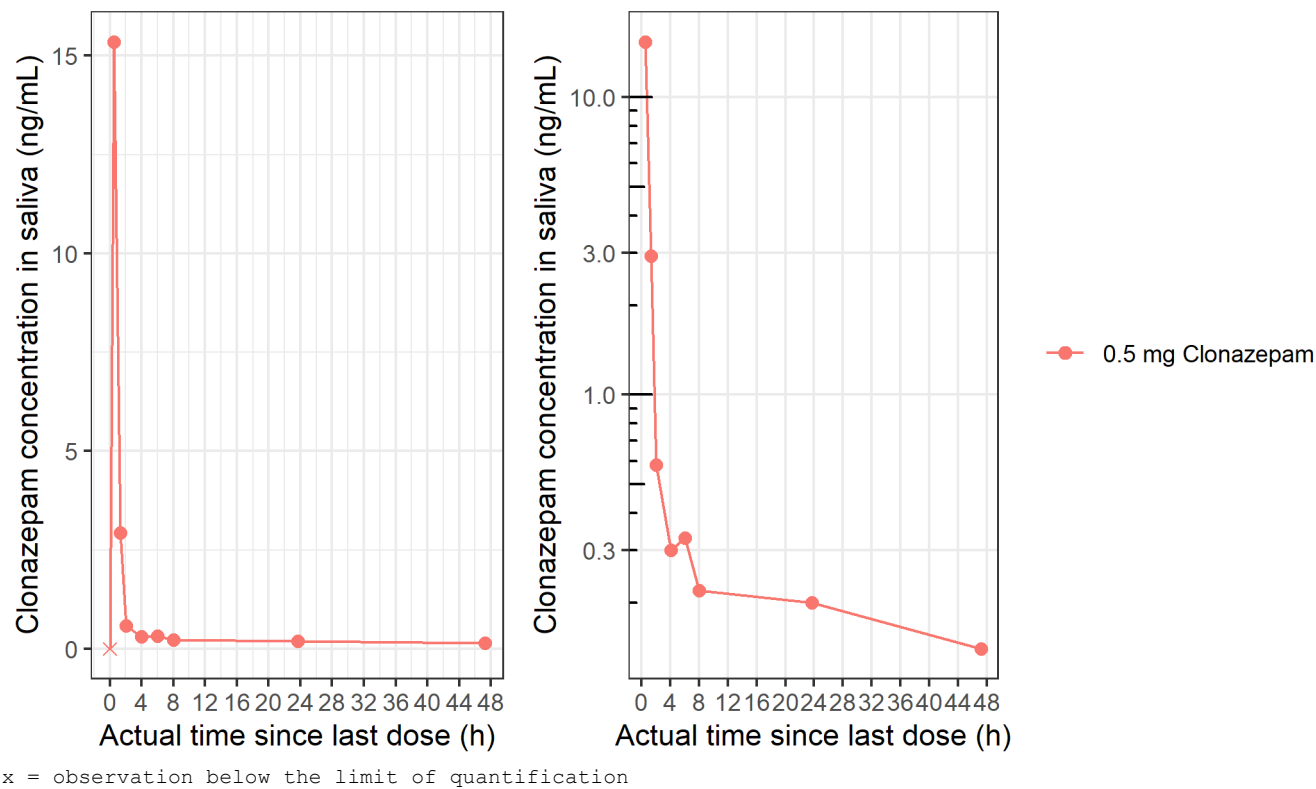
Subject 113 - Clonazepam concentration in Saliva (ng/mL)



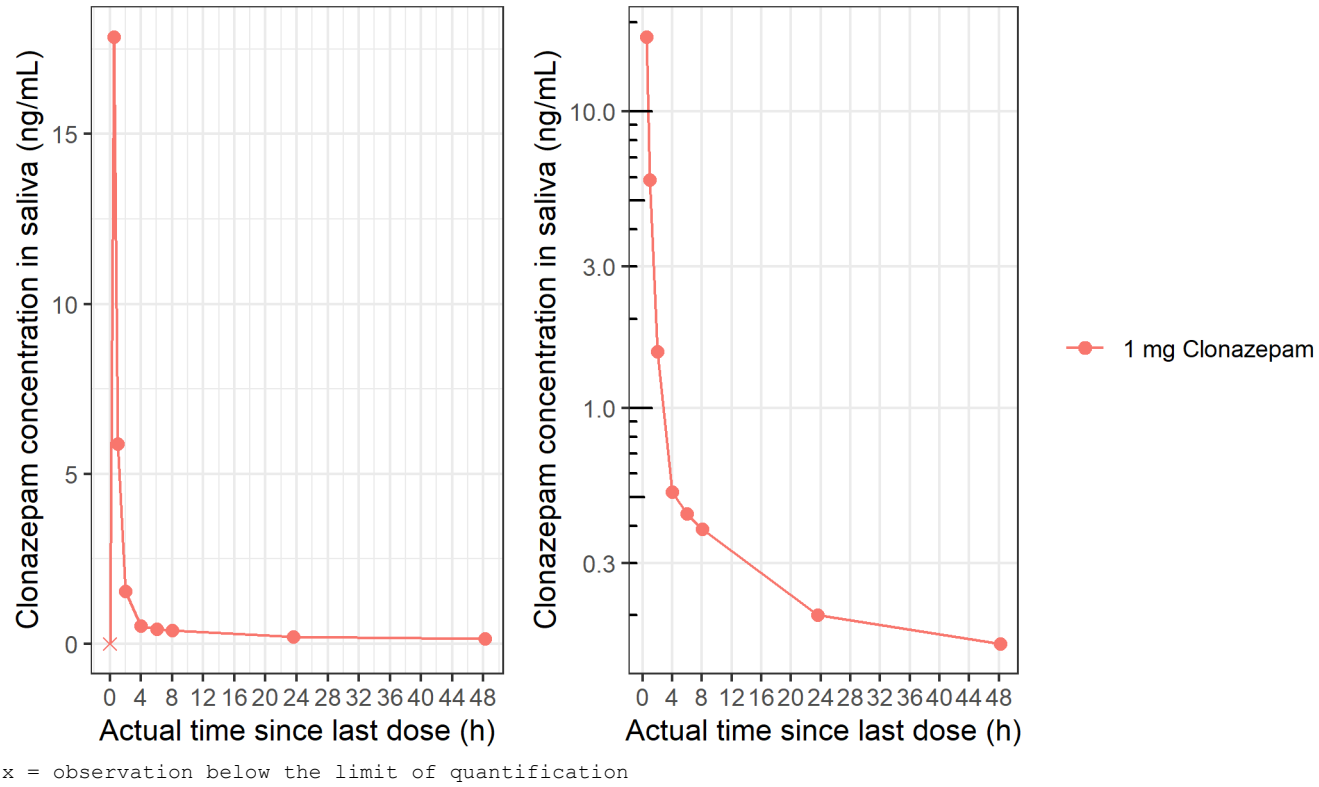
Subject 114 - Clonazepam concentration in Saliva (ng/mL)



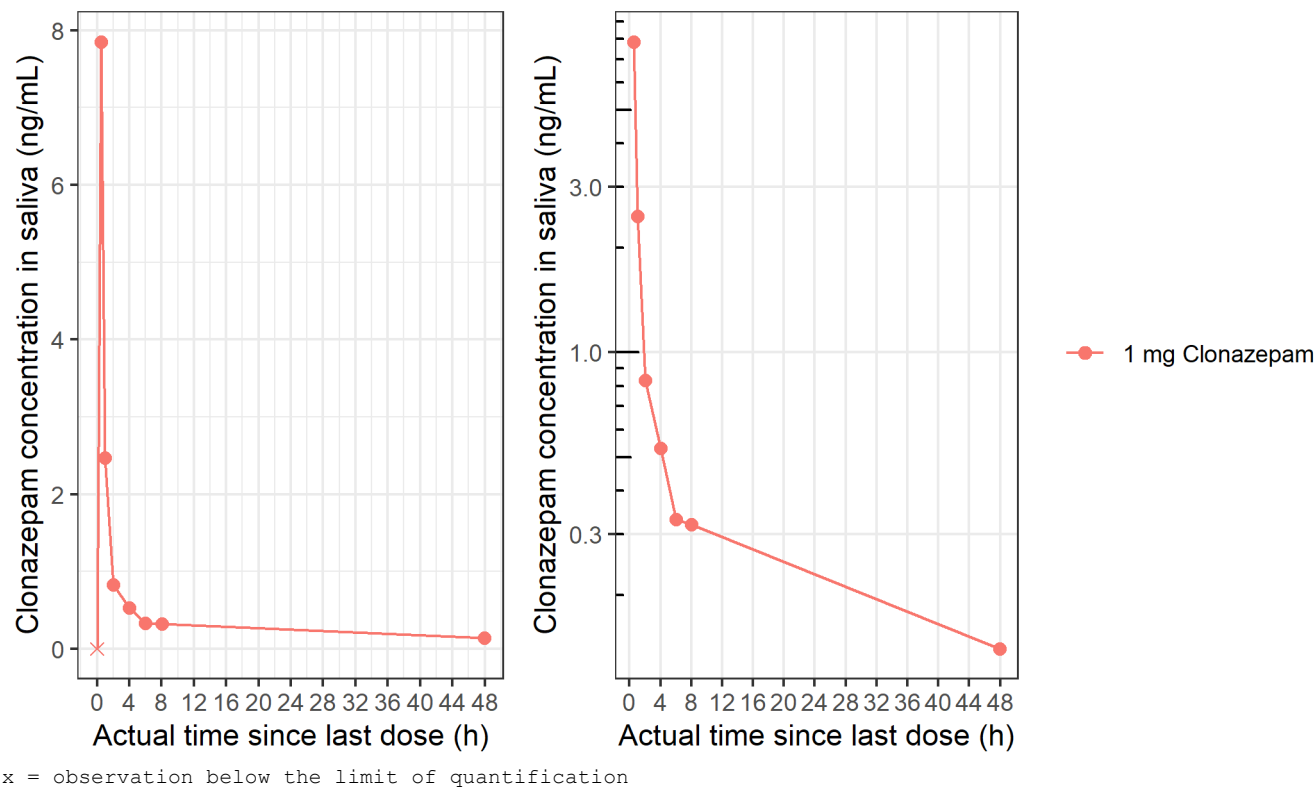
Subject 115 - Clonazepam concentration in Saliva (ng/mL)



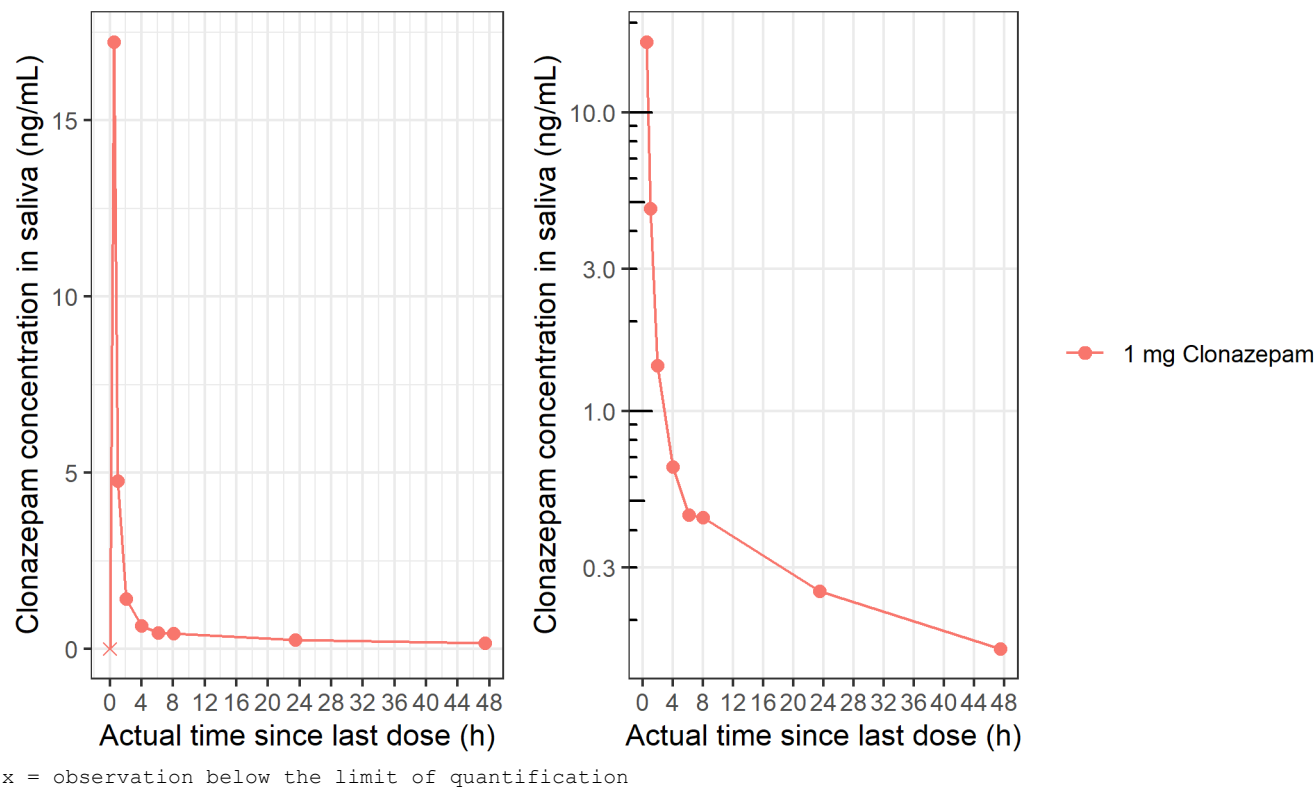
Subject 116 - Clonazepam concentration in Saliva (ng/mL)



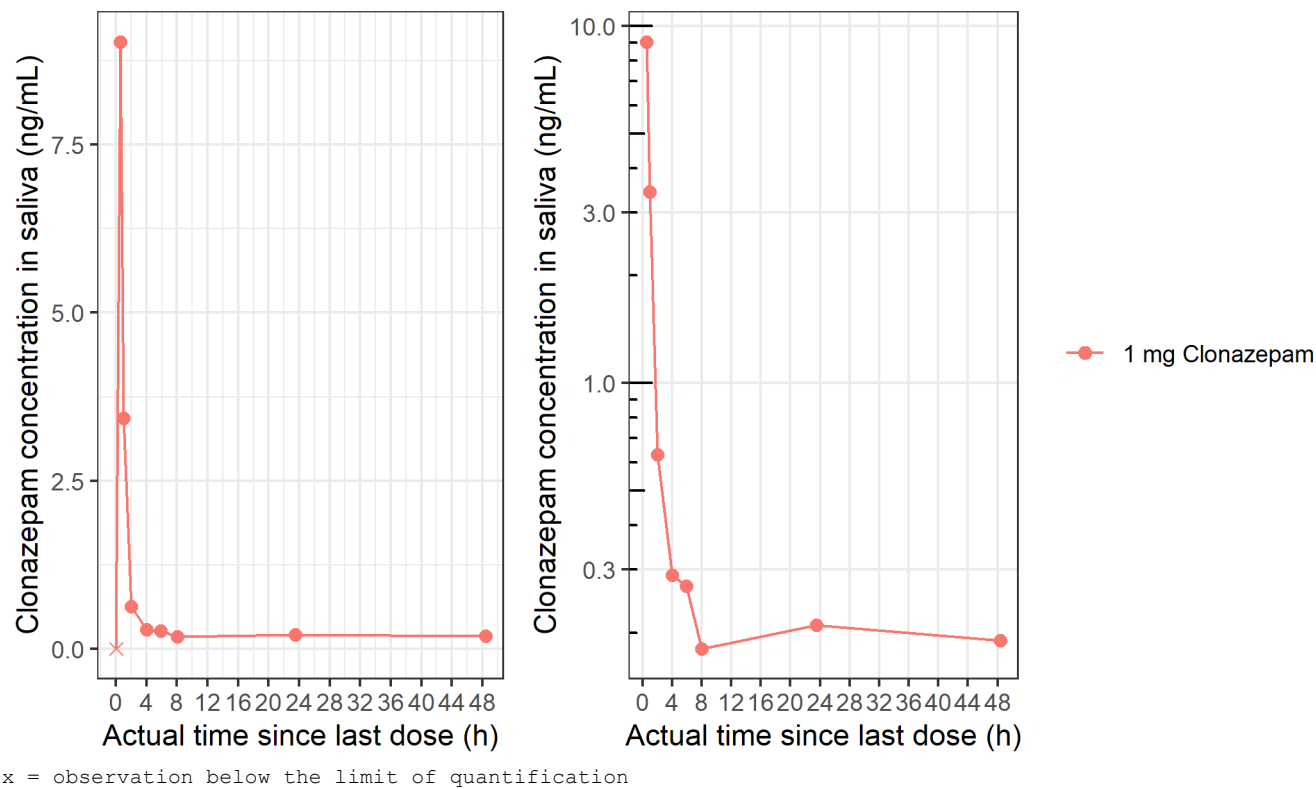
Subject 117 - Clonazepam concentration in Saliva (ng/mL)



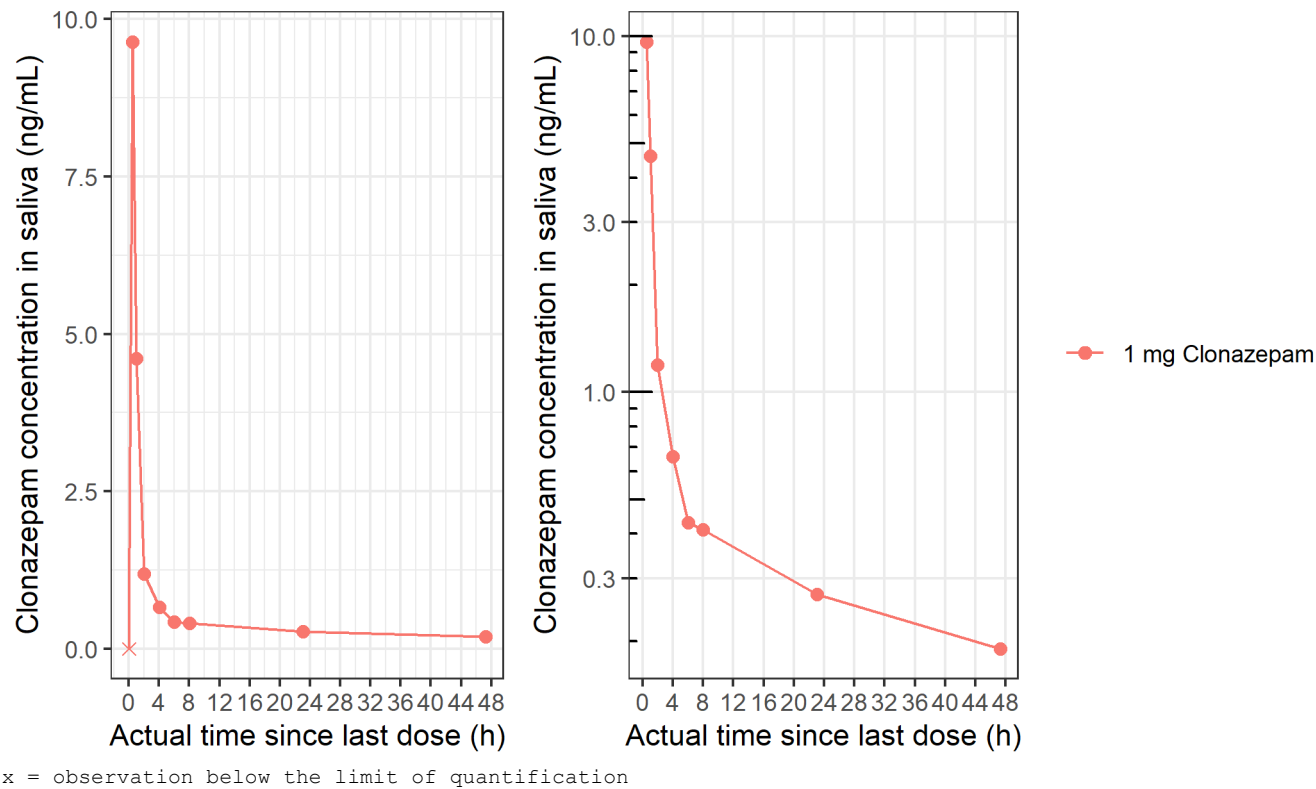
Subject 118 - Clonazepam concentration in Saliva (ng/mL)



Subject 119 - Clonazepam concentration in Saliva (ng/mL)



Subject 120 - Clonazepam concentration in Saliva (ng/mL)



Summary Tables and Figures

Table 1 Summary of Clonazepam concentration in Plasma (ng/mL)

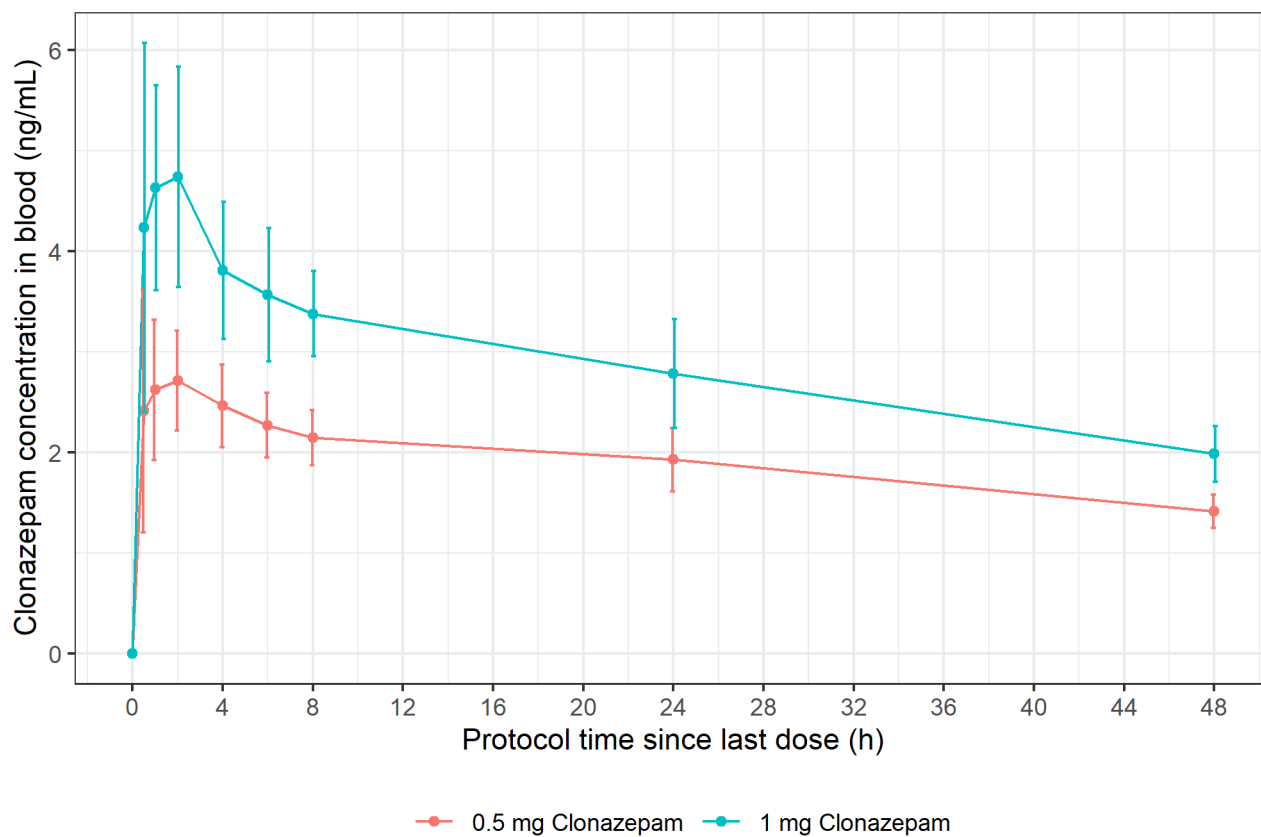
Summary of PK of Clonazepam in Plasma

Treatment	Protocol Time	N	Mean	SD	Median	CV%	Min	Max
0.5 mg Clonazepam	00H00M	10	0		0		0	0
	00H30M	10	2.412	1.2084	2.0	50.1	1.06	4.60
	01H00M	10	2.623	0.69781	2.44	26.6	1.58	3.49
	02H00M	10	2.714	0.49793	2.67	18.3	2.02	3.44
	04H00M	10	2.463	0.41126	2.45	16.7	1.87	3.15
	06H00M	10	2.270	0.31941	2.36	14.1	1.69	2.59
	08H00M	10	2.146	0.27464	2.23	12.8	1.66	2.53
	24H00M	10	1.927	0.31697	1.92	16.4	1.43	2.41
	48H00M	10	1.413	0.16674	1.42	11.8	1.07	1.63
1 mg Clonazepam	00H00M	10	0		0		0	0
	00H30M	10	4.236	1.8358	3.65	43.3	1.73	7.01
	01H00M	10	4.630	1.0174	4.65	22	2.94	6.07
	02H00M	10	4.741	1.0968	4.49	23.1	3.30	6.44
	04H00M	10	3.810	0.68217	3.85	17.9	2.53	4.61
	06H00M	10	3.569	0.66201	3.55	18.5	2.74	4.68
	08H00M	10	3.379	0.42207	3.38	12.5	2.74	4.04
	24H00M	10	2.785	0.54261	2.63	19.5	2.18	3.57
	48H00M	10	1.984	0.27973	1.94	14.1	1.61	2.42

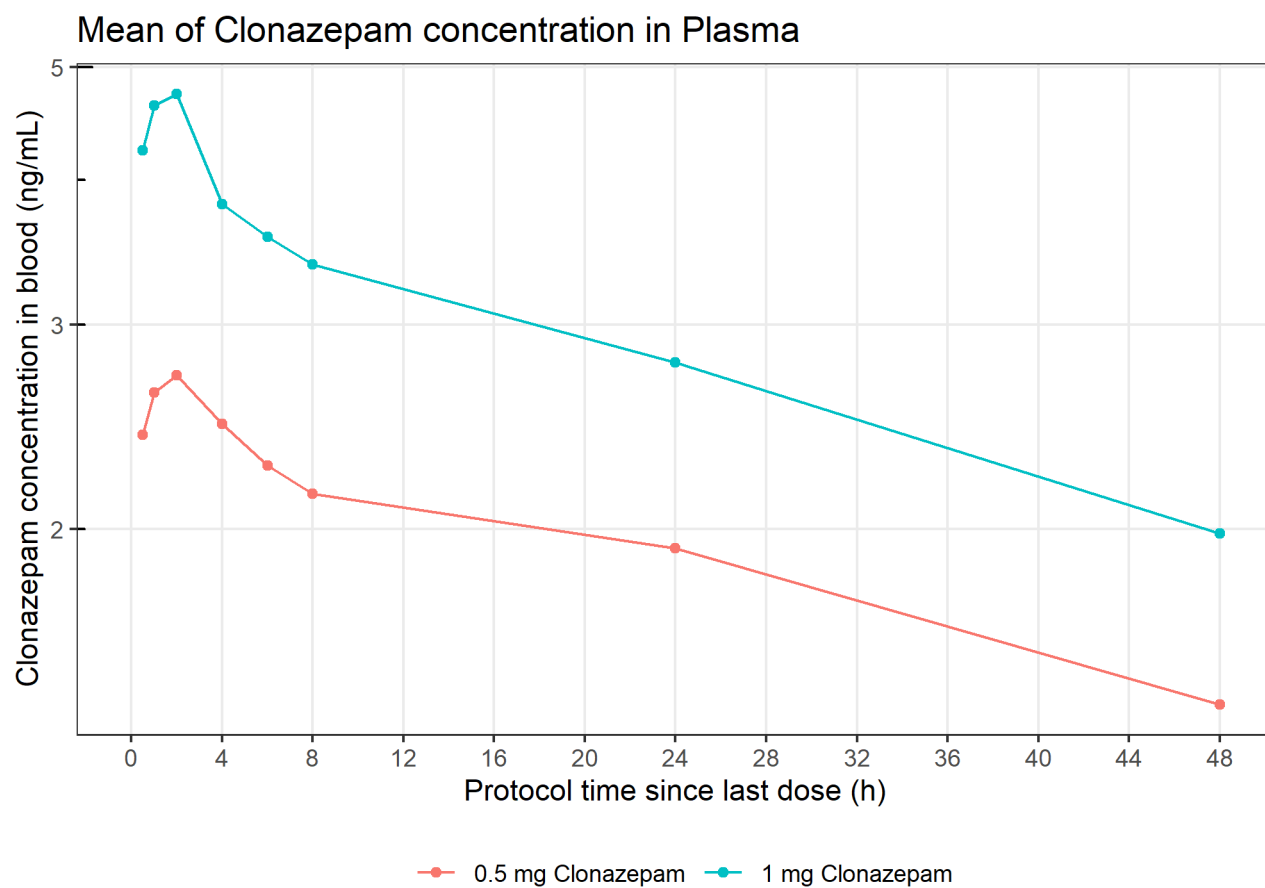
Page 1 of 1 (Created on 2022-10-05 14:48:47 by dvasten)

Summary of Clonazepam concentration in Plasma (ng/mL) (linear y-axis)

Mean (SD) of Clonazepam concentration in Plasma



2022-10-05 14:48:48

Summary of Clonazepam concentration in Plasma (ng/mL) (log y-axis)

2022-10-05 14:48:49

Table 2 Summary of Clonazepam concentration in Saliva (ng/mL)

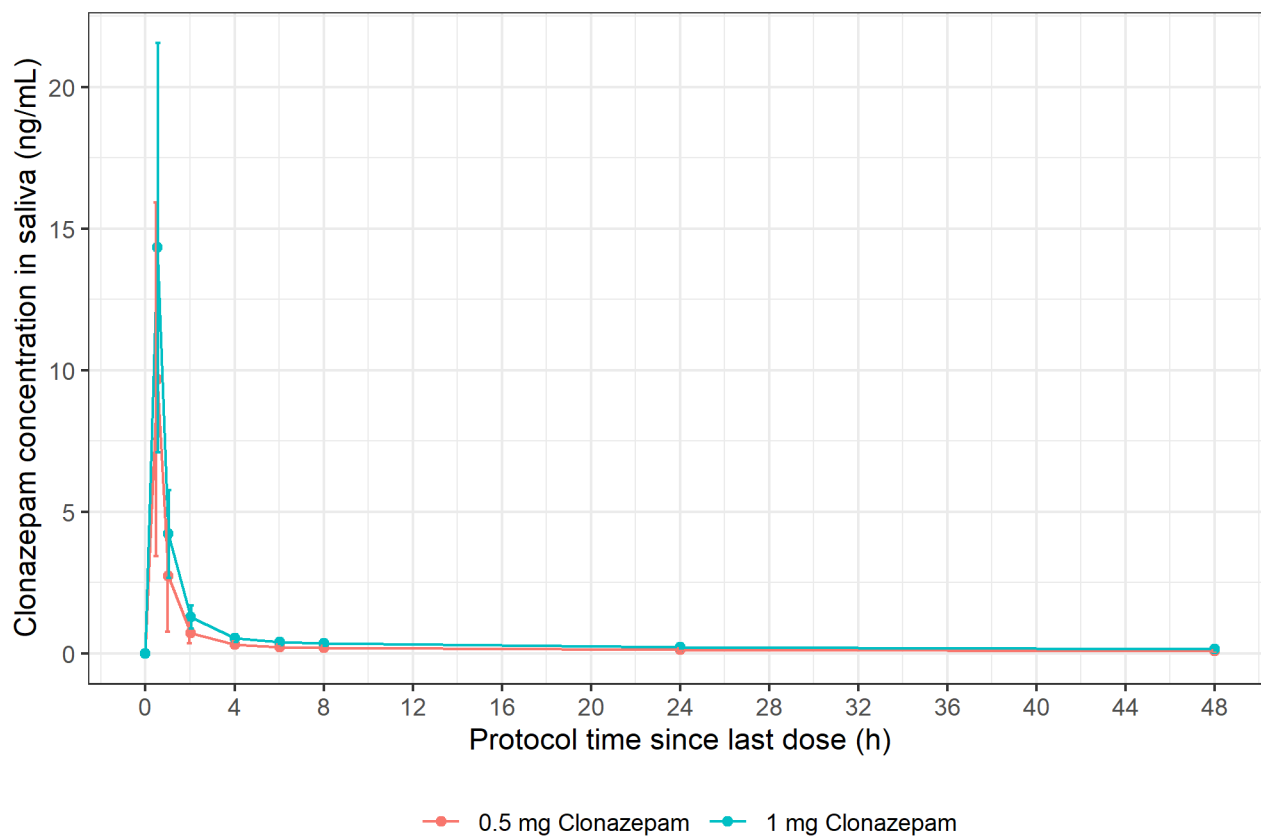
Summary of PK of Clonazepam in Saliva

Treatment	Protocol Time	N	Mean	SD	Median	CV%	Min	Max
0.5 mg Clonazepam	00H00M	10	0		0		0	0
	00H31M	9	9.680	6.2402	7.86	64.5	2.83	22.6
	01H01M	8	2.724	1.9476	2.51	71.5	1.16	7.18
	02H01M	9	0.7200	0.36997	0.650	51.4	0.300	1.45
	04H01M	10	0.3060	0.11067	0.305	36.2	0.160	0.510
	06H01M	10	0.2350	0.068516	0.265	29.2	0.120	0.330
	08H01M	10	0.2070	0.051651	0.225	25	0.140	0.280
	24H01M	10	0.1400	0.045947	0.120	32.8	0.100	0.220
	48H01M	10	0.09300	0.028304	0.0850	30.4	0.0600	0.140
1 mg Clonazepam	00H00M	10	0		0		0	0
	00H31M	10	14.33	7.2269	15.1	50.4	3.68	29.2
	01H01M	10	4.219	1.5522	4.21	36.8	1.58	7.01
	02H01M	9	1.290	0.40531	1.42	31.4	0.630	1.91
	04H01M	10	0.5430	0.13425	0.560	24.7	0.290	0.700
	06H01M	10	0.3960	0.065862	0.420	16.6	0.270	0.470
	08H01M	10	0.3670	0.093339	0.395	25.4	0.180	0.510
	24H01M	9	0.2211	0.032575	0.210	14.7	0.180	0.270
	48H01M	9	0.1589	0.039826	0.160	25.1	0.0800	0.220

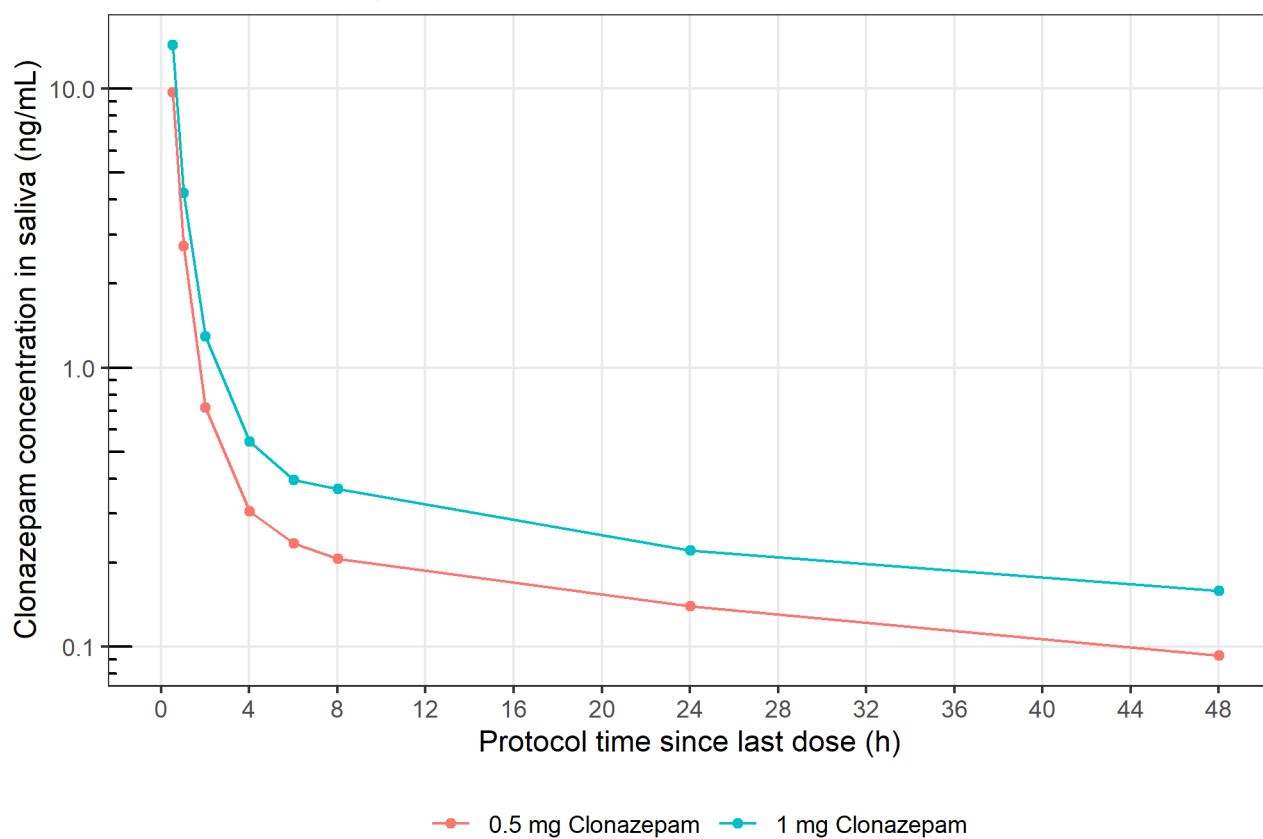
Page 1 of 1 (Created on 2022-10-05 14:48:50 by dvasten)

Summary of Clonazepam concentration in Saliva (ng/mL) (linear y-axis)

Mean (SD) of Clonazepam concentration in Saliva



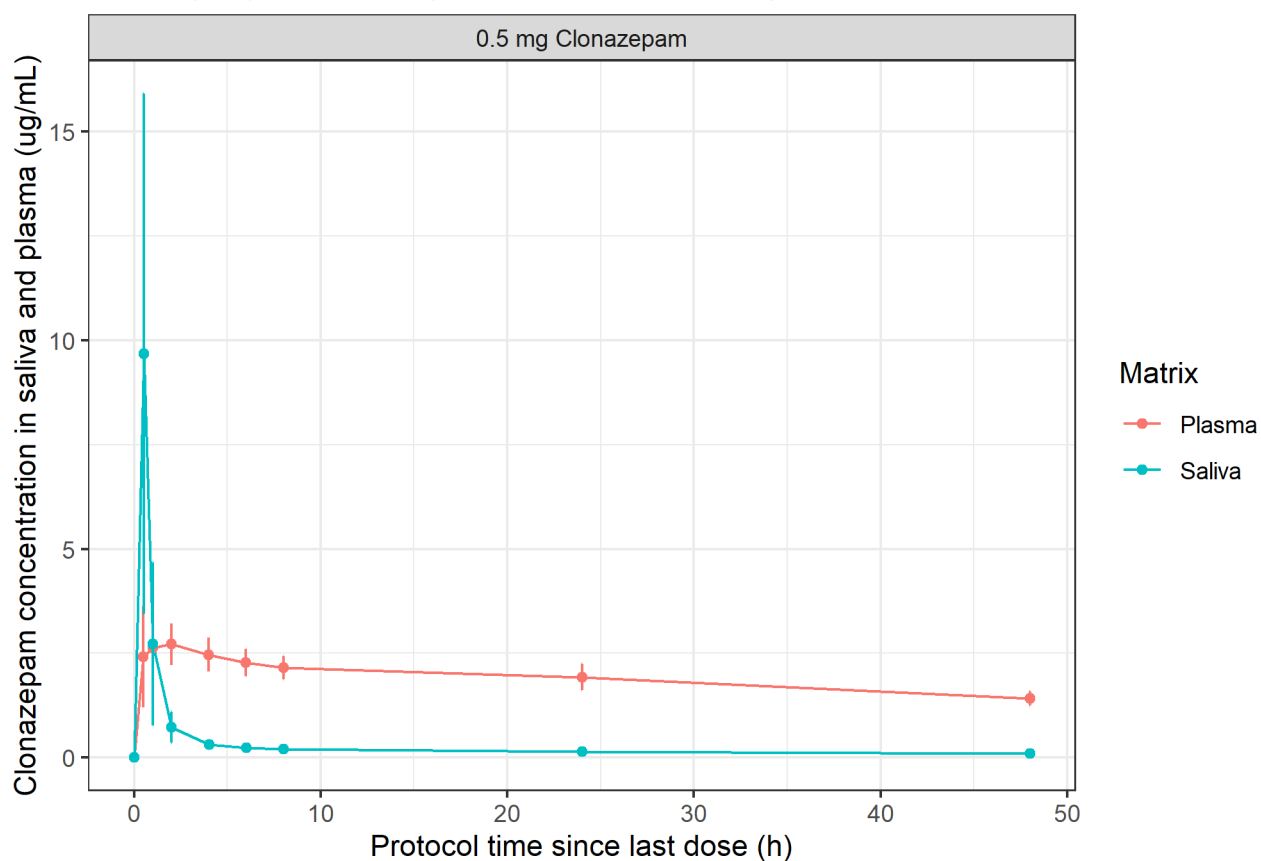
2022-10-05 14:48:51

Summary of Clonazepam concentration in Saliva (ng/mL) (log y-axis)**Mean of Clonazepam concentration in Saliva**

2022-10-05 14:48:51

Summary of Clonazepam concentration in Plasma and Saliva (ng/mL) (linear y-axis)

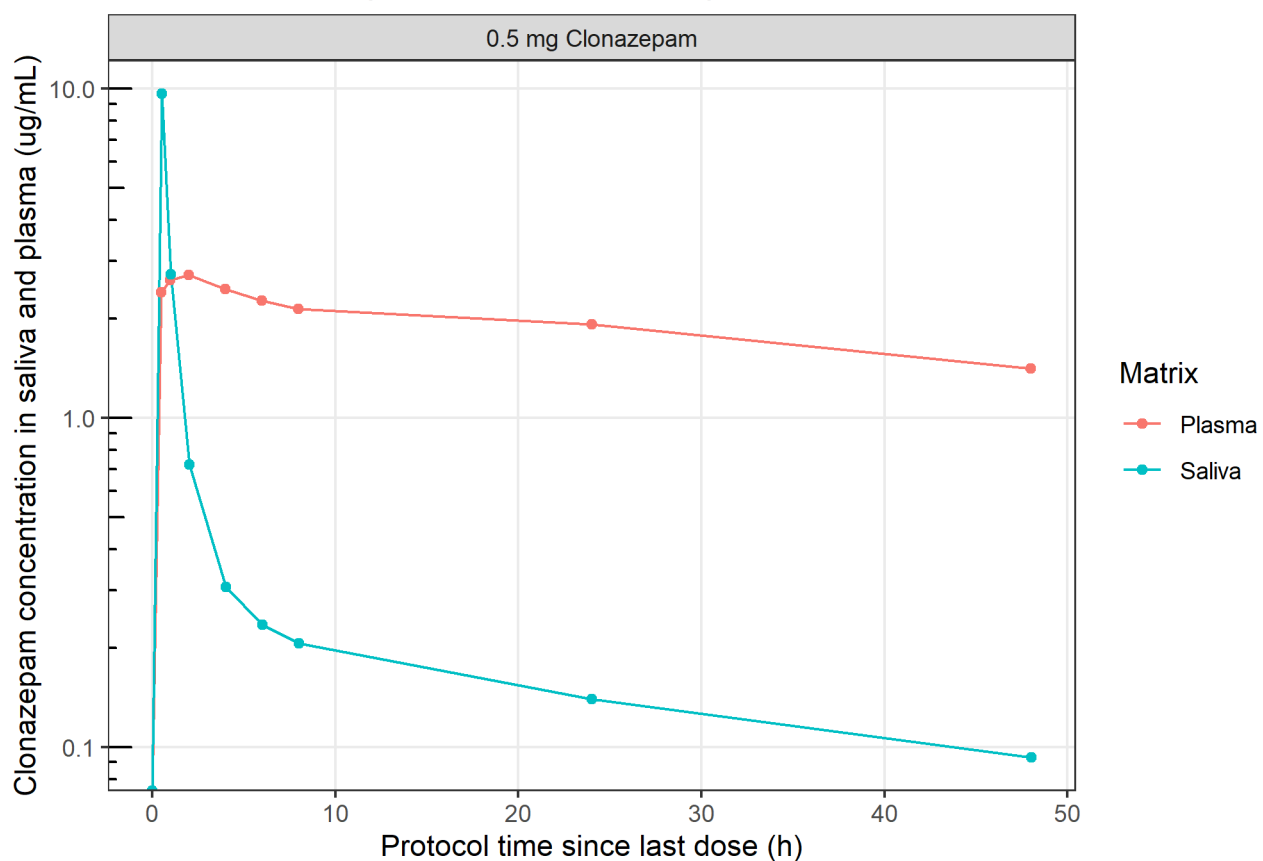
Mean (SD) of clonazepam concentration in plasma and saliva



2022-10-05 14:48:52

Summary of Clonazepam concentration in Plasma and Saliva (ng/mL) (log y-axis)

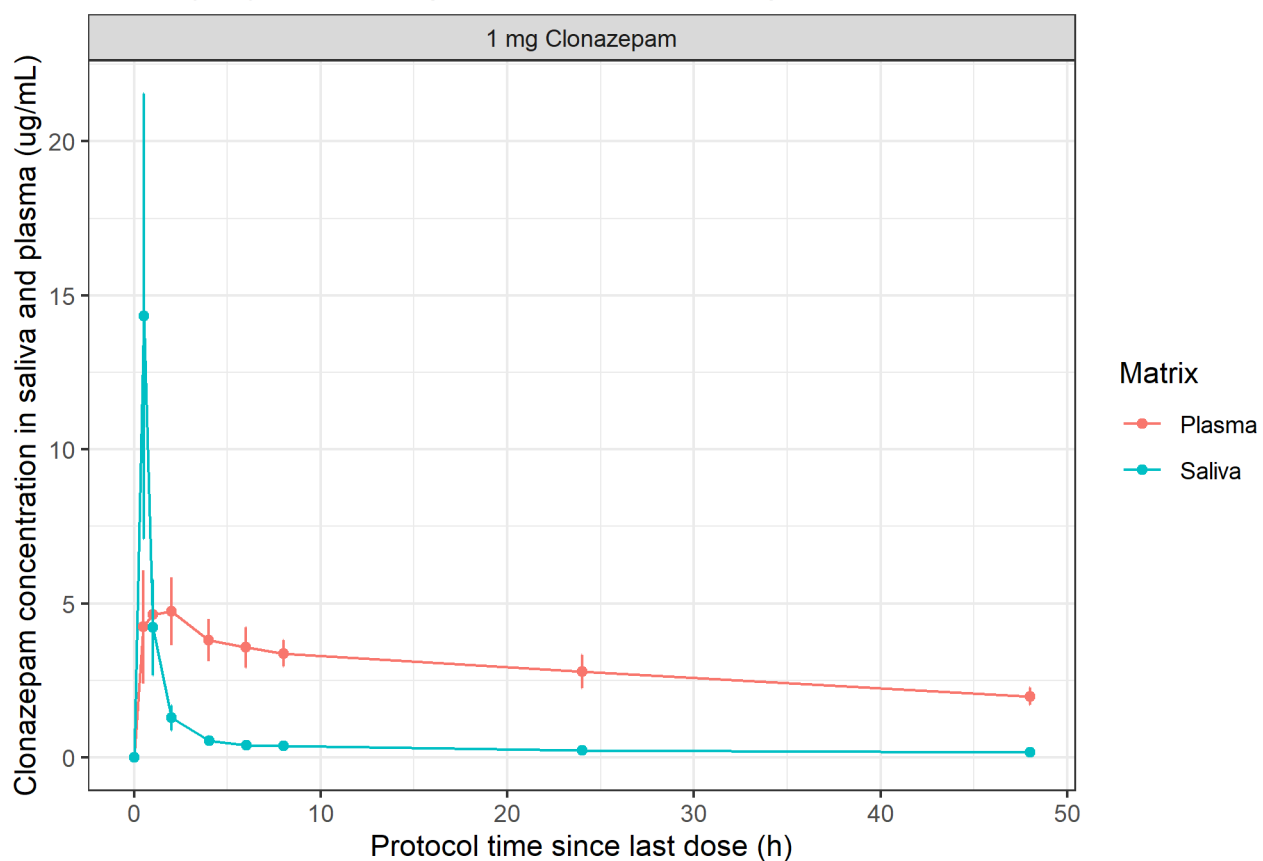
Mean of clonazepam concentration in plasma and saliva



2022-10-05 14:48:52

Summary of Clonazepam concentration in Plasma and Saliva (ng/mL) (linear y-axis)

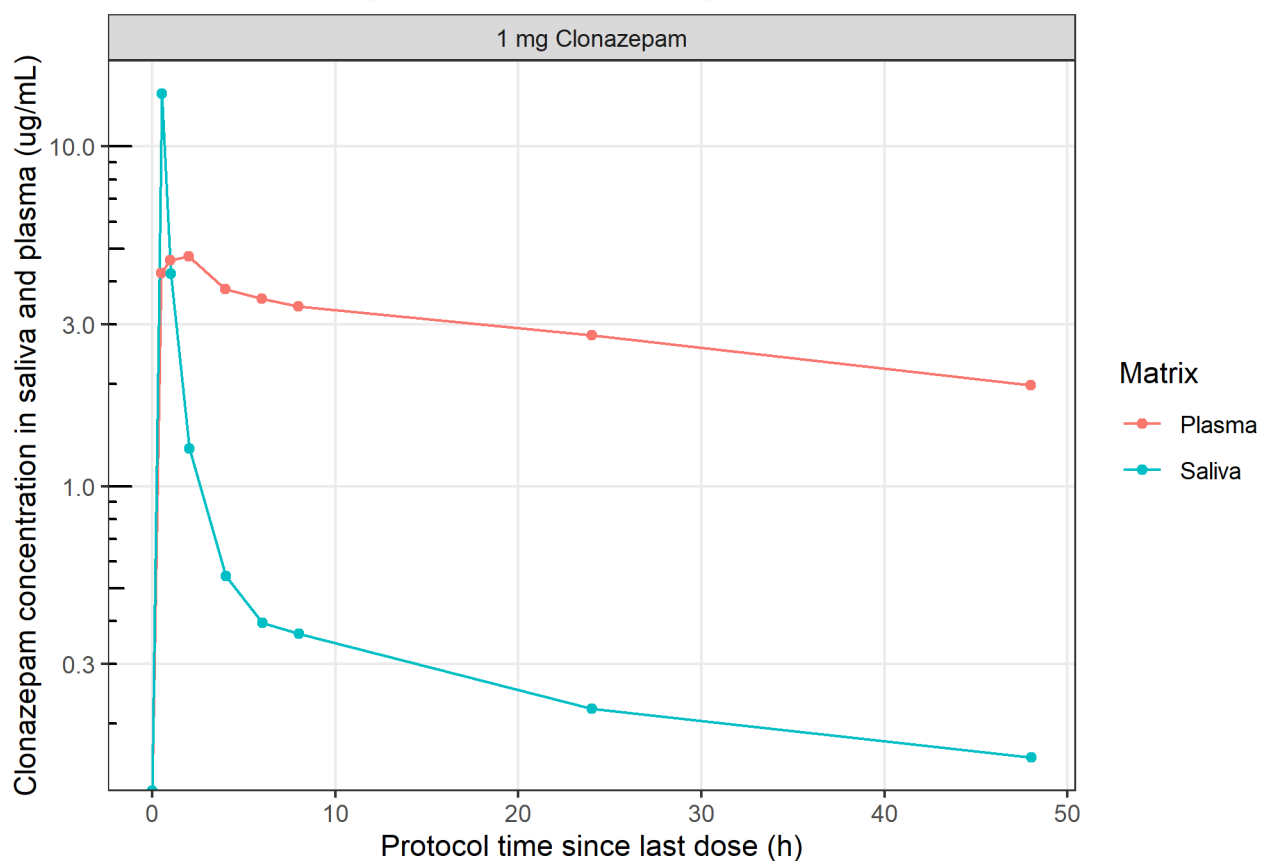
Mean (SD) of clonazepam concentration in plasma and saliva



2022-10-05 14:48:53

Summary of Clonazepam concentration in Plasma and Saliva (ng/mL) (log y-axis)

Mean of clonazepam concentration in plasma and saliva



2022-10-05 14:48:53

Pharmacokinetic Parameters Tables and Figures

PK parameters for Clonazepam in Plasma

Table 3 Summary of PK parameters for Clonazepam in Plasma

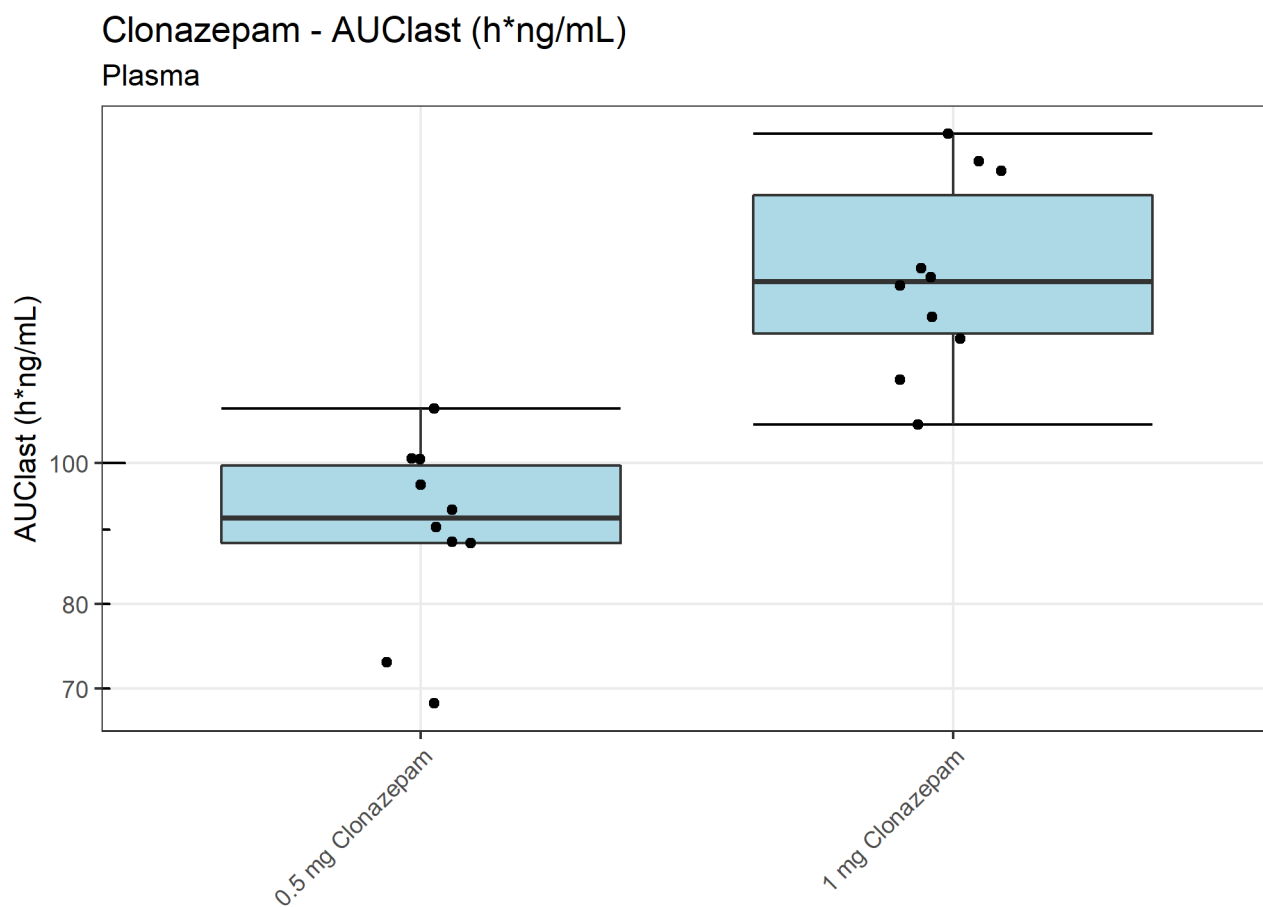
Summary of PK parameters of Clonazepam in Plasma

Treatment	Parameter	unit	N	Mean	SD	CV%	GeoMean	GeoCV%	Median	Min	Max
0.5 mg Clonazepam	AUCinf	h*ng/mL	10	226	34.2	15.1	224	15.5	231	167	290
	AUClast	h*ng/mL	10	90.8	12.5	13.7	90	14.5	91.6	68.4	109
	CL/F	L/h	10	2.26	0.356	15.8	2.23	15.5	2.17	1.72	3
	Cmax	ng/mL	10	3.040	0.87340	28.7	2.935	28.1	2.92	2.02	4.60
	t1/2	h	10	66.36	13.07	19.7	65.3	18.7	62.25	52.61	91.58
	tmax	h	10						1.5	0.5	4
	Vz/F	L	10	213	35.7	16.8	211	15.8	204	174	277

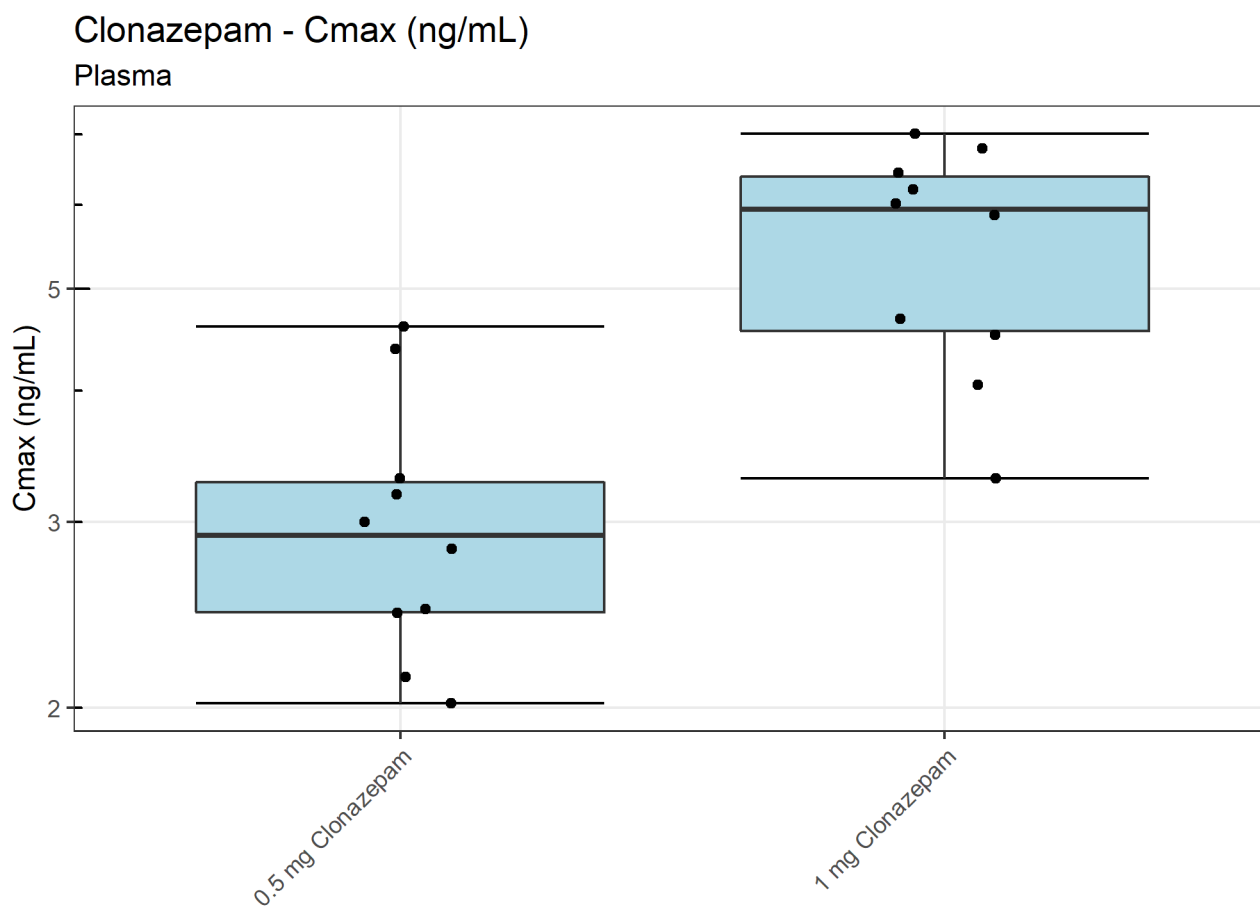
Summary of PK parameters of Clonazepam in Plasma

Treatment	Parameter	unit	N	Mean	SD	CV%	GeoMean	GeoCV%	Median	Min	Max
1 mg Clonazepam	AUCinf	h*ng/mL	10	290	57.3	19.8	285	19.1	279	227	402
	AUClast	h*ng/mL	10	136	20.8	15.3	135	15.3	133	106	168
	CL/F	L/h	10	3.56	0.644	18.1	3.51	19.1	3.59	2.49	4.4
	Cmax	ng/mL	10	5.489	1.2611	23	5.345	25.5	5.95	3.30	7.01
	t1/2	h	10	53.32	8.76	16.4	52.66	17	52.85	37.34	69.7
	tmax	h	10						2	0.5	6.12
	Vz/F	L	10	269	39.4	14.7	266	14.8	266	207	336

Page 2 of 2 (Created on 2022-10-05 14:48:55 by dvasten)

Boxplots of PK parameters for Clonazepam in Plasma**Summary boxplot of auclast**

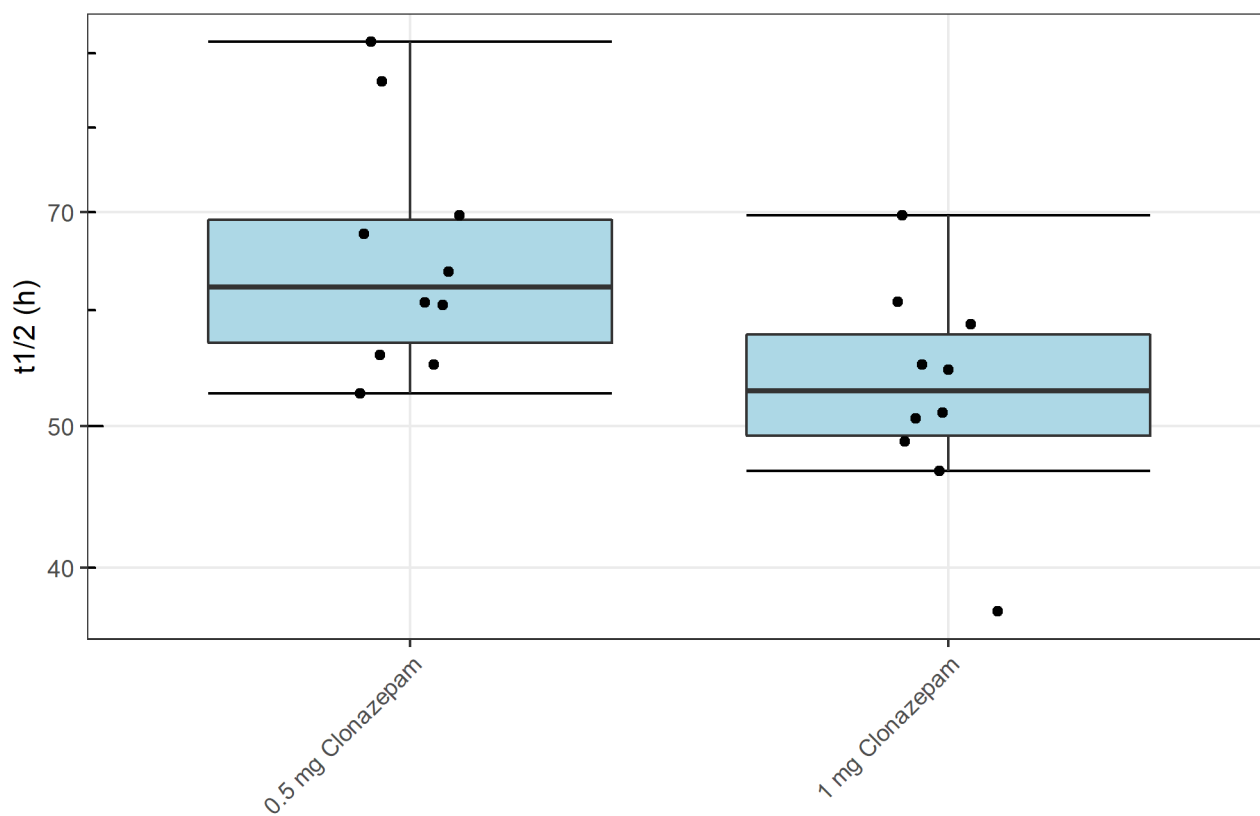
2022-10-05 14:48:57

Summary boxplot of cmax

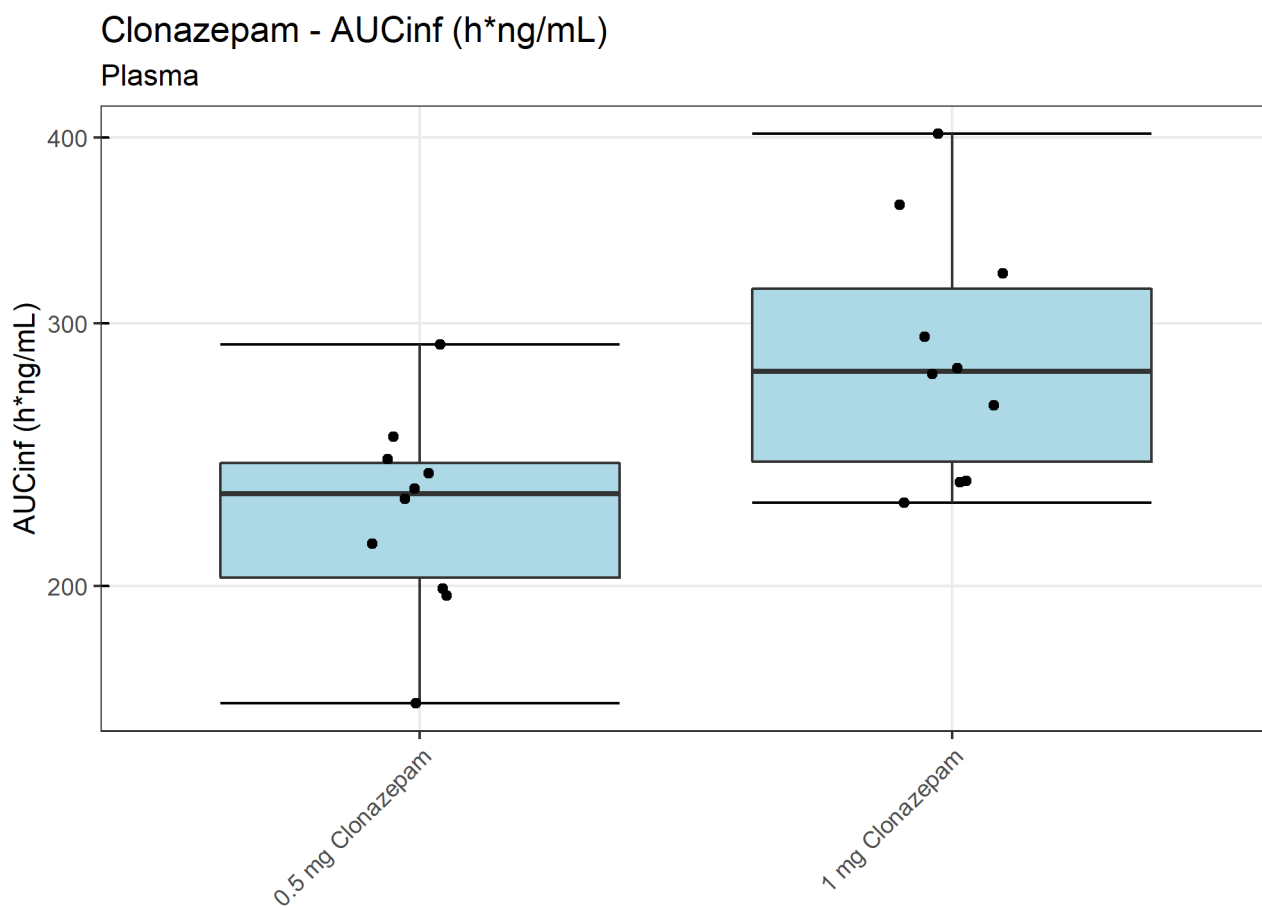
2022-10-05 14:48:57

Summary boxplot of half.lifeClonazepam - t_{1/2} (h)

Plasma

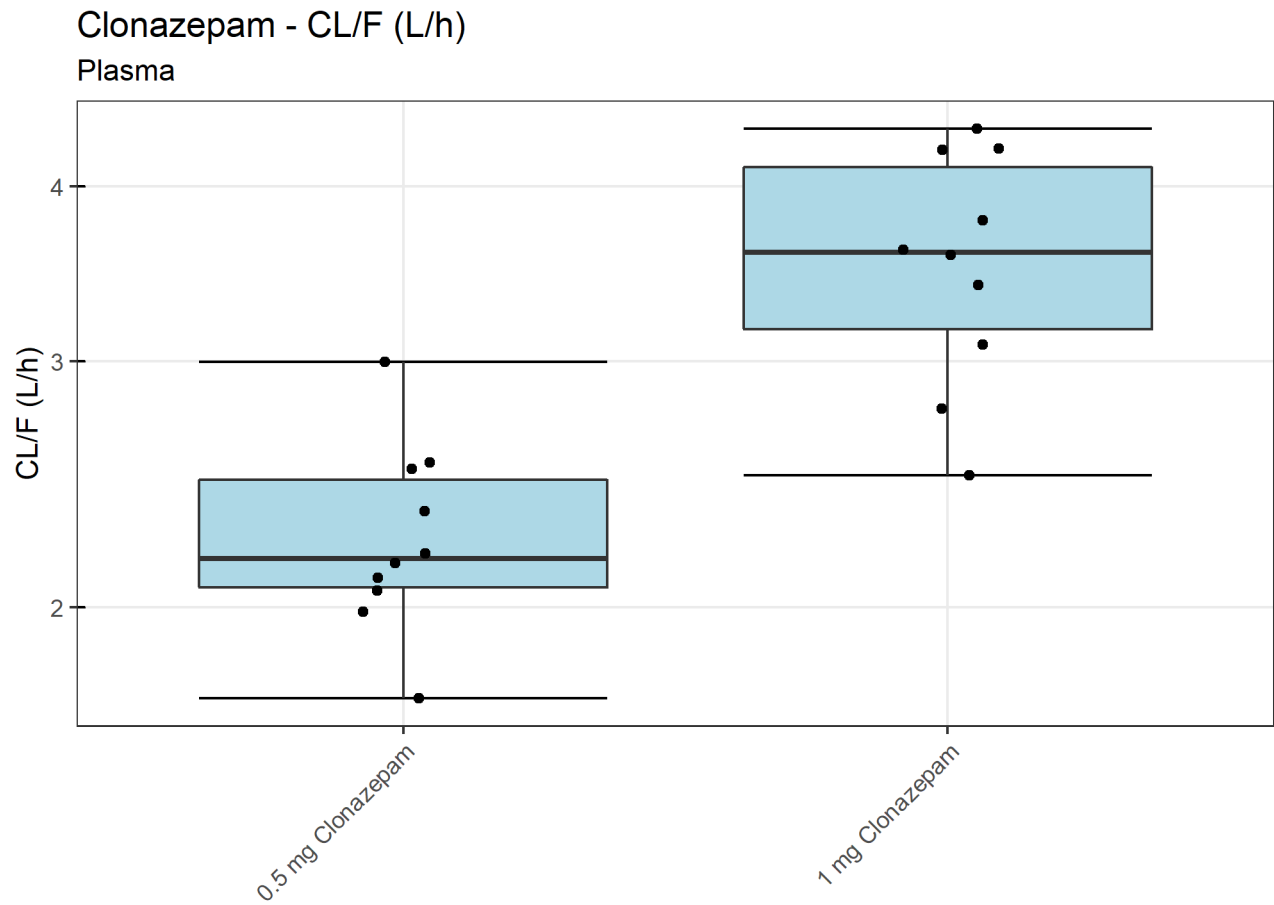


2022-10-05 14:48:57

Summary boxplot of aucinf.obs

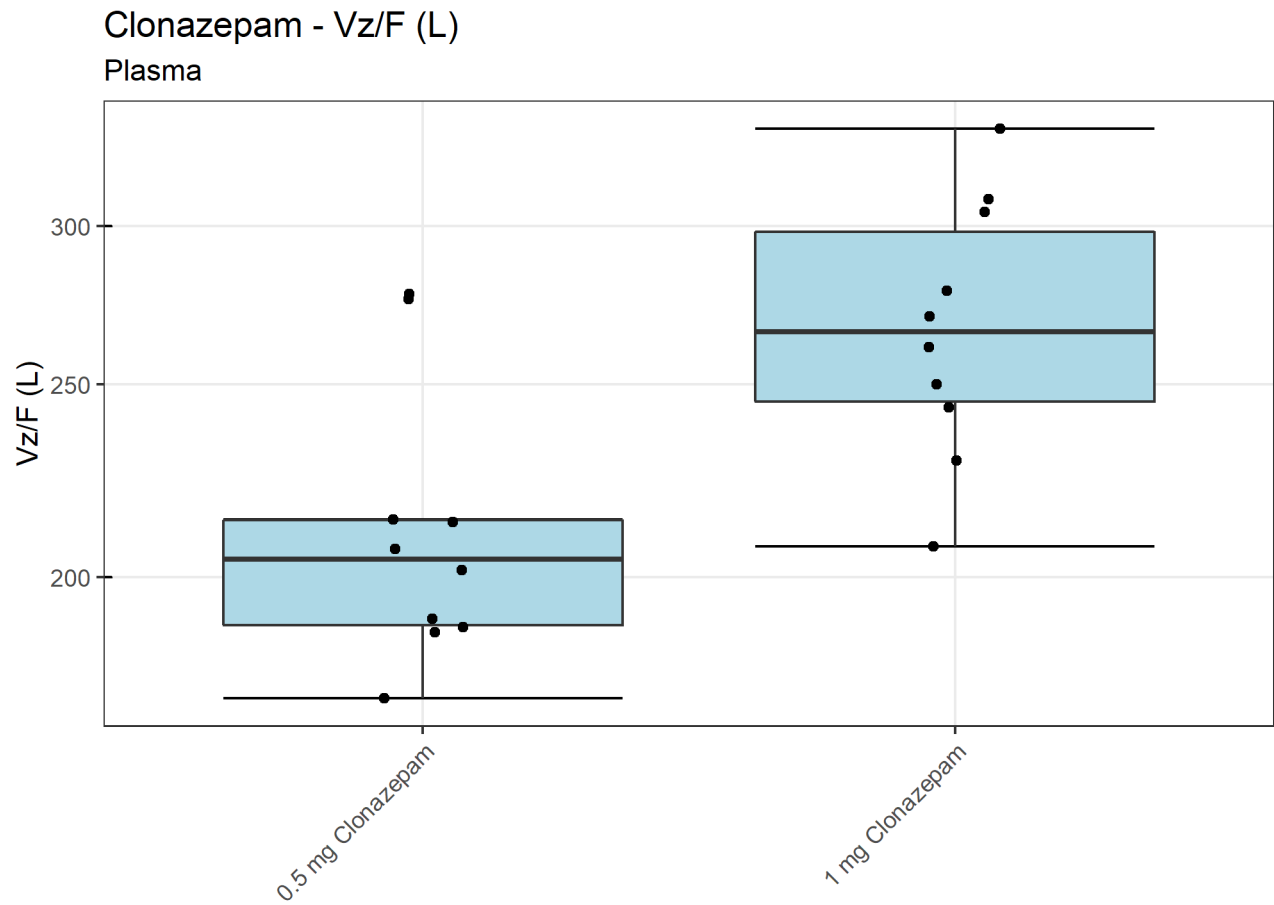
2022-10-05 14:48:58

Summary boxplot of cl.obs



2022-10-05 14:48:58

Summary boxplot of vz.obs



2022-10-05 14:48:58

PK parameters for Clonazepam in Saliva

Table 4 Summary of PK parameters for Clonazepam in Saliva

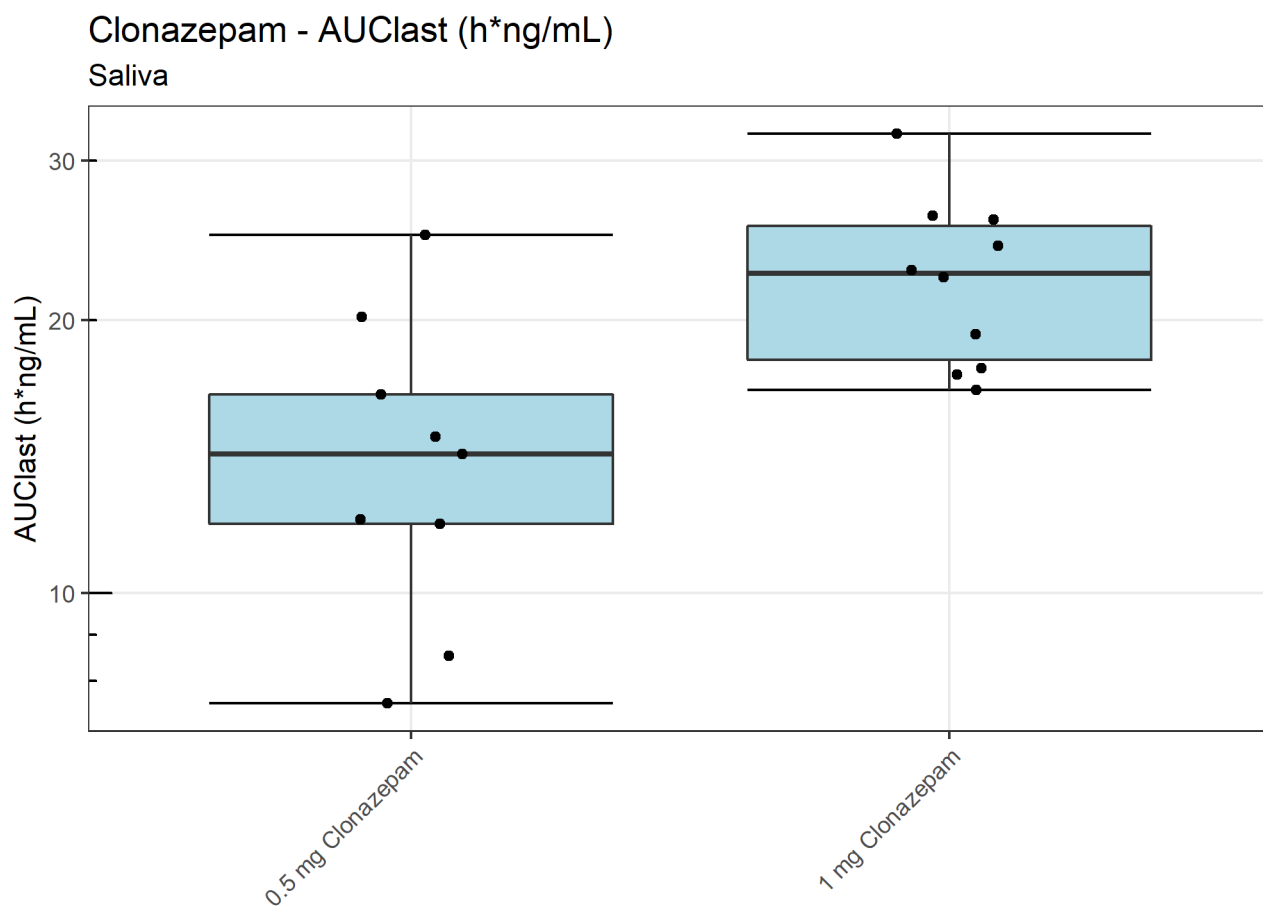
Summary of PK parameters of Clonazepam in Saliva

Treatment	Parameter	unit	N	Mean	SD	CV%	GeoMean	GeoCV%	Median	Min	Max
0.5 mg Clonazepam	AUCinf	h*ng/mL	9	19.8	6.59	33.3	18.9	33.8	20	11.3	32
	AUClast	h*ng/mL	9	14.5	5.47	37.7	13.6	39.5	14.2	7.56	24.8
	CL/F	L/h	9	27.8	9.02	32.5	26.5	33.8	25	15.6	44.3
	Cmax	ng/mL	9	9.680	6.2402	64.5	8.071	72.3	7.86	2.83	22.6
	t1/2	h	9	37.46	11.33	30.3	35.99	30.7	36.84	22.05	58.72
	tmax	h	9						0.52	0.52	0.53
	Vz/F	L	9	1496	624	41.7	1376	47	1323	588	2515

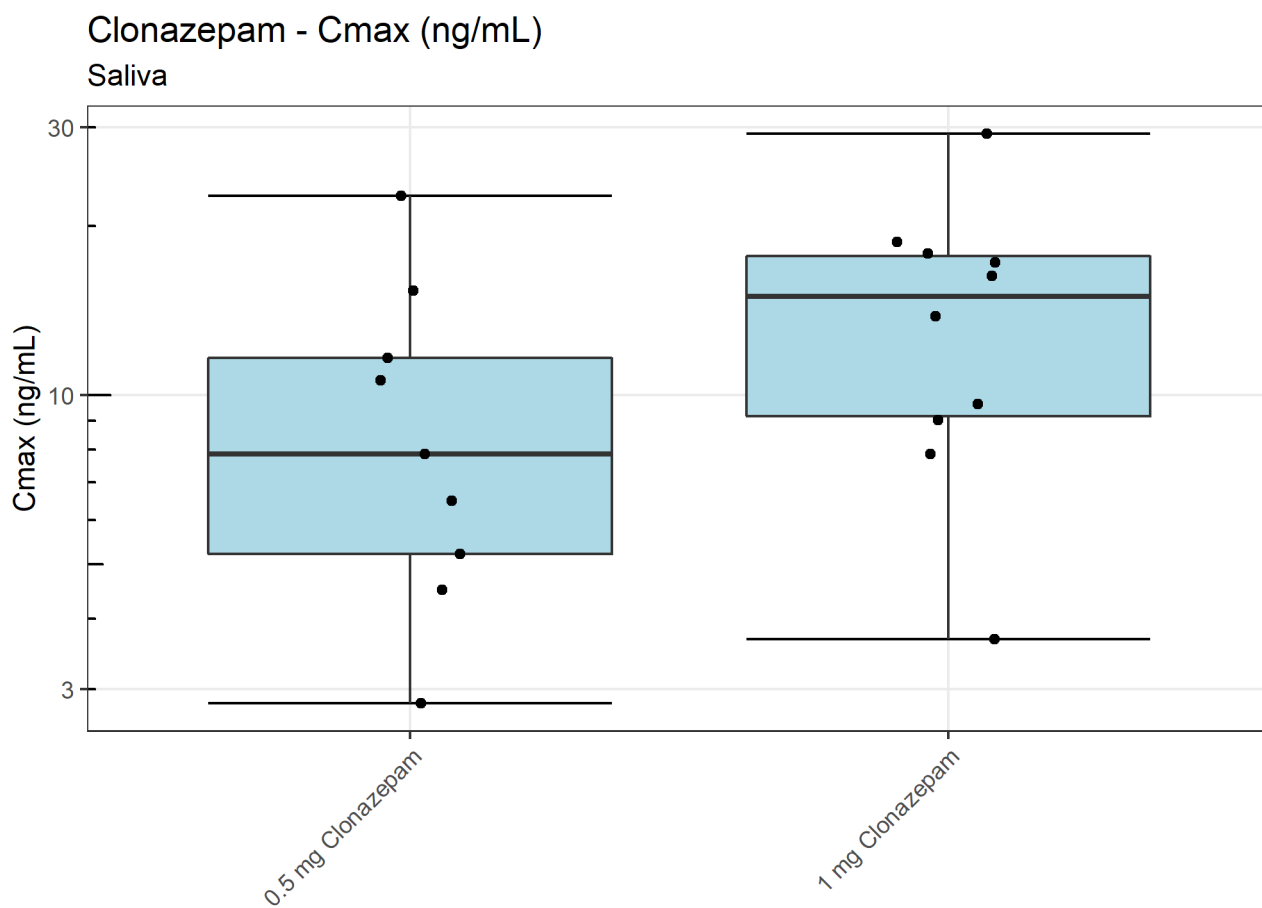
Summary of PK parameters of Clonazepam in Saliva

Treatment	Parameter	unit	N	Mean	SD	CV%	GeoMean	GeoCV%	Median	Min	Max
1 mg Clonazepam	AUCinf	h*ng/mL	9	29.9	4.2	14.1	29.6	14.4	31.9	24.2	36.6
	AUClast	h*ng/mL	10	22.4	4.84	21.6	22	21.3	22.5	16.7	32.1
	CL/F	L/h	9	34.1	4.95	14.5	33.7	14.4	31.3	27.3	41.3
	Cmax	ng/mL	10	14.33	7.2269	50.4	12.53	63.8	15.1	3.68	29.2
	t1/2	h	9	28.5	8.07	28.3	27.58	27	26.52	19.15	45.15
	tmax	h	10						0.52	0.52	0.53
	Vz/F	L	9	1391	402	28.9	1343	28.3	1208	882	2035

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Boxplots of PK parameters for Clonazepam in Saliva**Summary boxplot of auclast**

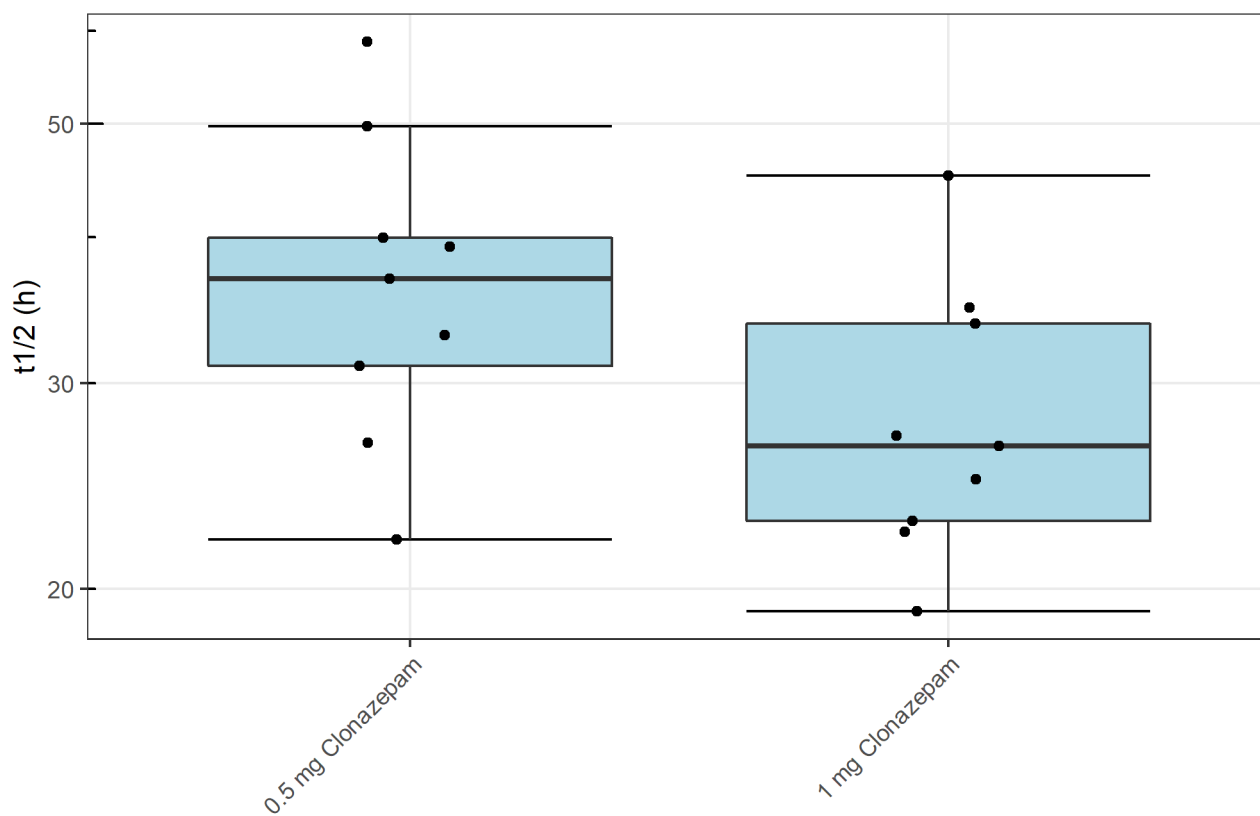
2022-10-05 14:49:01

Summary boxplot of cmax

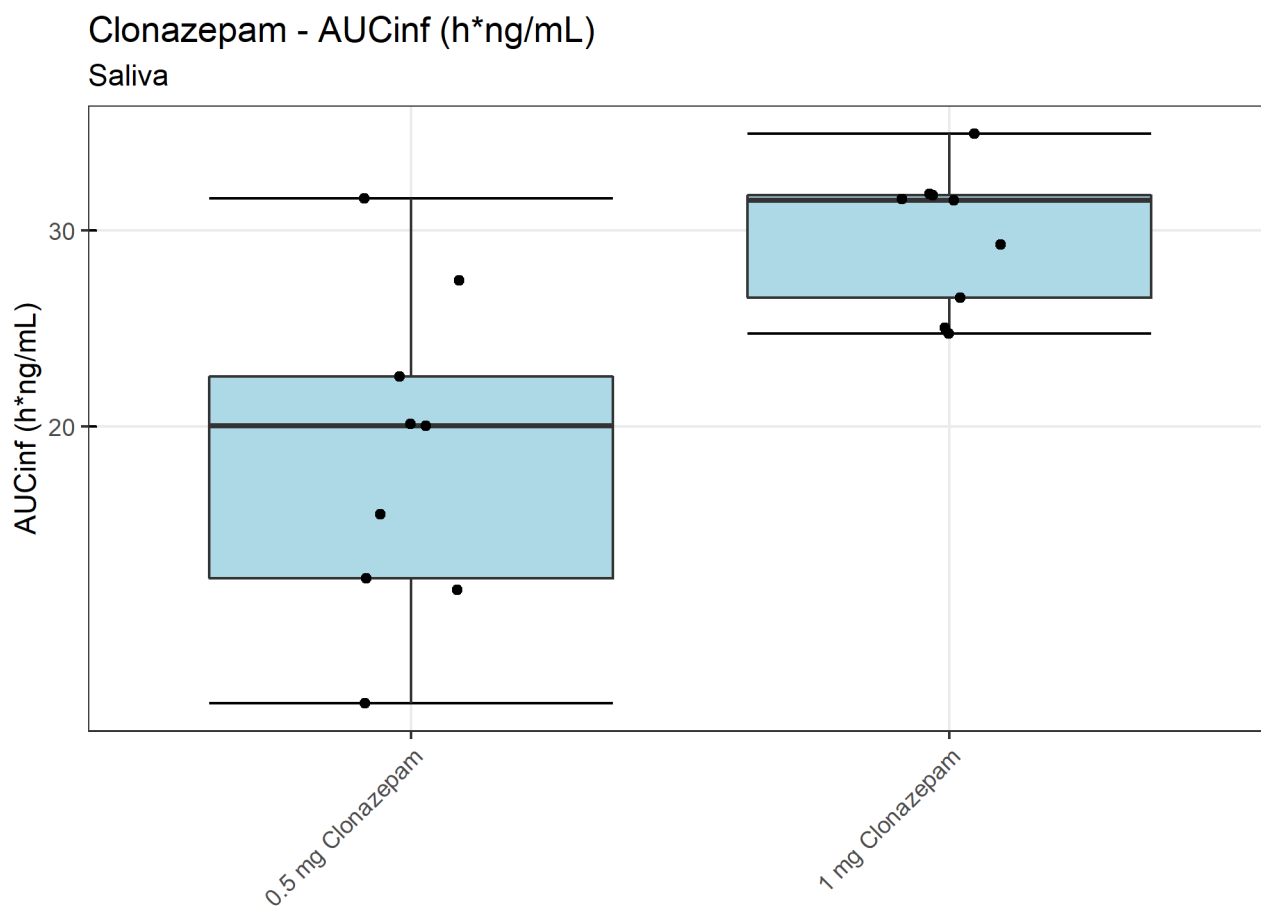
2022-10-05 14:49:02

Summary boxplot of half.lifeClonazepam - t_{1/2} (h)

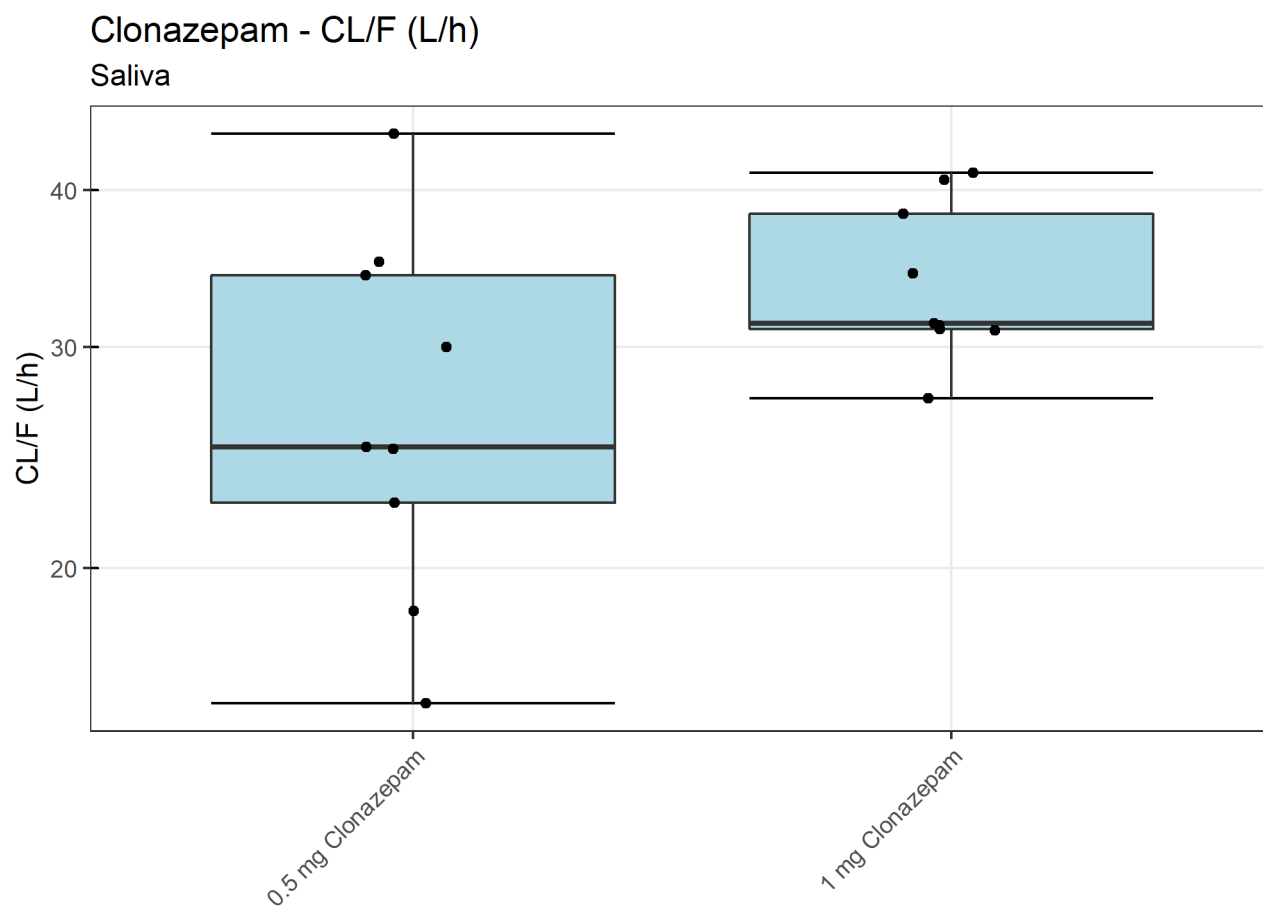
Saliva



2022-10-05 14:49:02

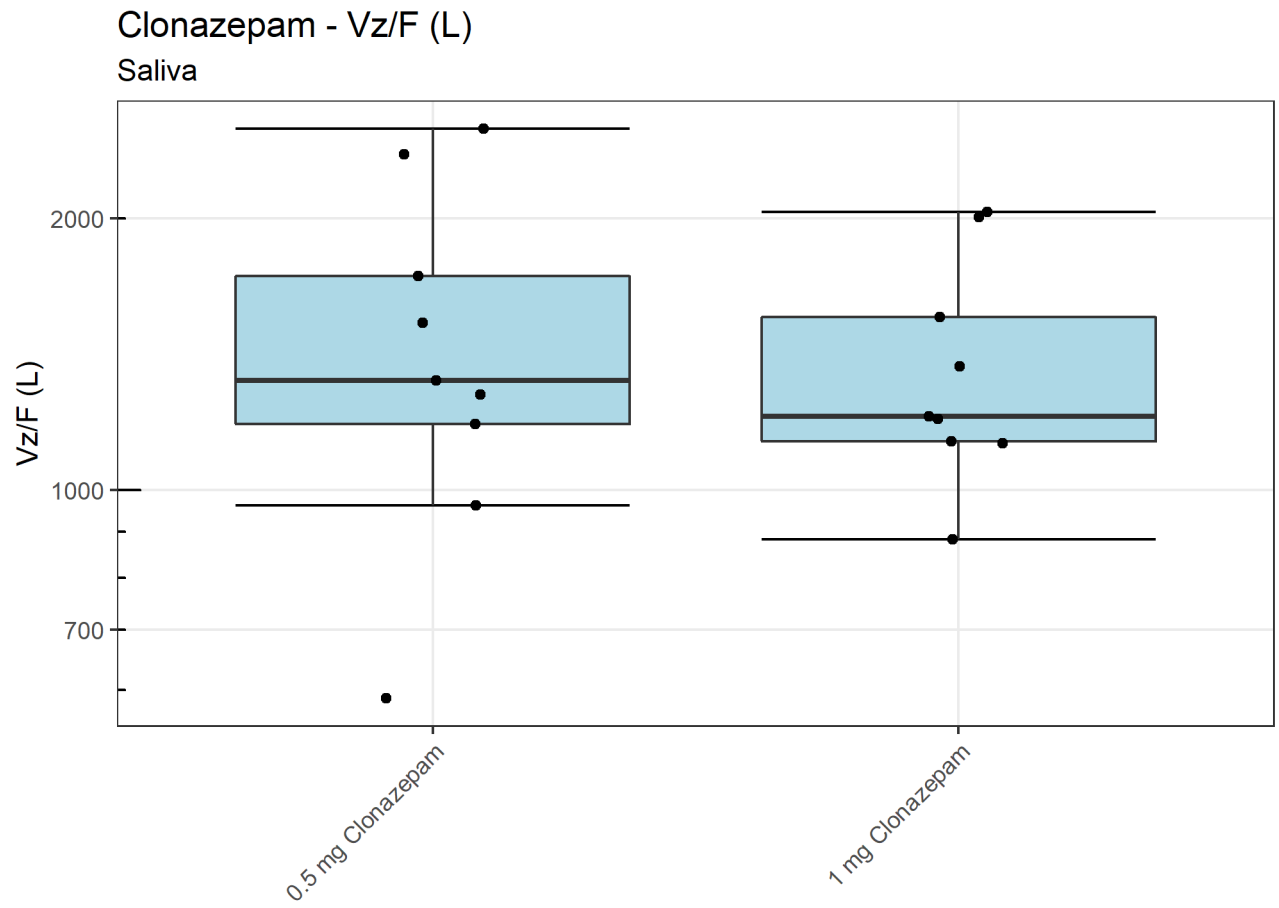
Summary boxplot of aucinf.obs

2022-10-05 14:49:03

Summary boxplot of cl.obs

2022-10-05 14:49:03

Summary boxplot of vz.obs



2022-10-05 14:49:03

Listing

Listing 1 Clonazepam concentration in Plasma

Clonazepam concentration in Plasma

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Plasma (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
101	0.5 mg Clonazepam	27JUL2020	08:24	0	0	L		
		27JUL2020	09:30	0.5	0.5	1.80		
		27JUL2020	10:00	1	1	2.41		
		27JUL2020	11:00	2	2	2.42		
		27JUL2020	13:00	4	4	2.48		
		27JUL2020	15:00	6	6	2.44		
		27JUL2020	17:00	8	8	2.33		
		28JUL2020	09:04	24	24.07	2.31		
		29JUL2020	09:43	48	48.72	1.40		
102	0.5 mg Clonazepam	27JUL2020	08:54	0	0	L		
		27JUL2020	09:37	0.5	0.5	4.38		
		27JUL2020	10:07	1	1	3.48		
		27JUL2020	11:07	2	2	2.91		
		27JUL2020	13:07	4	4	2.49		
		27JUL2020	15:07	6	6	2.48		
		27JUL2020	17:07	8	8	2.22		
		28JUL2020	09:15	24	24.13	2.06		
		29JUL2020	09:33	48	48.43	1.35		
103	0.5 mg Clonazepam	27JUL2020	08:27	0	0	L		
		27JUL2020	09:44	0.5	0.5	2.55		
		27JUL2020	10:14	1	1	3.30		
		27JUL2020	11:14	2	2	3.25		
		27JUL2020	13:14	4	4	2.89		
		27JUL2020	15:14	6	6	2.59		
		27JUL2020	17:14	8	8	2.53		
		28JUL2020	09:13	24	23.98	2.41		
		29JUL2020	08:59	48	47.75	1.63		
104	0.5 mg Clonazepam	27JUL2020	08:28	0	0	L		
		27JUL2020	09:51	0.5	0.5	1.64		
		27JUL2020	10:21	1	1	2.39		
		27JUL2020	11:21	2	2	3.00		
		27JUL2020	13:21	4	4	2.32		
		27JUL2020	15:21	6	6	2.28		
		27JUL2020	17:21	8	8	2.08		
		28JUL2020	09:00	24	23.65	1.97		
		29JUL2020	09:10	48	47.82	1.59		

L=Below limit of Quantification (0.01ng/mL), M=Missing
 R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing

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Clonazepam concentration in Plasma

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Plasma (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
105	0.5 mg Clonazepam	27JUL2020	08:45	0	0	L		
		27JUL2020	09:58	0.5	0.5	1.59		
		27JUL2020	10:28	1	1	2.10		
		27JUL2020	11:28	2	2	2.14		
		27JUL2020	13:28	4	4	1.89		
		27JUL2020	15:28	6	6	1.74		
		27JUL2020	17:28	8	8	1.69		
		28JUL2020	09:08	24	23.67	1.51		
		29JUL2020	09:25	48	47.95	1.25		
106	1 mg Clonazepam	01AUG2020	08:38	48	47.72	1.88		
		30JUL2020	08:42	0	0	L		
		30JUL2020	09:25	0.5	0.5	3.16		
		30JUL2020	09:55	1	1	4.00		
		30JUL2020	10:55	2	2	4.05		
		30JUL2020	12:55	4	4	3.71		
		30JUL2020	14:55	6	6	3.18		
		30JUL2020	16:55	8	8	3.23		
		31JUL2020	08:53	24	23.97	2.56		
107	1 mg Clonazepam	01AUG2020	08:56	48	47.9	2.02		
		30JUL2020	08:33	0	0	L		
		30JUL2020	09:32	0.5	0.5	4.46		
		30JUL2020	10:02	1	1	4.28		
		30JUL2020	11:02	2	2	4.52		
		30JUL2020	13:02	4	4	3.29		
		30JUL2020	15:02	6	6	3.58		
		30JUL2020	17:02	8	8	3.45		
		31JUL2020	08:51	24	23.82	2.61		
108	1 mg Clonazepam	01AUG2020	09:01	48	47.87	2.42		
		30JUL2020	08:42	0	0	L		
		30JUL2020	09:39	0.5	0.5	2.79		
		30JUL2020	10:09	1	1	4.33		
		30JUL2020	11:09	2	2	6.02		
		30JUL2020	13:09	4	4	4.56		
		30JUL2020	15:09	6	6	3.81		
		30JUL2020	17:09	8	8	3.52		
		31JUL2020	09:03	24	23.9	3.45		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
Page 2 of 5 (Created on 2022-10-05 14:49:05 by dvasten)								

Clonazepam concentration in Plasma

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Plasma (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
109	1 mg Clonazepam	01AUG2020	09:15	48	47.98	1.63		
		30JUL2020	08:47	0	0	L		
		30JUL2020	09:46	0.5	0.5	2.91		
		30JUL2020	10:16	1	1	2.94		
		30JUL2020	11:16	2	2	3.30		
		30JUL2020	13:16	4	4	2.53		
		30JUL2020	15:16	6	6	2.74		
		30JUL2020	17:16	8	8	2.74		
		31JUL2020	09:08	24	23.87	2.18		
110	1 mg Clonazepam	01AUG2020	09:18	48	47.92	1.61		
		30JUL2020	08:48	0	0	L		
		30JUL2020	09:53	0.5	0.5	6.79		
		30JUL2020	10:23	1	1	5.01		
		30JUL2020	11:25	2	2.03	3.51		
		30JUL2020	13:23	4	4	3.22		
		30JUL2020	15:23	6	6	3.06		
		30JUL2020	17:23	8	8	2.84		
		31JUL2020	09:12	24	23.82	2.26		
111	0.5 mg Clonazepam	18AUG2020	08:50	0	0	L		
		18AUG2020	09:30	0.5	0.5	1.52		
		18AUG2020	10:00	1	1	1.83		
		18AUG2020	11:00	2	2	2.02		
		18AUG2020	13:00	4	4	1.87		
		18AUG2020	15:00	6	6	1.69		
		18AUG2020	17:00	8	8	1.66		
		19AUG2020	08:55	24	23.92	1.43		
		20AUG2020	09:00	48	48	1.07		
112	0.5 mg Clonazepam	18AUG2020	08:57	0	0	L		
		18AUG2020	09:37	0.5	0.5	2.19		
		18AUG2020	10:07	1	1	2.46		
		18AUG2020	11:07	2	2	2.36		
		18AUG2020	13:07	4	4	2.29		
		18AUG2020	15:07	6	6	2.28		
		18AUG2020	17:07	8	8	2.30		
		19AUG2020	08:51	24	23.73	1.86		
		20AUG2020	08:30	48	47.38	1.52		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
Page 3 of 5 (Created on 2022-10-05 14:49:06 by dvasten)								

Clonazepam concentration in Plasma

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Plasma (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
113	0.5 mg Clonazepam	18AUG2020	09:04	0	0	L		
		18AUG2020	09:45	0.5	0.5	2.79		
		18AUG2020	10:15	1	1	3.19		
		18AUG2020	11:15	2	2	3.16		
		18AUG2020	13:16	4	4.02	2.42		
		18AUG2020	15:15	6	6	2.19		
		18AUG2020	17:15	8	8	2.16		
		19AUG2020	09:04	24	23.82	1.73		
		20AUG2020	08:59	48	47.73	1.44		
114	0.5 mg Clonazepam	18AUG2020	09:11	0	0	L		
		18AUG2020	09:51	0.5	0.5	4.60		
		18AUG2020	10:22	1	1.02	3.49		
		18AUG2020	11:22	2	2.02	3.44		
		18AUG2020	13:21	4	4	3.15		
		18AUG2020	15:21	6	6	2.57		
		18AUG2020	17:21	8	8	2.25		
		19AUG2020	09:20	24	23.98	2.12		
		20AUG2020	08:43	48	47.37	1.51		
115	0.5 mg Clonazepam	18AUG2020	08:37	0	0	L		
		18AUG2020	09:58	0.5	0.5	1.06		
		18AUG2020	10:28	1	1	1.58		
		18AUG2020	11:28	2	2	2.44		
		18AUG2020	13:28	4	4	2.83		
		18AUG2020	15:28	6	6	2.44		
		18AUG2020	17:28	8	8	2.24		
		19AUG2020	09:06	24	23.63	1.87		
		20AUG2020	08:41	48	47.22	1.37		
116	1 mg Clonazepam	21AUG2020	08:29	0	0	L		
		21AUG2020	09:30	0.5	0.5	7.01		
		21AUG2020	10:00	1	1	5.56		
		21AUG2020	11:00	2	2	5.25		
		21AUG2020	13:00	4	4	4.50		
		21AUG2020	15:00	6	6	4.62		
		21AUG2020	17:00	8	8	4.04		
		22AUG2020	08:31	24	23.52	3.57		
		23AUG2020	09:13	48	48.22	2.32		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Clonazepam concentration in Plasma

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Plasma (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
117	1 mg Clonazepam	21AUG2020	08:20	0	0	L		
		21AUG2020	09:37	0.5	0.5	3.96		
		21AUG2020	10:07	1	1	6.07		
		21AUG2020	11:07	2	2	6.44		
		21AUG2020	13:07	4	4	4.00		
		21AUG2020	15:07	6	6	3.59		
		21AUG2020	17:07	8	8	3.69		
		22AUG2020	08:35	24	23.47	3.57		
		23AUG2020	09:04	48	47.95	2.27		
118	1 mg Clonazepam	21AUG2020	08:50	0	0	L		
		21AUG2020	09:44	0.5	0.5	1.73		
		21AUG2020	10:14	1	1	3.42		
		21AUG2020	11:14	2	2	4.47		
		21AUG2020	13:14	4	4	4.61		
		21AUG2020	15:21	6	6.12	4.68		
		21AUG2020	17:14	8	8	3.87		
		22AUG2020	08:38	24	23.4	2.68		
		23AUG2020	08:41	48	47.45	1.84		
119	1 mg Clonazepam	21AUG2020	09:03	0	0	L		
		21AUG2020	09:51	0.5	0.5	6.21		
		21AUG2020	10:21	1	1	4.97		
		21AUG2020	11:21	2	2	3.98		
		21AUG2020	13:21	4	4	3.52		
		21AUG2020	15:14	6	5.88	2.90		
		21AUG2020	17:21	8	8	3.10		
		22AUG2020	08:52	24	23.52	2.31		
		23AUG2020	09:44	48	48.38	1.84		
120	1 mg Clonazepam	21AUG2020	08:25	0	0	L		
		21AUG2020	09:58	0.5	0.5	3.34		
		21AUG2020	10:28	1	1	5.72		
		21AUG2020	11:28	2	2	5.87		
		21AUG2020	13:29	4	4.02	4.16		
		21AUG2020	15:28	6	6	3.53		
		21AUG2020	17:28	8	8	3.31		
		22AUG2020	08:26	24	22.97	2.66		
		23AUG2020	08:45	48	47.28	2.01		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Listing 2 Clonazepam concentration in Saliva

Clonazepam concentration in Saliva

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
101	0.5 mg Clonazepam	27JUL2020	08:32	0	0	L		Not enough material for sample
		27JUL2020	09:31	0.52	0.52	22.6		
		27JUL2020	10:06	1.02	1.1	7.18		
		27JUL2020	11:01	2.02	2.02	1.45		
		27JUL2020	13:01	4.02	4.02	0.370		
		27JUL2020	15:01	6.02	6.02	0.260		
		27JUL2020	17:01	8.02	8.02	0.250		
		28JUL2020	09:05	24.02	24.08	0.120		
		29JUL2020	09:43	48.02	48.72	0.0700		
102	0.5 mg Clonazepam	27JUL2020	08:52	0	0	L		
		27JUL2020	09:39	0.52	0.53	11.6		
		27JUL2020	10:09	1.02	1.03	2.86		
		27JUL2020	11:10	2.02	2.05	1.01		
		27JUL2020	13:08	4.02	4.02	0.510		
		27JUL2020	15:08	6.02	6.02	0.270		
		27JUL2020	17:08	8.02	8.02	0.250		
		28JUL2020	09:16	24.02	24.15	0.140		
		29JUL2020	09:35	48.02	48.47	0.0900		
103	0.5 mg Clonazepam	27JUL2020	08:31	0	0	L		
		27JUL2020	09:45	0.52	0.52	6.48		
		27JUL2020	10:15	1.02	1.02	2.95		
		27JUL2020	11:15	2.02	2.02	0.960		
		27JUL2020	13:15	4.02	4.02	0.310		
		27JUL2020	15:15	6.02	6.02	0.280		
		27JUL2020	17:15	8.02	8.02	0.240		
		28JUL2020	09:13	24.02	23.98	0.190		
		29JUL2020	09:01	48.02	47.78	0.110		
104	0.5 mg Clonazepam	27JUL2020	08:30	0	0	L		
		27JUL2020	09:52	0.52	0.52	7.86		
		27JUL2020	10:23	1.02	1.03	2.30		
		27JUL2020	11:22	2.02	2.02	0.650		
		27JUL2020	13:22	4.02	4.02	0.390		
		27JUL2020	15:22	6.02	6.02	0.160		
		27JUL2020	17:22	8.02	8.02	0.160		
		28JUL2020	09:00	24.02	23.65	0.120		
		29JUL2020	09:11	48.02	47.83	0.0800		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Clonazepam concentration in Saliva

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
105	0.5 mg Clonazepam	27JUL2020	08:46	0	0	L		
		27JUL2020	09:59	0.52	0.52	4.50		
		27JUL2020	10:29	1.02	1.02	1.28		
		27JUL2020	11:29	2.02	2.02	0.370		
		27JUL2020	13:29	4.02	4.02	0.190		
		27JUL2020	15:29	6.02	6.02	0.120		
		27JUL2020	17:29	8.02	8.02	0.140		
		28JUL2020	09:10	24.02	23.7	0.110		
106	1 mg Clonazepam	01AUG2020	08:39	48.02	47.73	M		Not enough material for sample
		30JUL2020	08:44	0	0	L		
		30JUL2020	09:26	0.52	0.52	18.7		
		30JUL2020	09:56	1.02	1.02	4.26		
		30JUL2020	10:56	2.02	2.02	M		Not enough material for sample
		30JUL2020	12:56	4.02	4.02	0.340		
		30JUL2020	14:56	6.02	6.02	0.320		
		30JUL2020	16:56	8.02	8.02	0.270		
107	1 mg Clonazepam	01AUG2020	08:56	48.02	47.9	0.150		
		30JUL2020	08:35	0	0	L		
		30JUL2020	09:33	0.52	0.52	13.8		
		30JUL2020	10:03	1.02	1.02	4.02		
		30JUL2020	11:04	2.02	2.03	1.53		
		30JUL2020	13:03	4.02	4.02	0.620		
		30JUL2020	15:03	6.02	6.02	0.410		
		30JUL2020	17:03	8.02	8.02	0.510		
108	1 mg Clonazepam	01AUG2020	09:01	48.02	47.87	0.220		
		30JUL2020	08:50	0	0	L		
		30JUL2020	09:40	0.52	0.52	3.68		
		30JUL2020	10:10	1.02	1.02	1.58		
		30JUL2020	11:10	2.02	2.02	1.02		
		30JUL2020	13:10	4.02	4.02	0.560		
		30JUL2020	15:10	6.02	6.02	0.410		
		30JUL2020	17:10	8.02	8.02	0.400		
		31JUL2020	09:04	24.02	23.92	0.260		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Clonazepam concentration in Saliva

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
109	1 mg Clonazepam	01AUG2020	09:16	48.02	48	0.0800		
		30JUL2020	08:48	0	0	L		
		30JUL2020	09:47	0.52	0.52	16.3		
		30JUL2020	10:17	1.02	1.02	4.17		
		30JUL2020	11:17	2.02	2.02	1.53		
		30JUL2020	13:17	4.02	4.02	0.700		
		30JUL2020	15:17	6.02	6.02	0.430		
		30JUL2020	17:33	8.02	8.28	0.340		
		31JUL2020	09:10	24.02	23.9	0.180		
110	1 mg Clonazepam	01AUG2020	09:19	48.02	47.93	0.140		
		30JUL2020	08:50	0	0	L		
		30JUL2020	09:54	0.52	0.52	29.2		
		30JUL2020	10:24	1.02	1.02	7.01		
		30JUL2020	11:25	2.02	2.03	1.91		
		30JUL2020	13:24	4.02	4.02	0.560		
		30JUL2020	15:24	6.02	6.02	0.470		
		30JUL2020	17:24	8.02	8.02	0.410		
		31JUL2020	09:13	24.02	23.83	0.200		
111	0.5 mg Clonazepam	18AUG2020	08:51	0	0	L		
		18AUG2020	09:31	0.52	0.52	10.6		
		18AUG2020	10:01	1.02	1.02	2.72		
		18AUG2020	11:01	2.02	2.02	0.410		
		18AUG2020	13:01	4.02	4.02	0.180		
		18AUG2020	15:01	6.02	6.02	0.150		
		18AUG2020	17:01	8.02	8.02	0.150		
		19AUG2020	08:56	24.02	23.93	0.100		
		20AUG2020	09:05	48.02	48.08	0.0600		
112	0.5 mg Clonazepam	18AUG2020	08:58	0	0	L		
		18AUG2020	09:38	0.52	0.52	M		Not enough material for sample
		18AUG2020	10:08	1.02	1.02	M		Not enough material for sample
		18AUG2020	11:08	2.02	2.02	M		Not enough material for sample
		18AUG2020	13:08	4.02	4.02	0.270		
		18AUG2020	15:08	6.02	6.02	0.230		
		18AUG2020	17:08	8.02	8.02	0.230		
		19AUG2020	08:52	24.02	23.75	0.100		
		20AUG2020	08:39	48.02	47.53	0.0900		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Clonazepam concentration in Saliva

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
113	0.5 mg Clonazepam	18AUG2020	09:05	0	0	L		
		18AUG2020	09:46	0.52	0.52	2.83		
		18AUG2020	10:16	1.02	1.02	1.16		
		18AUG2020	11:16	2.02	2.02	0.300		
		18AUG2020	13:16	4.02	4.02	0.160		
		18AUG2020	15:16	6.02	6.02	0.270		
		18AUG2020	17:16	8.02	8.02	0.150		
		19AUG2020	09:06	24.02	23.85	0.100		
		20AUG2020	09:03	48.02	47.8	0.0700		
114	0.5 mg Clonazepam	18AUG2020	09:12	0	0	L		
		18AUG2020	09:52	0.52	0.52	5.22		
		18AUG2020	10:22	1.02	1.02	1.34		
		18AUG2020	11:22	2.02	2.02	0.750		
		18AUG2020	13:22	4.02	4.02	0.380		
		18AUG2020	15:22	6.02	6.02	0.280		
		18AUG2020	17:22	8.02	8.02	0.280		
		19AUG2020	09:21	24.02	24	0.220		
		20AUG2020	08:52	48.02	47.52	0.140		
115	0.5 mg Clonazepam	18AUG2020	08:38	0	0	L		
		18AUG2020	09:59	0.52	0.52	15.3		
		18AUG2020	10:46	1.02	1.3	2.93	R	More than 10% time deviation
		18AUG2020	11:29	2.02	2.02	0.580		
		18AUG2020	13:29	4.02	4.02	0.300		
		18AUG2020	15:29	6.02	6.02	0.330		
		18AUG2020	17:29	8.02	8.02	0.220		
		19AUG2020	09:08	24.02	23.67	0.200		
		20AUG2020	08:44	48.02	47.27	0.140		
116	1 mg Clonazepam	21AUG2020	08:30	0	0	L		
		21AUG2020	09:31	0.52	0.52	17.9		
		21AUG2020	10:01	1.02	1.02	5.88		
		21AUG2020	11:01	2.02	2.02	1.55		
		21AUG2020	13:01	4.02	4.02	0.520		
		21AUG2020	15:01	6.02	6.02	0.440		
		21AUG2020	17:01	8.02	8.02	0.390		
		22AUG2020	08:35	24.02	23.58	0.200		
		23AUG2020	09:14	48.02	48.23	0.160		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Clonazepam concentration in Saliva

Subject	Treatment	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
				Protocol Time	Actual Time			
117	1 mg Clonazepam	21AUG2020	08:34	0	0	L		
		21AUG2020	09:38	0.52	0.52	7.85		
		21AUG2020	10:08	1.02	1.02	2.47		
		21AUG2020	11:08	2.02	2.02	0.830		
		21AUG2020	13:08	4.02	4.02	0.530		
		21AUG2020	15:08	6.02	6.02	0.330		
		21AUG2020	17:08	8.02	8.02	0.320		
		22AUG2020	08:42	24.02	23.58	M		Not enough material for sample
118	1 mg Clonazepam	23AUG2020	09:05	48.02	47.97	0.140		
		21AUG2020	08:52	0	0	L		
		21AUG2020	09:45	0.52	0.52	17.2		
		21AUG2020	10:15	1.02	1.02	4.76		
		21AUG2020	11:15	2.02	2.02	1.42		
		21AUG2020	13:15	4.02	4.02	0.650		
		21AUG2020	15:22	6.02	6.13	0.450		
		21AUG2020	17:15	8.02	8.02	0.440		
119	1 mg Clonazepam	22AUG2020	08:41	24.02	23.45	0.250		
		23AUG2020	08:42	48.02	47.47	0.160		
		21AUG2020	09:06	0	0	L		
		21AUG2020	09:53	0.52	0.53	9.03		
		21AUG2020	10:22	1.02	1.02	3.43		
		21AUG2020	11:22	2.02	2.02	0.630		
		21AUG2020	13:22	4.02	4.02	0.290		
		21AUG2020	15:15	6.02	5.9	0.270		
120	1 mg Clonazepam	21AUG2020	17:22	8.02	8.02	0.180		
		22AUG2020	08:53	24.02	23.53	0.210		
		23AUG2020	09:45	48.02	48.4	0.190		
		21AUG2020	08:30	0	0	L		
		21AUG2020	09:59	0.52	0.52	9.64		
		21AUG2020	10:29	1.02	1.02	4.61		
		21AUG2020	11:29	2.02	2.02	1.19		
		21AUG2020	13:30	4.02	4.03	0.660		
		21AUG2020	15:29	6.02	6.02	0.430		
		21AUG2020	17:30	8.02	8.03	0.410		
		22AUG2020	08:31	24.02	23.05	0.270		
		23AUG2020	08:46	48.02	47.3	0.190		
L=Below limit of Quantification (0.01ng/mL), M=Missing								
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing								
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Listing 3 PK parameters for Clonazepam in Plasma

PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
101	0.5 mg Clonazepam	Adjusted R squared		0.810		
		AUC extrapolated	%	52.9		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	213		AUC percent extrapolated > 20
		AUClast	h*ng/mL	101		
		CL/F	L/h	2.34		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.40		
		Clast predicted	ng/mL	1.48		
		Cmax	ng/mL	2.48		
		Lambda_z	1/h	0.0124		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.874		
		Span-ratio		0.764		
		t1/2	h	55.89		
		tlast	h	48.72		
		tmax	h	4		
		Vz/F	L	189		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
102	0.5 mg Clonazepam	Adjusted R squared		0.944		
		AUC extrapolated	%	51.5		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	199		AUC percent extrapolated > 20
		AUClast	h*ng/mL	96.6		
		CL/F	L/h	2.51		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.35		
		Clast predicted	ng/mL	1.39		
		Cmax	ng/mL	4.38		
		Lambda_z	1/h	0.0132		
		Lambda_z first time point	h	4		
		Lambda_z number of time points		5		
		R squared		0.958		
		Span-ratio		0.845		
		t1/2	h	52.61		
		tlast	h	48.43		
		tmax	h	0.5		
		Vz/F	L	191		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
Page 2 of 21 (Created on 2022-10-05 14:49:20 by dvasten)						

PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
103	0.5 mg Clonazepam	Adjusted R squared		0.898		
		AUC extrapolated	%	56.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	252		AUC percent extrapolated > 20
		AUClast	h*ng/mL	109		
		CL/F	L/h	1.99		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.63		
		Clast predicted	ng/mL	1.68		
		Cmax	ng/mL	3.30		
		Lambda_z	1/h	0.0114		
		Lambda_z first time point	h	4		
		Lambda_z number of time points		5		
		R squared		0.924		
		Span-ratio		0.720		
		t1/2	h	60.73		
		tlast	h	47.75		
		tmax	h	1		
		Vz/F	L	174		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
104	0.5 mg Clonazepam	Adjusted R squared		0.939		
		AUC extrapolated	%	68		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	290		AUC percent extrapolated > 20
		AUClast	h*ng/mL	92.9		
		CL/F	L/h	1.72		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.59		
		Clast predicted	ng/mL	1.6		
		Cmax	ng/mL	3.00		
		Lambda_z	1/h	0.00805		
		Lambda_z first time point	h	4		
		Lambda_z number of time points		5		
		R squared		0.954		
		Span-ratio		0.509		
		t1/2	h	86.07		
		tlast	h	47.82		
		tmax	h	2		
		Vz/F	L	214		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
Page 4 of 21 (Created on 2022-10-05 14:49:22 by dvasten)						

PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
105	0.5 mg Clonazepam	Adjusted R squared		0.999		
		AUC extrapolated	%	69.4		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	238		AUC percent extrapolated > 20
		AUClast	h*ng/mL	73		
		CL/F	L/h	2.1		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.25		
		Clast predicted	ng/mL	1.25		
		Cmax	ng/mL	2.14		
		Lambda_z	1/h	0.00757		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		1.00		
		Span-ratio		0.436		
		t1/2	h	91.58		
		tlast	h	47.95		
		tmax	h	2		
		Vz/F	L	277		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
Page 5 of 21 (Created on 2022-10-05 14:49:23 by dvasten)						

PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
106	1 mg Clonazepam	Adjusted R squared		0.998		
		AUC extrapolated	%	52.4		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	264		AUC percent extrapolated > 20
		AUClast	h*ng/mL	126		
		CL/F	L/h	3.78		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.88		
		Clast predicted	ng/mL	1.87		
		Cmax	ng/mL	4.05		
		Lambda_z	1/h	0.0136		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		0.999		
		Span-ratio		0.778		
		t1/2	h	51.05		
		tlast	h	47.72		
		tmax	h	2		
		Vz/F	L	279		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
107	1 mg Clonazepam	Adjusted R squared		0.974		
		AUC extrapolated	%	52.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	280		AUC percent extrapolated > 20
		AUClast	h*ng/mL	132		
		CL/F	L/h	3.57		AUC percent extrapolated > 20
		Clast observed	ng/mL	2.02		
		Clast predicted	ng/mL	1.98		
		Cmax	ng/mL	4.52		
		Lambda_z	1/h	0.0137		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.983		
		Span-ratio		0.828		
		t1/2	h	50.61		
		tlast	h	47.9		
		tmax	h	2		
		Vz/F	L	261		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
108	1 mg Clonazepam	Adjusted R squared		0.864		
		AUC extrapolated	%	60.5		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	402		AUC percent extrapolated > 20
		AUClast	h*ng/mL	159		
		CL/F	L/h	2.49		AUC percent extrapolated > 20
		Clast observed	ng/mL	2.42		
		Clast predicted	ng/mL	2.5		
		Cmax	ng/mL	6.02		
		Lambda_z	1/h	0.00994		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.910		
		Span-ratio		0.601		
		t1/2	h	69.7		
		tlast	h	47.87		
		tmax	h	2		
		Vz/F	L	250		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
109	1 mg Clonazepam	Adjusted R squared		0.996		
		AUC extrapolated	%	54.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	235		AUC percent extrapolated > 20
		AUClast	h*ng/mL	106		
		CL/F	L/h	4.26		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.63		
		Clast predicted	ng/mL	1.62		
		Cmax	ng/mL	3.30		
		Lambda_z	1/h	0.0127		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.997		
		Span-ratio		0.768		
		t1/2	h	54.65		
		tlast	h	47.98		
		tmax	h	2		
		Vz/F	L	336		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
110	1 mg Clonazepam	Adjusted R squared		1.00		
		AUC extrapolated	%	49.8		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	227		AUC percent extrapolated > 20
		AUClast	h*ng/mL	114		
		CL/F	L/h	4.4		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.61		
		Clast predicted	ng/mL	1.61		
		Cmax	ng/mL	6.79		
		Lambda_z	1/h	0.0142		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		1.00		
		Span-ratio		0.818		
		t1/2	h	48.79		
		tlast	h	47.92		
		tmax	h	0.5		
		Vz/F	L	309		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
111	0.5 mg Clonazepam	Adjusted R squared		0.994		
		AUC extrapolated	%	59		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	167		AUC percent extrapolated > 20
		AUClast	h*ng/mL	68.4		
		CL/F	L/h	3		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.07		
		Clast predicted	ng/mL	1.08		
		Cmax	ng/mL	2.02		
		Lambda_z	1/h	0.0109		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.996		
		Span-ratio		0.659		
		t1/2	h	63.78		
		tlast	h	48		
		tmax	h	2		
		Vz/F	L	276		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
112	0.5 mg Clonazepam	Adjusted R squared		0.985		
		AUC extrapolated	%	62.8		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	243		AUC percent extrapolated > 20
		AUClast	h*ng/mL	90.3		
		CL/F	L/h	2.06		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.52		
		Clast predicted	ng/mL	1.51		
		Cmax	ng/mL	2.46		
		Lambda_z	1/h	0.00995		
		Lambda_z first time point	h	2		
		Lambda_z number of time points		6		
		R squared		0.988		
		Span-ratio		0.651		
		t1/2	h	69.7		
		tlast	h	47.38		
		tmax	h	1		
		Vz/F	L	207		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
113	0.5 mg Clonazepam	Adjusted R squared		0.968		
		AUC extrapolated	%	61.4		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	229		AUC percent extrapolated > 20
		AUClast	h*ng/mL	88.3		
		CL/F	L/h	2.18		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.44		
		Clast predicted	ng/mL	1.41		
		Cmax	ng/mL	3.19		
		Lambda_z	1/h	0.0102		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.978		
		Span-ratio		0.617		
		t1/2	h	67.65		
		tlast	h	47.73		
		tmax	h	1		
		Vz/F	L	213		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
114	0.5 mg Clonazepam	Adjusted R squared		0.906		
		AUC extrapolated	%	56.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	232		AUC percent extrapolated > 20
		AUClast	h*ng/mL	101		
		CL/F	L/h	2.15		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.51		
		Clast predicted	ng/mL	1.54		
		Cmax	ng/mL	4.60		
		Lambda_z	1/h	0.0115		
		Lambda_z first time point	h	6		
		Lambda_z number of time points		4		
		R squared		0.937		
		Span-ratio		0.684		
		t1/2	h	60.49		
		tlast	h	47.37		
		tmax	h	0.5		
		Vz/F	L	188		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
115	0.5 mg Clonazepam	Adjusted R squared		0.997		
		AUC extrapolated	%	55.3		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	197		AUC percent extrapolated > 20
		AUClast	h*ng/mL	88.1		
		CL/F	L/h	2.54		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.37		
		Clast predicted	ng/mL	1.38		
		Cmax	ng/mL	2.83		
		Lambda_z	1/h	0.0126		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		0.999		
		Span-ratio		0.712		
		t1/2	h	55.06		
		tlast	h	47.22		
		tmax	h	4		
		Vz/F	L	202		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
116	1 mg Clonazepam	Adjusted R squared		0.965		
		AUC extrapolated	%	48.1		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	324		AUC percent extrapolated > 20
		AUClast	h*ng/mL	168		
		CL/F	L/h	3.08		AUC percent extrapolated > 20
		Clast observed	ng/mL	2.32		
		Clast predicted	ng/mL	2.36		
		Cmax	ng/mL	7.01		
		Lambda_z	1/h	0.0149		
		Lambda_z first time point	h	4		
		Lambda_z number of time points		5		
		R squared		0.974		
		Span-ratio		0.949		
		t1/2	h	46.59		
		tlast	h	48.22		
		tmax	h	0.5		
		Vz/F	L	207		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
117	1 mg Clonazepam	Adjusted R squared		0.845		
		AUC extrapolated	%	55.2		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	360		AUC percent extrapolated > 20
		AUClast	h*ng/mL	161		
		CL/F	L/h	2.77		AUC percent extrapolated > 20
		Clast observed	ng/mL	2.27		
		Clast predicted	ng/mL	2.39		
		Cmax	ng/mL	6.44		
		Lambda_z	1/h	0.0114		
		Lambda_z first time point	h	4		
		Lambda_z number of time points		5		
		R squared		0.884		
		Span-ratio		0.723		
		t1/2	h	60.79		
		tlast	h	47.95		
		tmax	h	2		
		Vz/F	L	243		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
118	1 mg Clonazepam	Adjusted R squared		0.972		
		AUC extrapolated	%	42.1		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	235		AUC percent extrapolated > 20
		AUClast	h*ng/mL	136		
		CL/F	L/h	4.25		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.84		
		Clast predicted	ng/mL	1.8		
		Cmax	ng/mL	4.68		
		Lambda_z	1/h	0.0186		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		0.986		
		Span-ratio		1.06		
		t1/2	h	37.34		
		tlast	h	47.45		
		tmax	h	6.12		
		Vz/F	L	229		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
119	1 mg Clonazepam	Adjusted R squared		0.934		
		AUC extrapolated	%	56.1		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	277		AUC percent extrapolated > 20
		AUClast	h*ng/mL	122		
		CL/F	L/h	3.6		AUC percent extrapolated > 20
		Clast observed	ng/mL	1.84		
		Clast predicted	ng/mL	1.81		
		Cmax	ng/mL	6.21		
		Lambda_z	1/h	0.0118		
		Lambda_z first time point	h	5.88		
		Lambda_z number of time points		4		
		R squared		0.956		
		Span-ratio		0.725		
		t1/2	h	58.66		
		tlast	h	48.38		
		tmax	h	0.5		
		Vz/F	L	305		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
120	1 mg Clonazepam	Adjusted R squared		0.991		
		AUC extrapolated	%	54.3		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	294		AUC percent extrapolated > 20
		AUClast	h*ng/mL	134		
		CL/F	L/h	3.4		AUC percent extrapolated > 20
		Clast observed	ng/mL	2.01		
		Clast predicted	ng/mL	2		
		Cmax	ng/mL	5.87		
		Lambda_z	1/h	0.0126		
		Lambda_z first time point	h	8		
		Lambda_z number of time points		3		
		R squared		0.996		
		Span-ratio		0.713		
		t1/2	h	55.07		
		tlast	h	47.28		
		tmax	h	2		
		Vz/F	L	270		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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Listing 4 PK parameters for Clonazepam in Saliva

PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
101	0.5 mg Clonazepam	Adjusted R squared		0.952		
		AUC extrapolated	%	8.23		
		AUCinf	h*ng/mL	27.1		
		AUClast	h*ng/mL	24.8		
		CL/F	L/h	18.5		
		Clast observed	ng/mL	0.0700		
		Clast predicted	ng/mL	0.0654		
		Cmax	ng/mL	22.6		
		Lambda_z	1/h	0.0314		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.968		
		Span-ratio		1.94		
		t1/2	h	22.05		
		tlast	h	48.72		
		tmax	h	0.52		
		Vz/F	L	588		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
102	0.5 mg Clonazepam	Adjusted R squared		0.954		
		AUC extrapolated	%	17.3		
		AUCinf	h*ng/mL	20		
		AUClast	h*ng/mL	16.6		
		CL/F	L/h	25		
		Clast observed	ng/mL	0.0900		
		Clast predicted	ng/mL	0.0851		
		Cmax	ng/mL	11.6		
		Lambda_z	1/h	0.0260		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.970		
		Span-ratio		1.59		
		t1/2	h	26.67		
		tlast	h	48.47		
		tmax	h	0.53		
		Vz/F	L	961		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
103	0.5 mg Clonazepam	Adjusted R squared		0.976		
		AUC extrapolated	%	26		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	20.1		AUC percent extrapolated > 20
		AUClast	h*ng/mL	14.9		
		CL/F	L/h	24.9		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.110		
		Clast predicted	ng/mL	0.111		
		Cmax	ng/mL	6.48		
		Lambda_z	1/h	0.0210		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.984		
		Span-ratio		1.27		
		t1/2	h	32.96		
		tlast	h	47.78		
		tmax	h	0.52		
		Vz/F	L	1184		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
104	0.5 mg Clonazepam	Adjusted R squared		0.999		
		AUC extrapolated	%	27.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	16.7		AUC percent extrapolated > 20
		AUClast	h*ng/mL	12.1		
		CL/F	L/h	30		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.0800		
		Clast predicted	ng/mL	0.0797		
		Cmax	ng/mL	7.86		
		Lambda_z	1/h	0.0174		
		Lambda_z first time point	h	8.02		
		Lambda_z number of time points		3		
		R squared		0.999		
		Span-ratio		0.997		
		t1/2	h	39.94		
		tlast	h	47.83		
		tmax	h	0.52		
		Vz/F	L	1729		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
105	0.5 mg Clonazepam	Adjusted R squared		0.996		
		AUC extrapolated	%	40.2		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	14.3		AUC percent extrapolated > 20
		AUClast	h*ng/mL	8.52		
		CL/F	L/h	35.1		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.0800		
		Clast predicted	ng/mL	0.0796		
		Cmax	ng/mL	4.50		
		Lambda_z	1/h	0.0139		
		Lambda_z first time point	h	8.02		
		Lambda_z number of time points		3		
		R squared		0.998		
		Span-ratio		0.803		
		t1/2	h	49.73		
		tlast	h	47.95		
		tmax	h	0.52		
		Vz/F	L	2515		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
106	1 mg Clonazepam	Adjusted R squared		0.932		
		AUC extrapolated	%	26.1		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	26.1		AUC percent extrapolated > 20
		AUClast	h*ng/mL	19.3		
		CL/F	L/h	38.3		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.190		
		Clast predicted	ng/mL	0.188		
		Cmax	ng/mL	18.7		
		Lambda_z	1/h	0.0279		
		Lambda_z first time point	h	4.02		
		Lambda_z number of time points		4		
		R squared		0.955		
		Span-ratio		0.805		
		t1/2	h	24.83		
		tlast	h	24.02		
		tmax	h	0.52		
		Vz/F	L	1372		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
107	1 mg Clonazepam	Adjusted R squared		0.878		
		AUC extrapolated	%	17		
		AUCinf	h*ng/mL	29.1		
		AUClast	h*ng/mL	24.2		
		CL/F	L/h	34.3		
		Clast observed	ng/mL	0.150		
		Clast predicted	ng/mL	0.137		
		Cmax	ng/mL	13.8		
		Lambda_z	1/h	0.0303		
		Lambda_z first time point	h	4.02		
		Lambda_z number of time points		5		
		R squared		0.909		
		Span-ratio		1.92		
		t1/2	h	22.86		
		tlast	h	47.9		
		tmax	h	0.52		
		Vz/F	L	1133		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
108	1 mg Clonazepam	Adjusted R squared		0.861		
		AUC extrapolated	%	44.8		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	32		AUC percent extrapolated > 20
		AUClast	h*ng/mL	17.7		
		CL/F	L/h	31.2		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.220		
		Clast predicted	ng/mL	0.207		
		Cmax	ng/mL	3.68		
		Lambda_z	1/h	0.0154		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.907		
		Span-ratio		0.927		
		t1/2	h	45.15		
		tlast	h	47.87		
		tmax	h	0.52		
		Vz/F	L	2035		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
109	1 mg Clonazepam	Adjusted R squared		0.994		
		AUC extrapolated	%	9.01		
		AUCinf	h*ng/mL	24.5		
		AUClast	h*ng/mL	22.3		
		CL/F	L/h	40.8		
		Clast observed	ng/mL	0.0800		
		Clast predicted	ng/mL	0.0786		
		Cmax	ng/mL	16.3		
		Lambda_z	1/h	0.0362		
		Lambda_z first time point	h	8.28		
		Lambda_z number of time points		3		
		R squared		0.997		
		Span-ratio		2.07		
		t1/2	h	19.15		
		tlast	h	48		
		tmax	h	0.52		
		Vz/F	L	1127		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
110	1 mg Clonazepam	Adjusted R squared		0.896		
		AUC extrapolated	%	12.3		
		AUCinf	h*ng/mL	36.6		
		AUClast	h*ng/mL	32.1		
		CL/F	L/h	27.3		
		Clast observed	ng/mL	0.140		
		Clast predicted	ng/mL	0.124		
		Cmax	ng/mL	29.2		
		Lambda_z	1/h	0.0310		
		Lambda_z first time point	h	4.02		
		Lambda_z number of time points		5		
		R squared		0.922		
		Span-ratio		1.96		
		t1/2	h	22.38		
		tlast	h	47.93		
		tmax	h	0.52		
		Vz/F	L	882		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
111	0.5 mg Clonazepam	Adjusted R squared		0.996		
		AUC extrapolated	%	18.4		
		AUCinf	h*ng/mL	14.6		
		AUClast	h*ng/mL	11.9		
		CL/F	L/h	34.2		
		Clast observed	ng/mL	0.0600		
		Clast predicted	ng/mL	0.0595		
		Cmax	ng/mL	10.6		
		Lambda_z	1/h	0.0223		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.997		
		Span-ratio		1.36		
		t1/2	h	31.03		
		tlast	h	48.08		
		tmax	h	0.52		
		Vz/F	L	1532		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
112	0.5 mg Clonazepam	Adjusted R squared		NV	R	Half-life r-squared < 0.85
		AUC extrapolated	%	NV	R	First three samples were missing
		AUCinf	h*ng/mL	NV	R	First three samples were missing
		AUClast	h*ng/mL	6.21	R	First three samples were missing
		CL/F	L/h	NV	R	Half-life r-squared < 0.85
		Clast observed	ng/mL	0.0900		
		Clast predicted	ng/mL	NV	R	Half-life r-squared < 0.85
		Cmax	ng/mL	0.270	R	First three samples were missing
		Lambda_z	1/h	NV	R	Half-life r-squared < 0.85
		Lambda_z first time point	h	NV	R	Half-life r-squared < 0.85
		Lambda_z number of time points		NV	R	Half-life r-squared < 0.85
		R squared		NV	R	Half-life r-squared < 0.85
		Span-ratio		NV	R	Half-life r-squared < 0.85
		t1/2	h	NV	R	Half-life r-squared < 0.85
		tlast	h	47.53		
		tmax	h	4.02	R	First three samples were missing
		Vz/F	L	NV	R	Half-life r-squared < 0.85
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
113	0.5 mg Clonazepam	Adjusted R squared		0.953		
		AUC extrapolated	%	33		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	11.3		AUC percent extrapolated > 20
		AUClast	h*ng/mL	7.56		
		CL/F	L/h	44.3		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.0700		
		Clast predicted	ng/mL	0.0682		
		Cmax	ng/mL	2.83		
		Lambda_z	1/h	0.0188		
		Lambda_z first time point	h	8.02		
		Lambda_z number of time points		3		
		R squared		0.976		
		Span-ratio		1.08		
		t1/2	h	36.84		
		tlast	h	47.8		
		tmax	h	0.52		
		Vz/F	L	2356		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
114	0.5 mg Clonazepam	Adjusted R squared		0.992		
		AUC extrapolated	%	35.7		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	22.2		AUC percent extrapolated > 20
		AUClast	h*ng/mL	14.2		
		CL/F	L/h	22.6		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.140		
		Clast predicted	ng/mL	0.141		
		Cmax	ng/mL	5.22		
		Lambda_z	1/h	0.0177		
		Lambda_z first time point	h	8.02		
		Lambda_z number of time points		3		
		R squared		0.996		
		Span-ratio		1.01		
		t1/2	h	39.22		
		tlast	h	47.52		
		tmax	h	0.52		
		Vz/F	L	1276		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
115	0.5 mg Clonazepam	Adjusted R squared		0.916		
		AUC extrapolated	%	37		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	32		AUC percent extrapolated > 20
		AUClast	h*ng/mL	20.2		
		CL/F	L/h	15.6		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.140		
		Clast predicted	ng/mL	0.143		
		Cmax	ng/mL	15.3		
		Lambda_z	1/h	0.0118		
		Lambda_z first time point	h	8.02		
		Lambda_z number of time points		3		
		R squared		0.958		
		Span-ratio		0.668		
		t1/2	h	58.72		
		tlast	h	47.27		
		tmax	h	0.52		
		Vz/F	L	1323		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
116	1 mg Clonazepam	Adjusted R squared		0.842		
		AUC extrapolated	%	19.2		
		AUCinf	h*ng/mL	31.9		
		AUClast	h*ng/mL	25.8		
		CL/F	L/h	31.3		
		Clast observed	ng/mL	0.160		
		Clast predicted	ng/mL	0.141		
		Cmax	ng/mL	17.9		
		Lambda_z	1/h	0.0261		
		Lambda_z first time point	h	4.02		
		Lambda_z number of time points		5		
		R squared		0.881		
		Span-ratio		1.67		
		t1/2	h	26.52		
		tlast	h	48.23		
		tmax	h	0.52		
		Vz/F	L	1199		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
117	1 mg Clonazepam	Adjusted R squared		1.00		
		AUC extrapolated	%	28.1		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	24.2		AUC percent extrapolated > 20
		AUClast	h*ng/mL	17.4		
		CL/F	L/h	41.3		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.140		
		Clast predicted	ng/mL	0.140		
		Cmax	ng/mL	7.85		
		Lambda_z	1/h	0.0206		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		3		
		R squared		1.00		
		Span-ratio		1.24		
		t1/2	h	33.72		
		tlast	h	47.97		
		tmax	h	0.52		
		Vz/F	L	2009		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
118	1 mg Clonazepam	Adjusted R squared		0.960		
		AUC extrapolated	%	19.3		
		AUCinf	h*ng/mL	32.3		
		AUClast	h*ng/mL	26.1		
		CL/F	L/h	30.9		
		Clast observed	ng/mL	0.160		
		Clast predicted	ng/mL	0.152		
		Cmax	ng/mL	17.2		
		Lambda_z	1/h	0.0256		
		Lambda_z first time point	h	6.13		
		Lambda_z number of time points		4		
		R squared		0.973		
		Span-ratio		1.53		
		t1/2	h	27.05		
		tlast	h	47.47		
		tmax	h	0.52		
		Vz/F	L	1208		
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
119	1 mg Clonazepam	Adjusted R squared		NV	R	Half-life r-squared < 0.85
		AUC extrapolated	%	NV	R	Half-life r-squared < 0.85
		AUCinf	h*ng/mL	NV	R	Half-life r-squared < 0.85
		AUClast	h*ng/mL	16.7		
		CL/F	L/h	NV	R	Half-life r-squared < 0.85
		Clast observed	ng/mL	0.190		
		Clast predicted	ng/mL	NV	R	Half-life r-squared < 0.85
		Cmax	ng/mL	9.03		
		Lambda_z	1/h	NV	R	Half-life r-squared < 0.85
		Lambda_z first time point	h	NV	R	Half-life r-squared < 0.85
		Lambda_z number of time points		NV	R	Half-life r-squared < 0.85
		R squared		NV	R	Half-life r-squared < 0.85
		Span-ratio		NV	R	Half-life r-squared < 0.85
		t1/2	h	NV	R	Half-life r-squared < 0.85
		tlast	h	48.4		
		tmax	h	0.53		
		Vz/F	L	NV	R	Half-life r-squared < 0.85
NV=No value was calculated						
R=Removed from summary and analysis						
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PK parameters of Clonazepam

Subject	Treatment	Parameter	Unit	Result	Flag	Note
120	1 mg Clonazepam	Adjusted R squared		0.960		
		AUC extrapolated	%	29.6		AUC percent extrapolated > 20
		AUCinf	h*ng/mL	32.3		AUC percent extrapolated > 20
		AUClast	h*ng/mL	22.7		
		CL/F	L/h	31		AUC percent extrapolated > 20
		Clast observed	ng/mL	0.190		
		Clast predicted	ng/mL	0.183		
		Cmax	ng/mL	9.64		
		Lambda_z	1/h	0.0199		
		Lambda_z first time point	h	6.02		
		Lambda_z number of time points		4		
		R squared		0.973		
		Span-ratio		1.19		
		t1/2	h	34.79		
		tlast	h	47.3		
		tmax	h	0.52		
		Vz/F	L	1556		AUC percent extrapolated > 20
NV=No value was calculated						
R=Removed from summary and analysis						
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