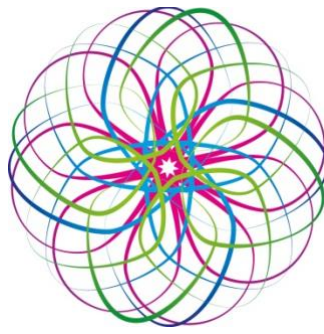




CHDR
Centre for Human Drug Research

Statistical appendix: Analysis of pharmacokinetic parameters

CHDR1939B

Randomized, double-blind, placebo-controlled, two way crossover, single center 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	CHDR1939B
Short title	Clonazepam in ARID1B Evaluation (CARE study)
Sponsor protocol ID	
File name	CHDR1939B_FPK_2022-10-19.docx
Date	2022-10-19

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

No parameters were calculated due to the small amount of PK samples in the study.

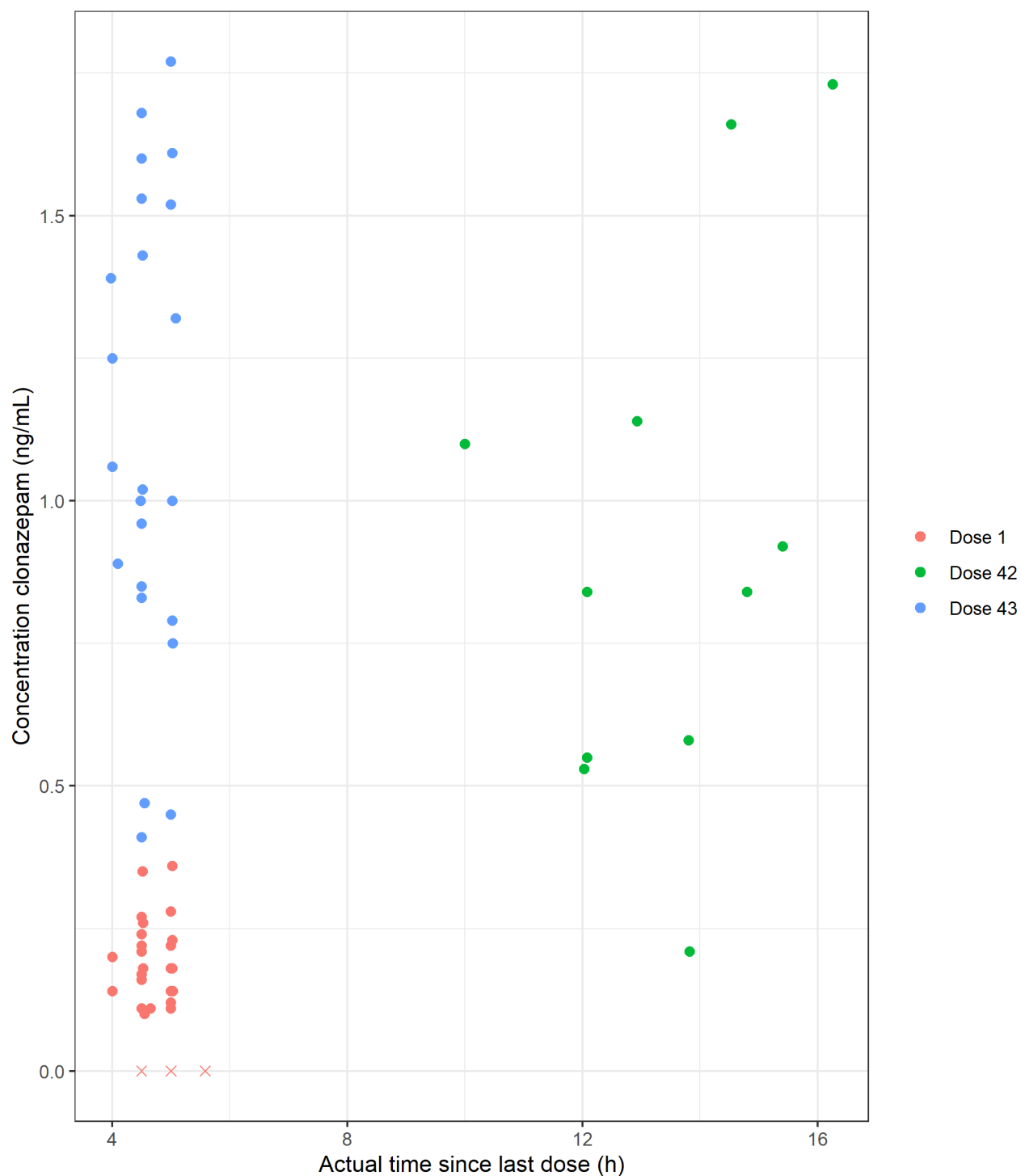
Reporting of drug concentration data

The concentrations are summarized (n, mean, SD, %CV, median, Min and Max values) by treatment and time. 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. The individual concentrations are listed by treatment, subject and time.

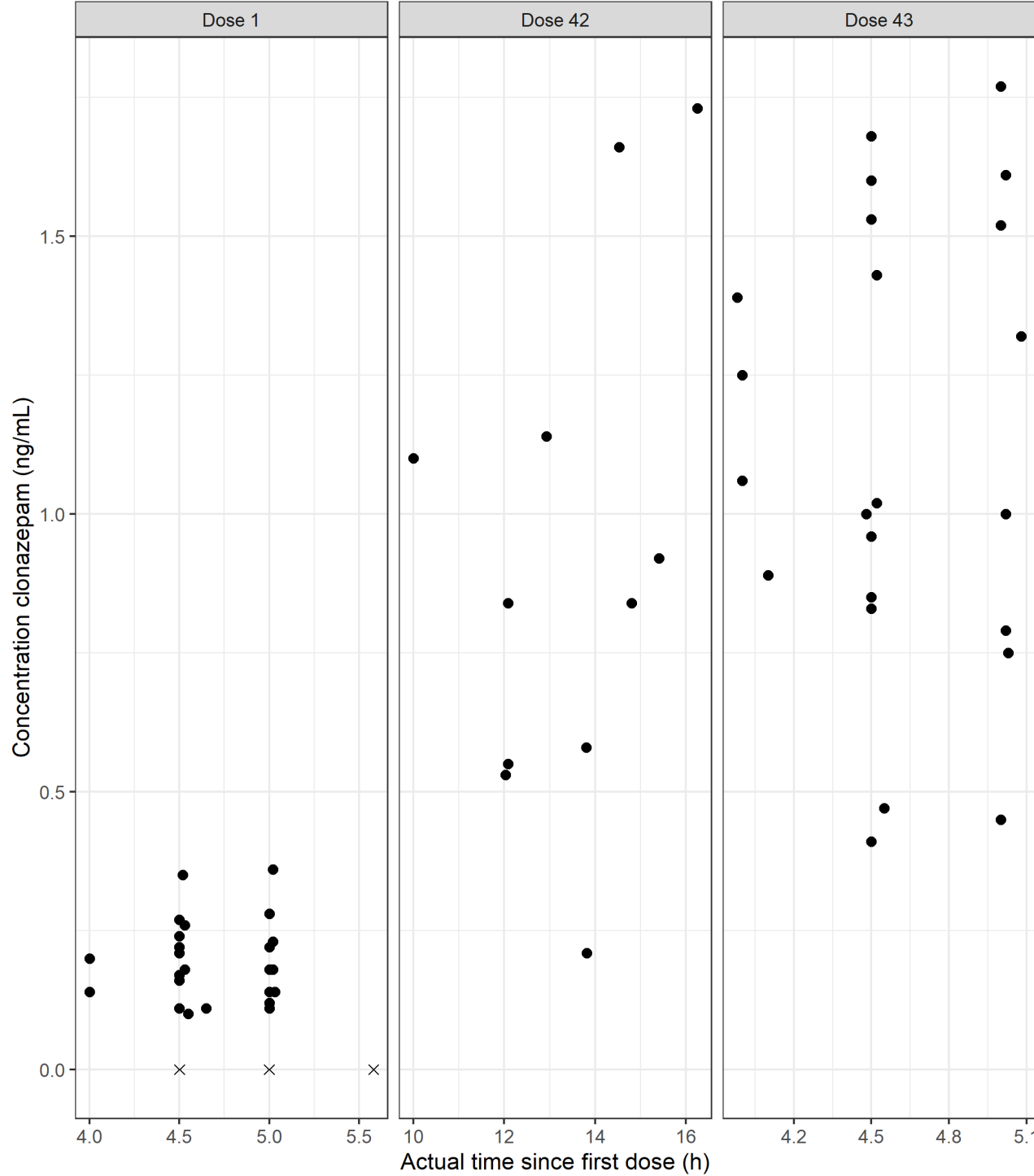
For calculation of the mean concentration per protocol time only data from samples after dose 1 and dose 43 were used. In this case, datapoints were excluded from mean calculations if the actual sampling time deviated more than 10% from the protocol time. Generally, in NCA's if more than one third of the concentrations are NA then Mean, SD and CV will not be provided. In this report this was the case for the mean calculation of 4.5h measurement after dose 43. However, the Mean, SD and CV are in this case provided due to the small amount of PK data in the study. For dose 42 no mean was calculated due to the large deviation between actual sampling time and protocol time and large differences in actual sampling time between subjects.

Drug Concentration Tables and Figures

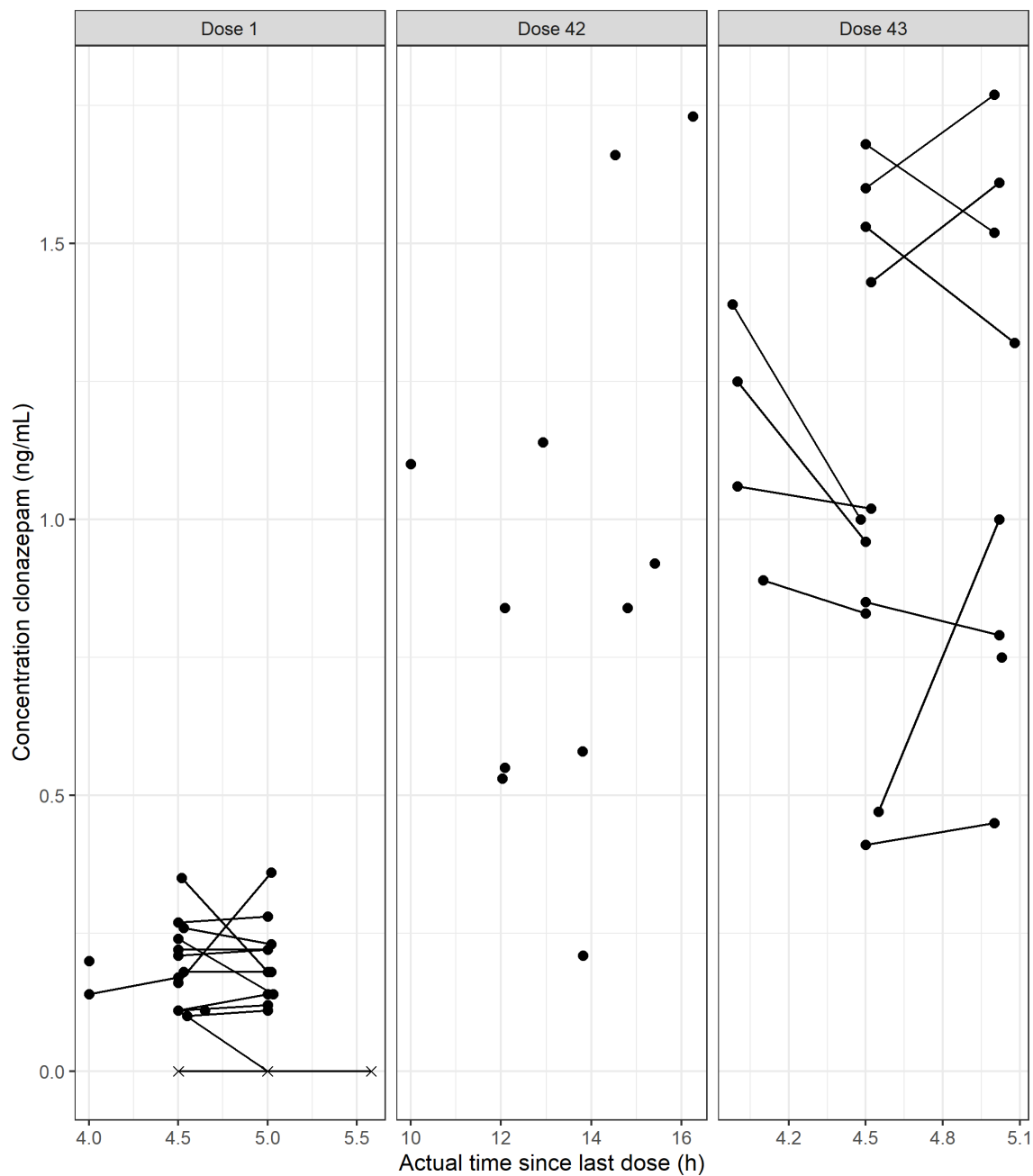
Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – colored per dose



Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per dose

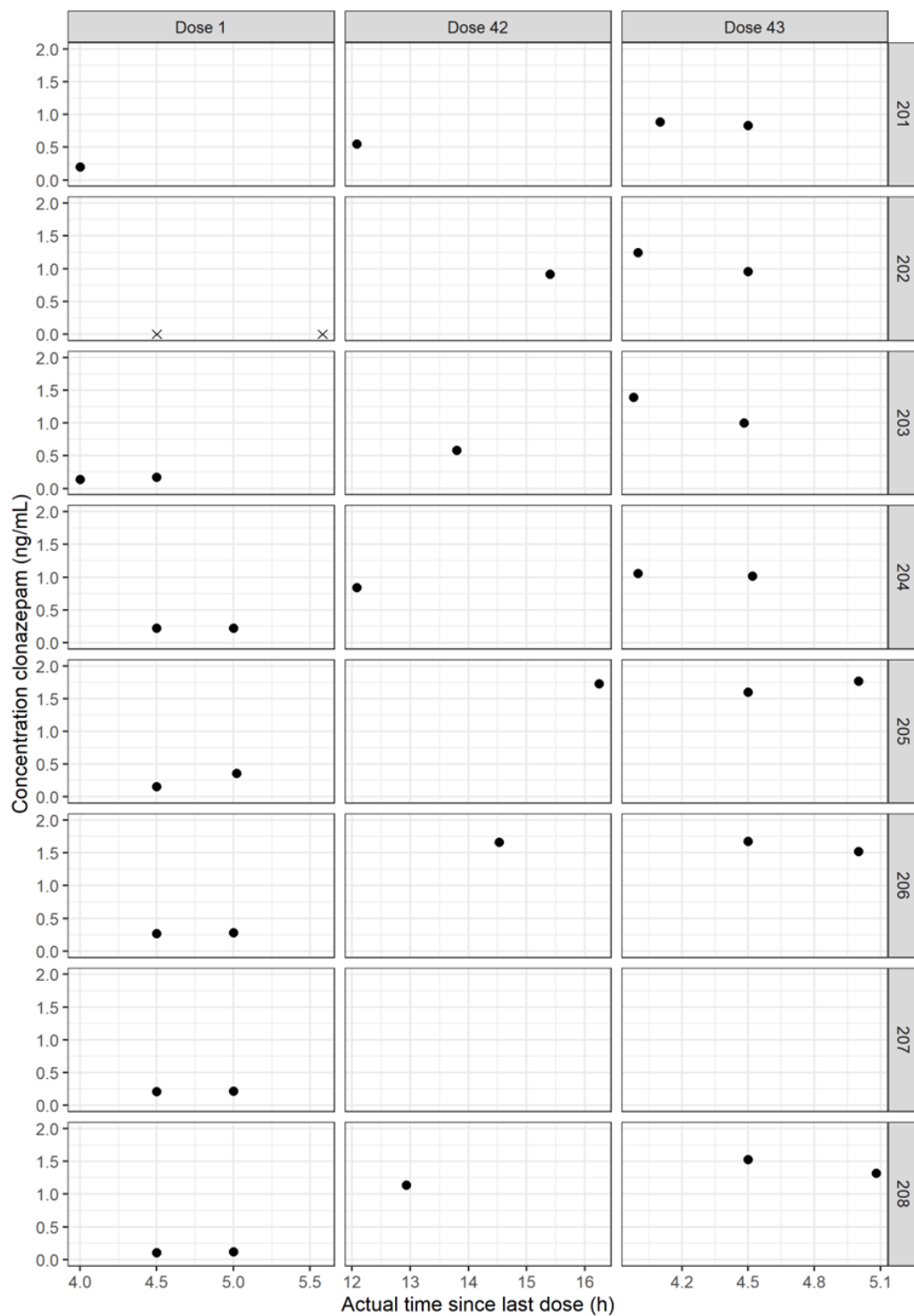


x = observation below the limit of quantification

Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per dose - including line

x = observation below the limit of quantification

Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual and dose number – subjects 201-208

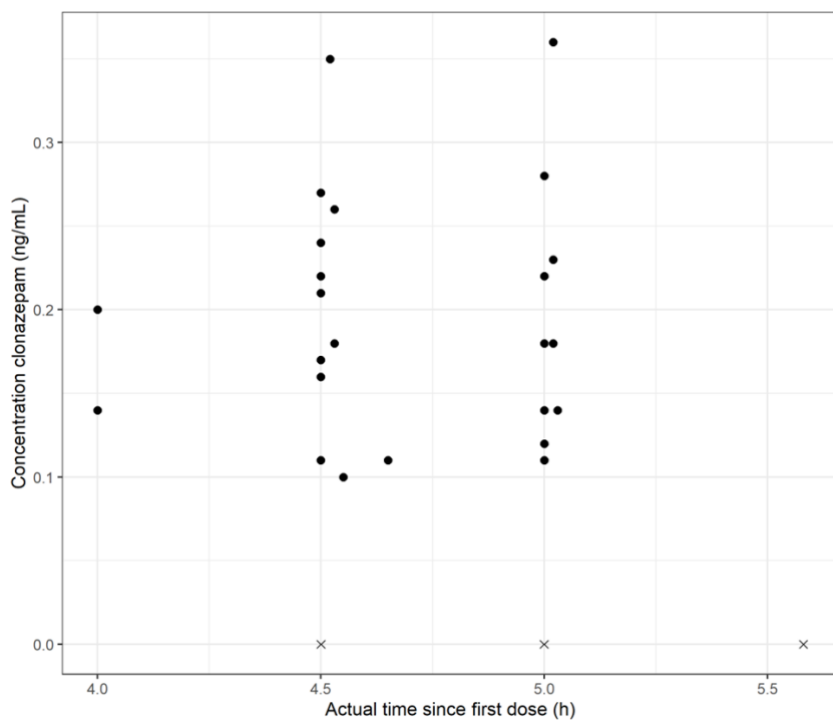


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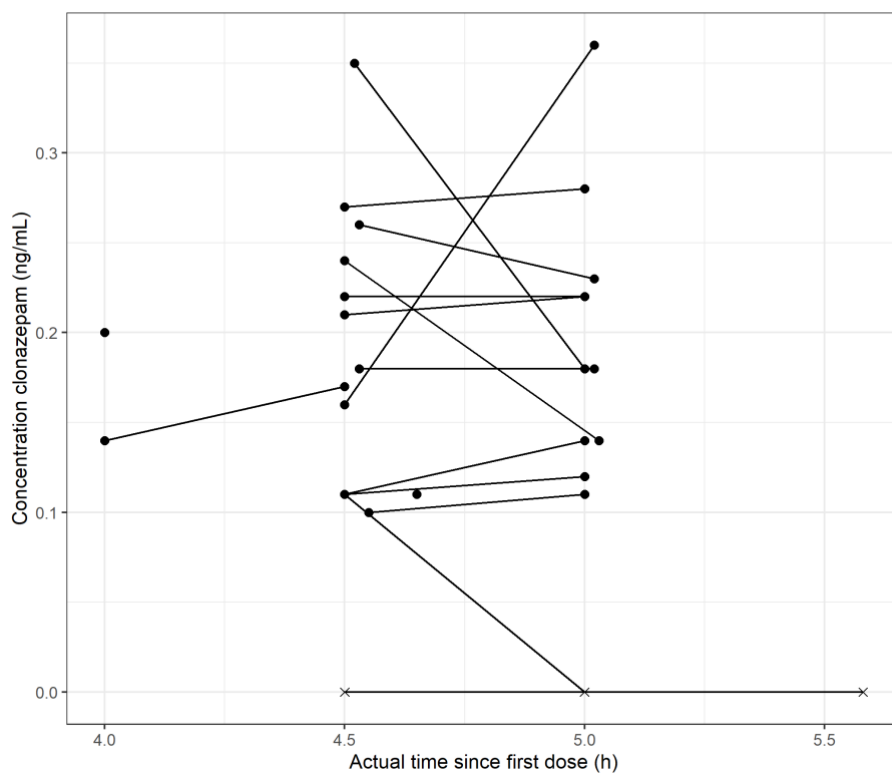
Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual and dose number – subjects 209-216



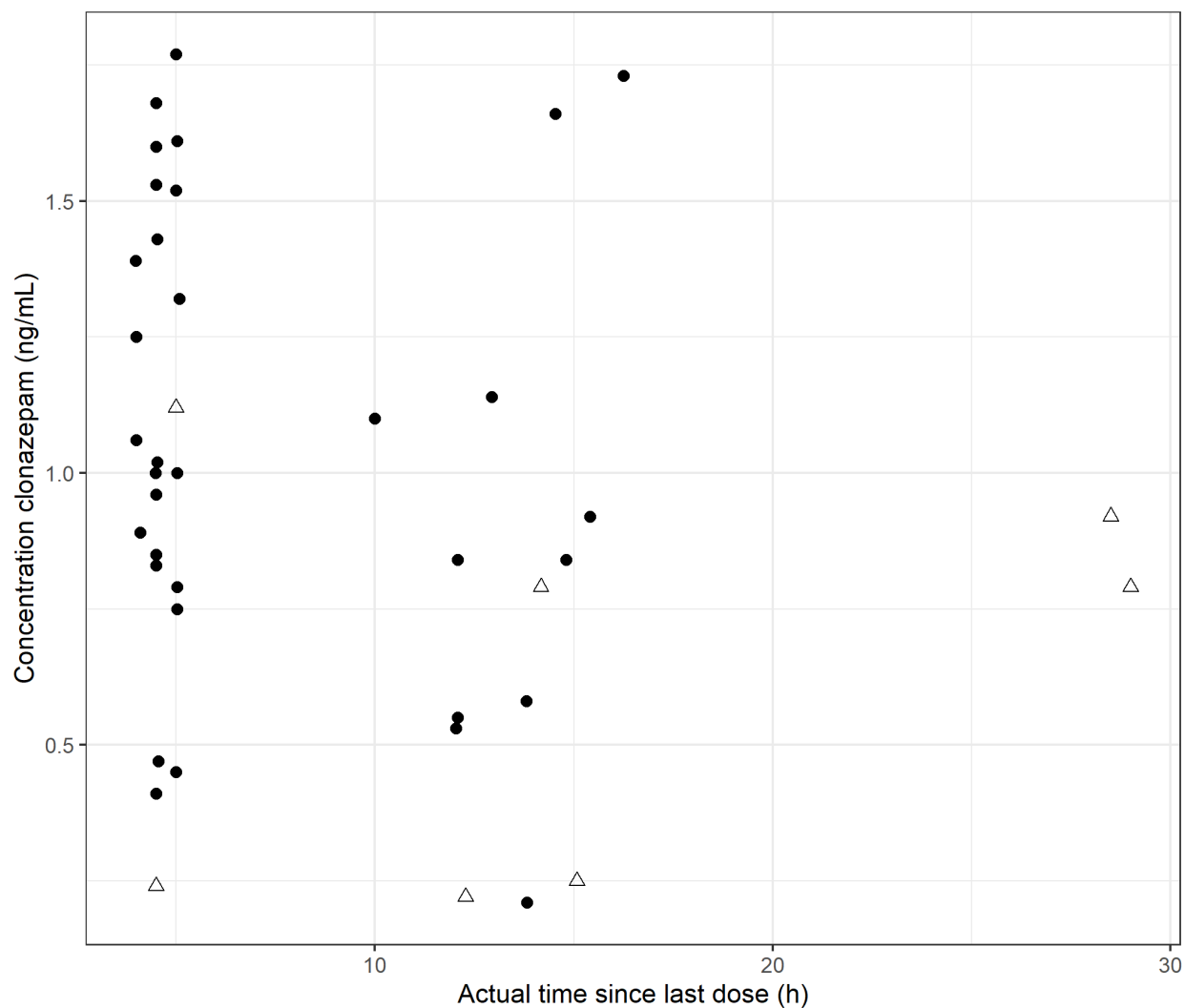
x = observation below the limit of quantification

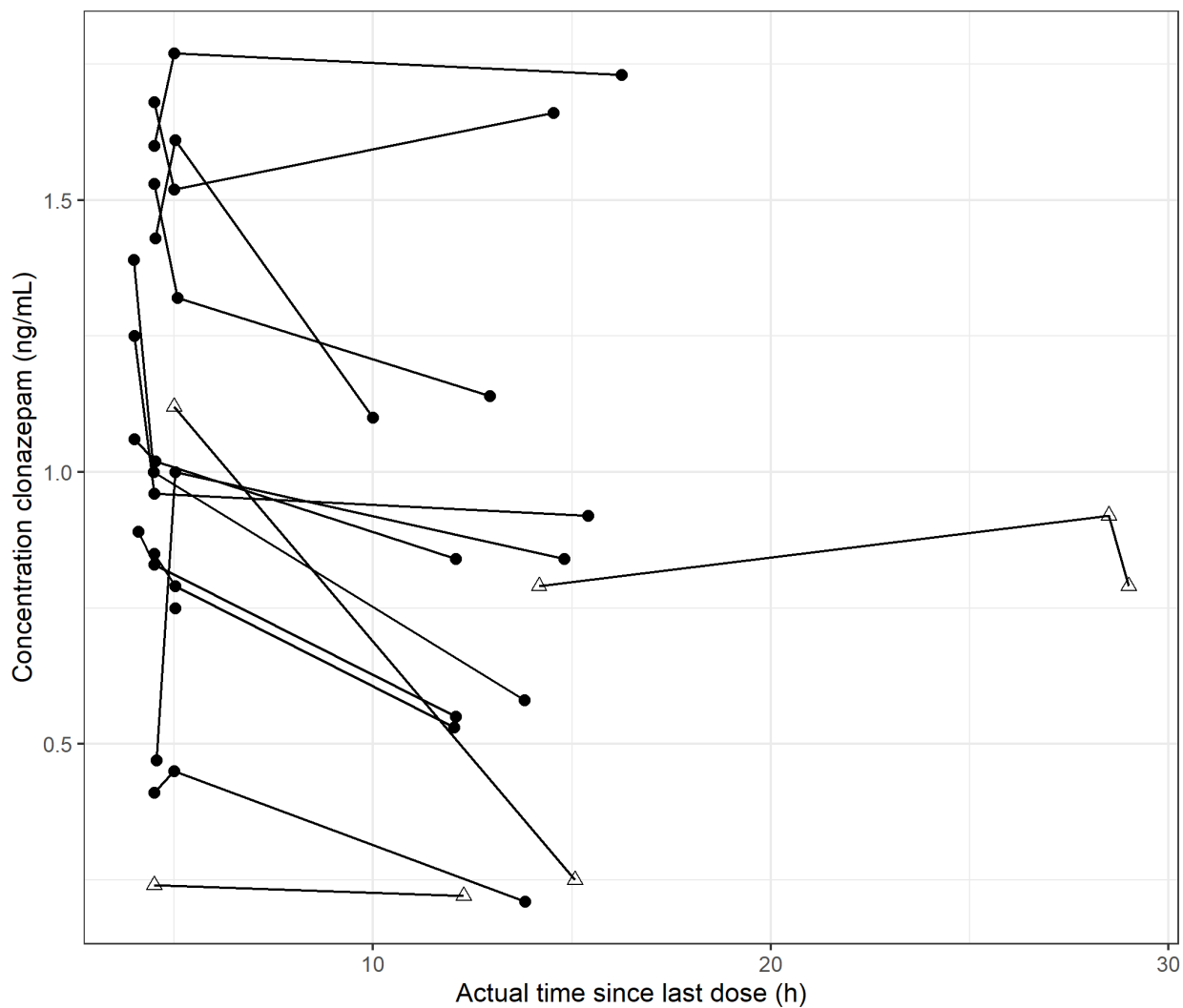
Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – Dose 1 – Day 1

x = observation below the limit of quantification

Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – Dose 1 – Day 1 - including line

x = observation below the limit of quantification

Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – Dose 42-43 -Day 21-22

Individual concentrations of Clonazepam concentration in Saliva (ng/mL) – Dose 42-43 -Day 21-22 – including line

Summary Tables and Figures

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

Summary of PK of Clonazepam in Saliva

Treatment	Interval	Protocol Time	N	Mean	SD	Median	CV%	Min	Max
Clonazepam	Dose 1	04H30M	14	0.1736	0.091029	0.170	52.4	0	0.350
		05H00M	13	0.1808	0.087698	0.180	48.5	0	0.360
	Dose 43	21D04H30M	8	1.107	0.51538	1.16	46.5	0.410	1.68
		21D05H00M	11	1.093	0.41027	1.00	37.5	0.450	1.77

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Listing

Listing 1 Clonazepam concentration in Saliva

Clonazepam concentration in Saliva

Subject	Treatment	Interval	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
					Protocol Time	Actual Time			
201	Clonazepam	Dose 1	23OCT2021	14:31	4.5	4	0.200	R	More than 10% time deviation
		Dose 42	13NOV2021	09:10	10	12.08	0.550	R	More than 10% time deviation
		Dose 43	13NOV2021	14:37	4.5	4.1	0.890		
			13NOV2021	15:01	5	4.5	0.830		
202	Clonazepam	Dose 1	11SEP2021	16:55	4.5	4.5	L		
			11SEP2021	18:00	5	5.58	L	R	More than 10% time deviation
		Dose 42	02OCT2021	09:54	10	15.4	0.920	R	More than 10% time deviation
		Dose 43	02OCT2021	15:11	4.5	4	1.25	R	More than 10% time deviation
			02OCT2021	15:41	5	4.5	0.960		
203	Clonazepam	Dose 1	23OCT2021	16:08	4.5	4	0.140	R	More than 10% time deviation
			23OCT2021	16:38	5	4.5	0.170		
		Dose 42	13NOV2021	10:48	10	13.8	0.580	R	More than 10% time deviation
		Dose 43	13NOV2021	16:00	4.5	3.98	1.39	R	More than 10% time deviation
			13NOV2021	16:30	5	4.48	1.00	R	More than 10% time deviation
204	Clonazepam	Dose 1	25SEP2021	16:45	4.5	4.5	0.220		
			25SEP2021	17:15	5	5	0.220		
		Dose 42	16OCT2021	09:35	10	12.08	0.840	R	More than 10% time deviation
		Dose 43	16OCT2021	14:46	4.5	4	1.06	R	More than 10% time deviation
			16OCT2021	15:17	5	4.52	1.02		
205	Clonazepam	Dose 1	06NOV2021	15:37	4.5	4.5	0.160		
			06NOV2021	16:08	5	5.02	0.360		
		Dose 42	27NOV2021	10:15	10	16.25	1.73	R	More than 10% time deviation
		Dose 43	27NOV2021	15:57	4.5	4.5	1.60		
			27NOV2021	16:27	5	5	1.77		
206	Clonazepam	Dose 1	25SEP2021	17:15	4.5	4.5	0.270		
			25SEP2021	17:45	5	5	0.280		

L=Below limit of Quantification (0.1ng/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	Interval	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
					Protocol Time	Actual Time			
206	Clonazepam	Dose 42	16OCT2021	10:32	10	14.53	1.66	R	More than 10% time deviation
		Dose 43	16OCT2021	16:43	4.5	4.5	1.68		
			16OCT2021	17:13	5	5	1.52		
207	Clonazepam	Dose 1	09OCT2021	15:32	4.5	4.5	0.210		
			09OCT2021	16:02	5	5	0.220		
		Dose 42			10		M	ATM/R	No sample taken
		Dose 43			4.5		M	ATM/R	No sample taken
					5		M	ATM/R	No sample taken
208	Clonazepam	Dose 1	21NOV2021	15:18	4.5	4.5	0.110		
			21NOV2021	15:48	5	5	0.120		
		Dose 42	12DEC2021	09:07	10	12.93	1.14	R	More than 10% time deviation
		Dose 43	12DEC2021	14:51	4.5	4.5	1.53		
			12DEC2021	15:26	5	5.08	1.32		
209	Clonazepam	Dose 1	10OCT2021	14:56	4.5	4.5	0.110		
			10OCT2021	15:26	5	5	0.140		
		Dose 42	31OCT2021	09:01	10	10	1.10		
		Dose 43	31OCT2021	14:24	4.5	4.52	1.43		
			31OCT2021	14:54	5	5.02	1.61		
210	Clonazepam	Dose 1	21NOV2021	15:07	4.5	4.5	0.240		
			21NOV2021	15:39	5	5.03	0.140		
		Dose 42	12DEC2021	09:51	10	14.8	0.840	R	More than 10% time deviation
		Dose 43	12DEC2021	15:23	4.5	4.55	0.470		
			12DEC2021	15:51	5	5.02	1.00		
211	Clonazepam	Dose 1	14MAY2022	15:03	4.5	4.53	0.180		
			14MAY2022	15:32	5	5.02	0.180		
		Dose 40	03JUN2022	10:10	34	14.17	0.790	R	Subject missed 2 out of 44 doses
L=Below limit of Quantification (0.1ng/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	Interval	Actual Date	Actual Time	Time from last dose		Concentration in Saliva (ng/mL)	Flag	Note
					Protocol Time	Actual Time			
211	Clonazepam	Dose 41	03JUN2022	14:48	28.5	28.5	0.920	R	Subject missed 2 out of 44 doses
			03JUN2022	15:18	29	29	0.790	R	Subject missed 2 out of 44 doses
212	Clonazepam	Dose 1	29JAN2022		4.5	4.5	0.110	ATM	
			29JAN2022		5	5	L	ATM	
		Dose 41	19FEB2022	09:42	10	12.28	0.220	R	Subject missed 1 out of 44 doses
		Dose 42	19FEB2022	15:05	4.5	4.5	0.240	R	Subject missed 1 out of 44 doses
					5		M	R	Subject missed 1 out of 44 doses
213	Clonazepam	Dose 1	29JAN2022	15:28	4.5	4.65	0.110		Subject did not want to keep the swab in her mouth for sufficient time.
			29JAN2022	15:49	5	5	M		
		Dose 43	19FEB2022	15:00	4.5	4.55	M		
			19FEB2022	15:29	5	5.03	0.750		Subject did not want to keep the swab in her mouth for sufficient time.
214	Clonazepam	Dose 1	12MAR2022	15:50	4.5	4.55	0.100		
			12MAR2022	16:17	5	5	0.110		
		Dose 42	02APR2022	10:04	10	12.03	0.530	R	More than 10% time deviation
		Dose 43	02APR2022	15:25	4.5	4.5	0.850		
			02APR2022	15:56	5	5.02	0.790		
215	Clonazepam	Dose 1	12MAR2022	17:37	4.5	4.53	0.260		
			12MAR2022	18:06	5	5.02	0.230		
		Dose 42	02APR2022	11:24	10	13.82	0.210	R	More than 10% time deviation
		Dose 43	02APR2022	16:52	4.5	4.5	0.410		
			02APR2022	17:22	5	5	0.450		
216	Clonazepam	Dose 1	23APR2022	14:14	4.5	4.52	0.350		Subject did not want to keep the swab in her mouth for sufficient time.
			23APR2022	14:43	5	5	0.180		
		Dose 38	12MAY2022	09:45	58	15.08	0.250	R	Subject missed 4 out of 44 doses
		Dose 39	12MAY2022	15:21	5	5	1.12	R	Subject missed 4 out of 44 doses

L=Below limit of Quantification (0.1ng/mL), M=Missing

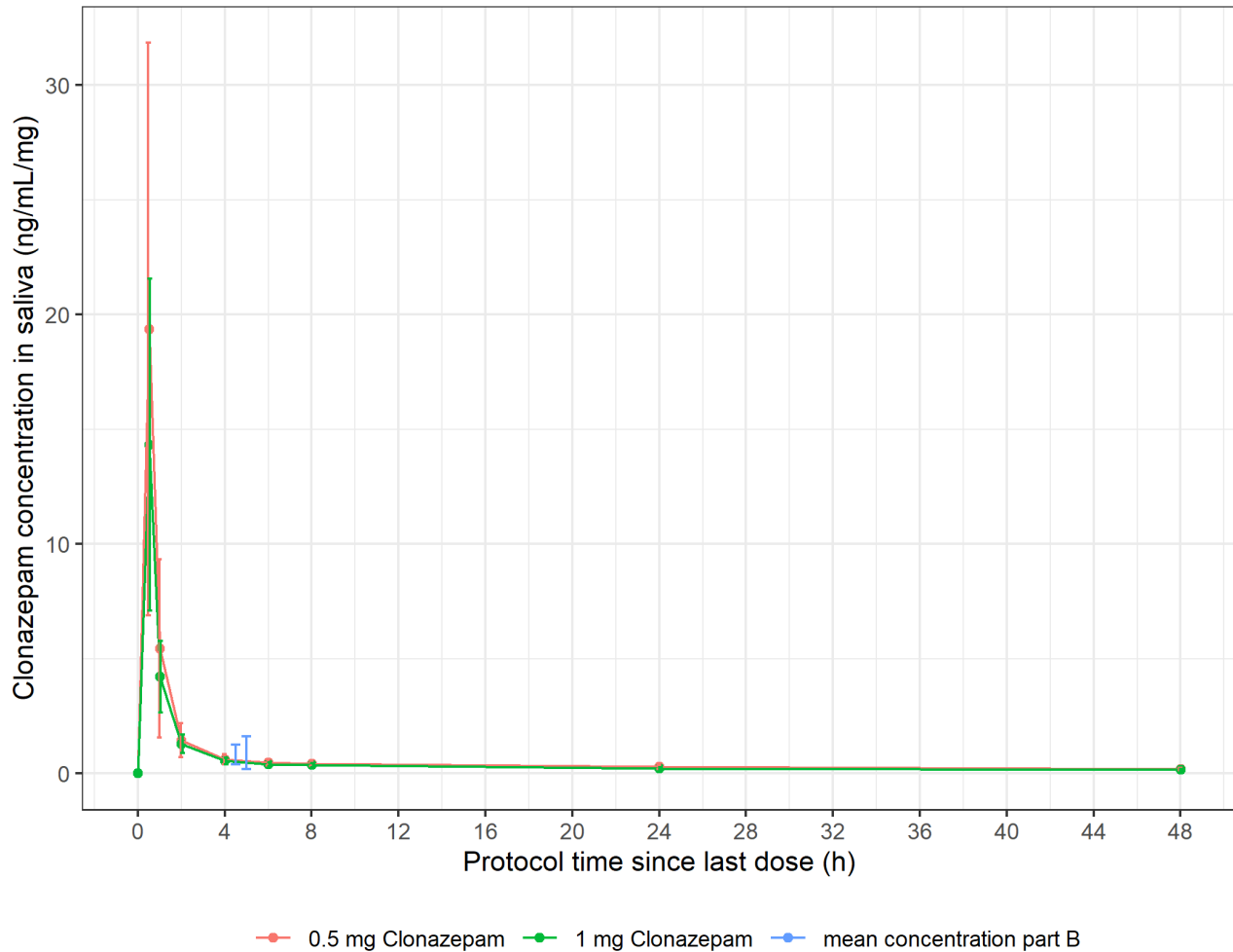
R=Removed from summary and analysis, RP=Removed from estimation of PK parameters, ATM=Actual time missing

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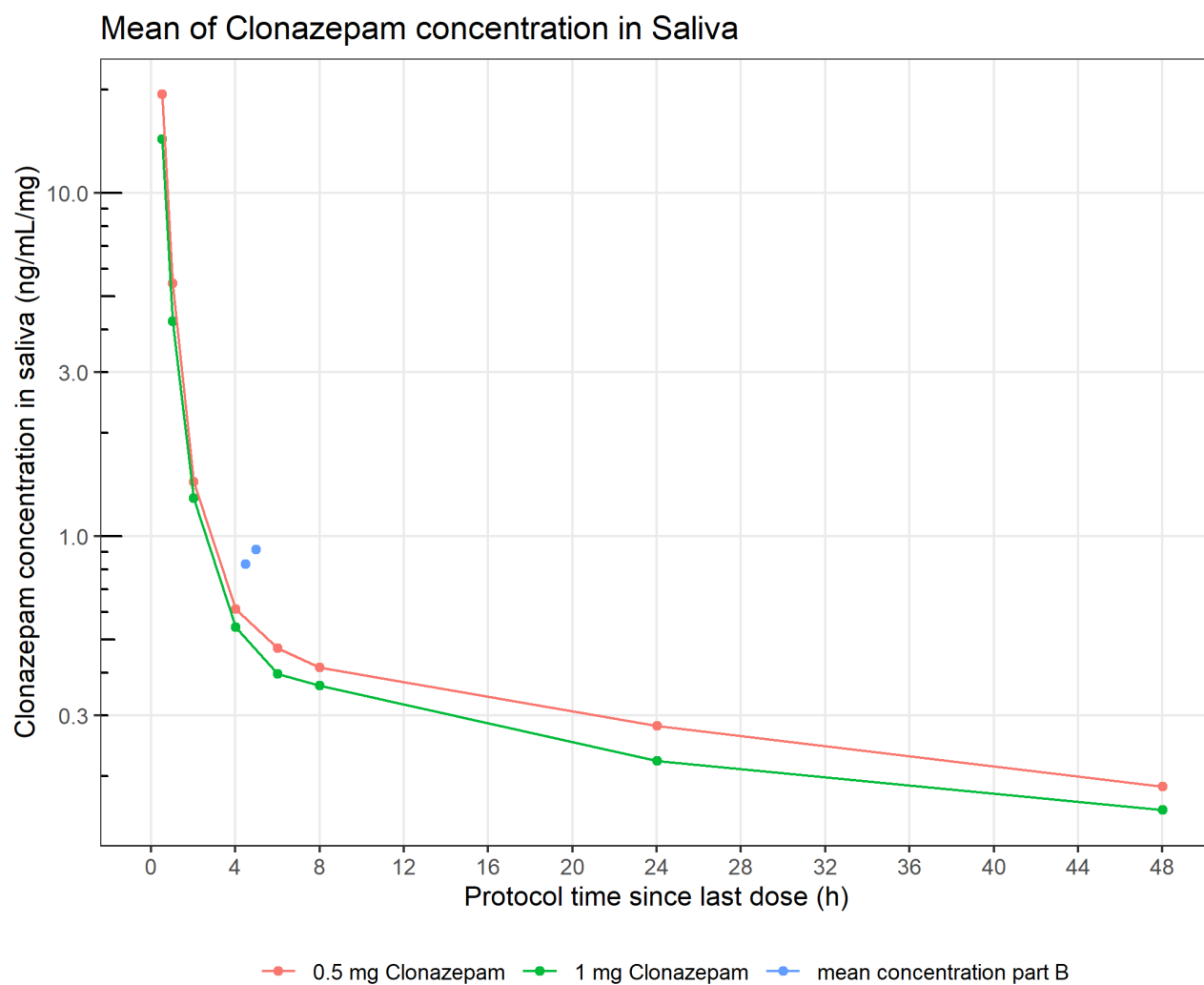
Comparison with CHDR1939A

Summary of Clonazepam dose normalized concentration in Saliva (ng/mL/mL) – Comparison part A and B (Dose 1)

Mean (SD) of Clonazepam concentration in Saliva



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Summary of Clonazepam dose normalized concentration in Saliva (ng/mL/mL) – log y-axis - Comparison part A and B (Dose 1)

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Table 1 Summary of Clonazepam dose normalized concentration in Saliva part A and part B (Dose 1) (ng/mL/mg)

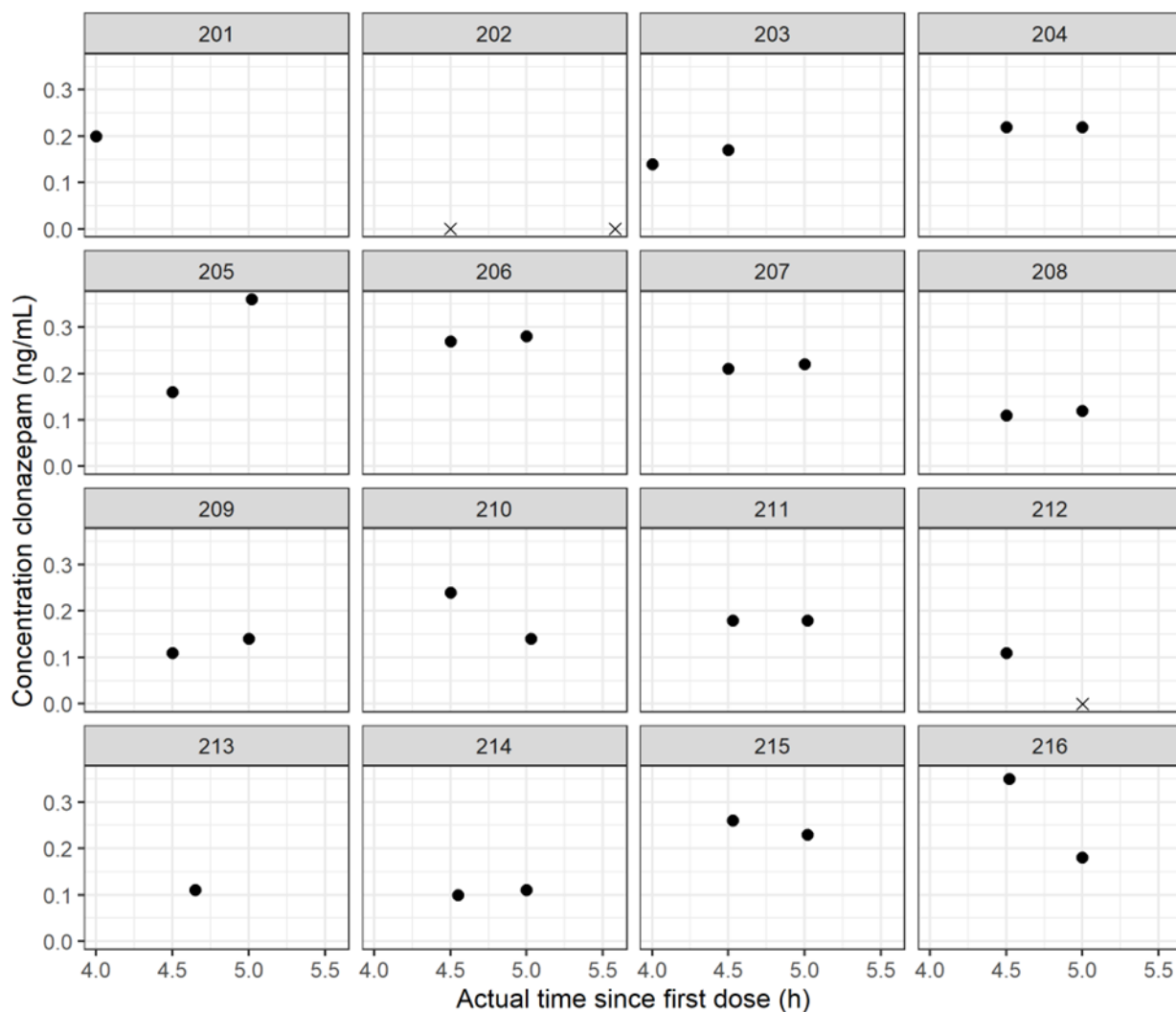
Summary of PK of Clonazepam in Saliva Dose normalized

Treatment	Interval	Protocol Time	N	Mean	SD	Median	CV%	Min	Max
Clonazepam part B	Dose 1	04H30M	12	0.828	0.4292257	0.856	51.8	0	1.35
		05H00M	11	0.911	0.7114886	0.692	78.1	0.4	2.98
Clonazepam part A: 0.5 mg Clonazepam		00H00M	10	0	.	0	.	0	0
		00H31M	10	19.36	12.4803165	15.72	64.5	5.66	45.24
		01H01M	10	5.440	3.895197593	5.02	71.5	2.32	14.36
		02H01M	10	1.44	0.739932429	1.3	51.4	0.6	2.9
		04H01M	10	0.612	0.221349397	0.61	36.2	0.32	1.02
		06H01M	10	0.47	0.137032032	0.53	29.2	0.24	0.66
		08H01M	10	0.414	0.10330107	0.45	25.0	0.28	0.56
		24H01M	10	0.28	0.091893658	0.24	32.8	0.2	0.44
		48H01M	10	0.186	0.056607813	0.17	30.4	0.12	0.28
		00H00M	10	0	.	0	.	0	0
1 mg Clonazepam		00H31M	10	14.33	7.226934189	15.1	50.4	3.68	29.17
		01H01M	10	4.219	1.552191641	4.215	36.8	1.58	7.01
		02H01M	10	1.29	0.405308524	1.42	31.4	0.63	1.91
		04H01M	10	0.543	0.134251009	0.56	24.7	0.29	0.7
		06H01M	10	0.396	0.065861808	0.42	16.6	0.27	0.47
		08H01M	10	0.367	0.093339286	0.395	25.4	0.18	0.51
		24H01M	10	0.221	0.0325747	0.21	14.7	0.18	0.27
		48H01M	10	0.159	0.03982601	0.16	25.1	0.08	0.22

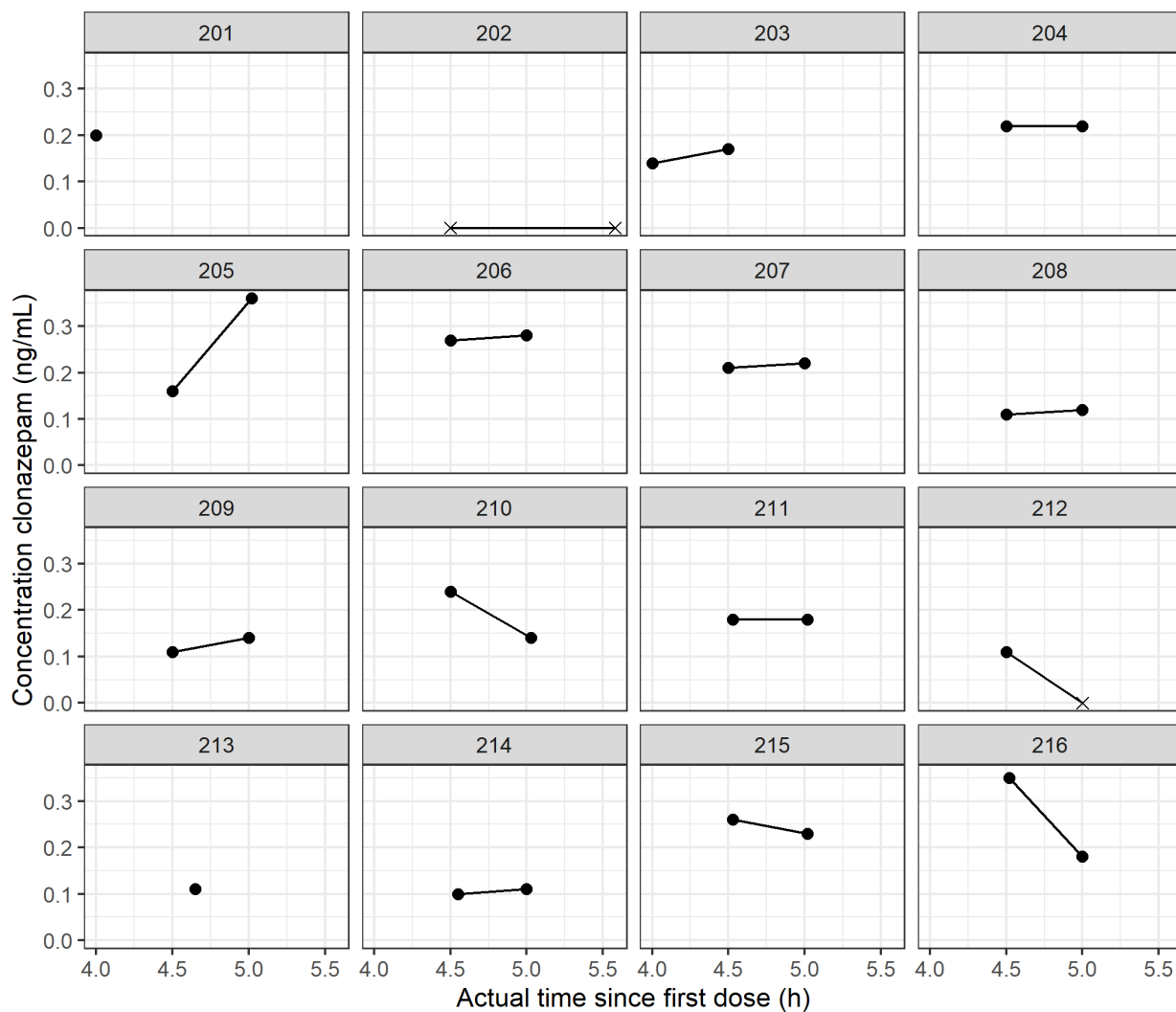
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Additional Figures

Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual –
Dose 1 – Day 1

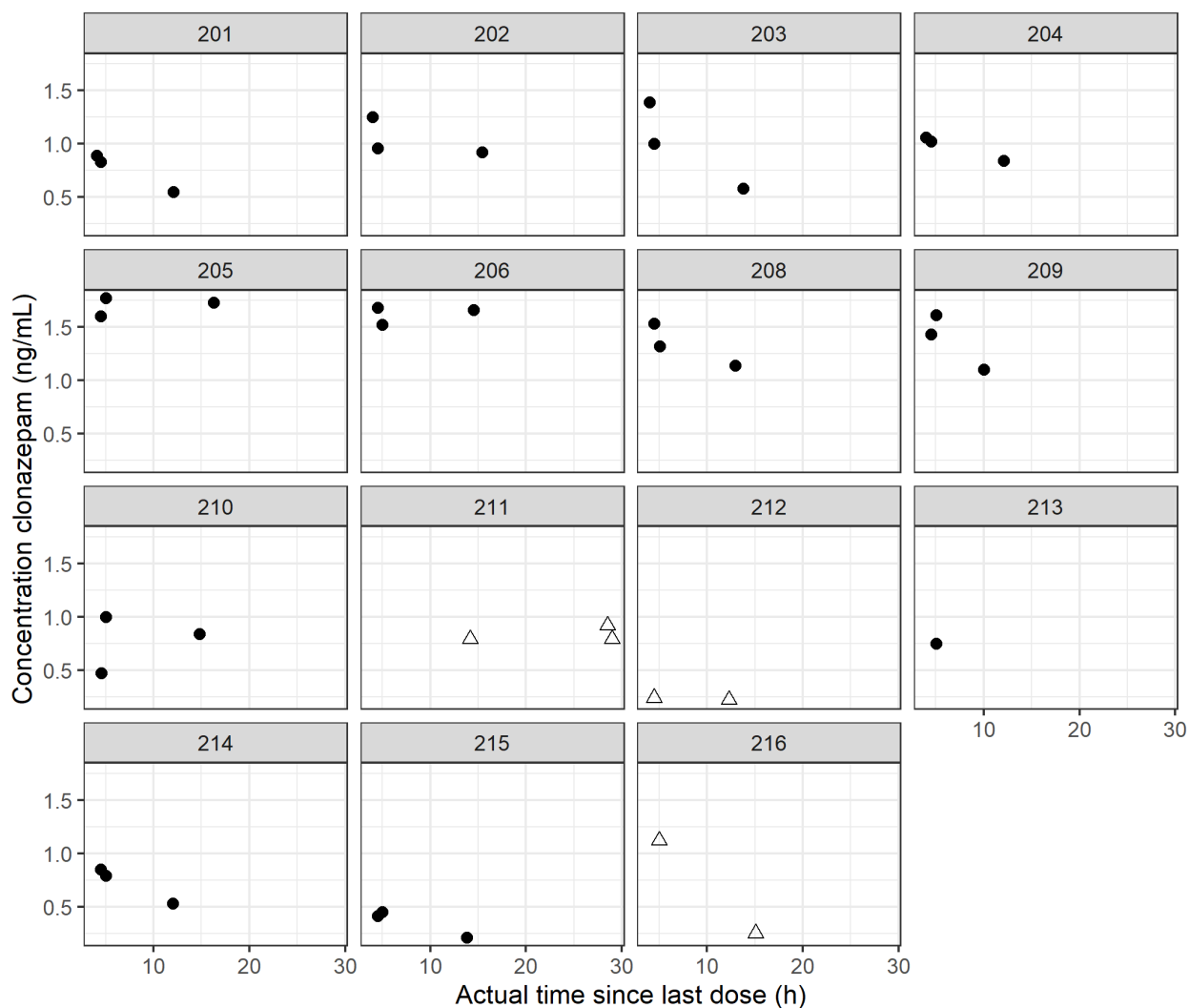


Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual – Dose 1 – Day 1 - including line



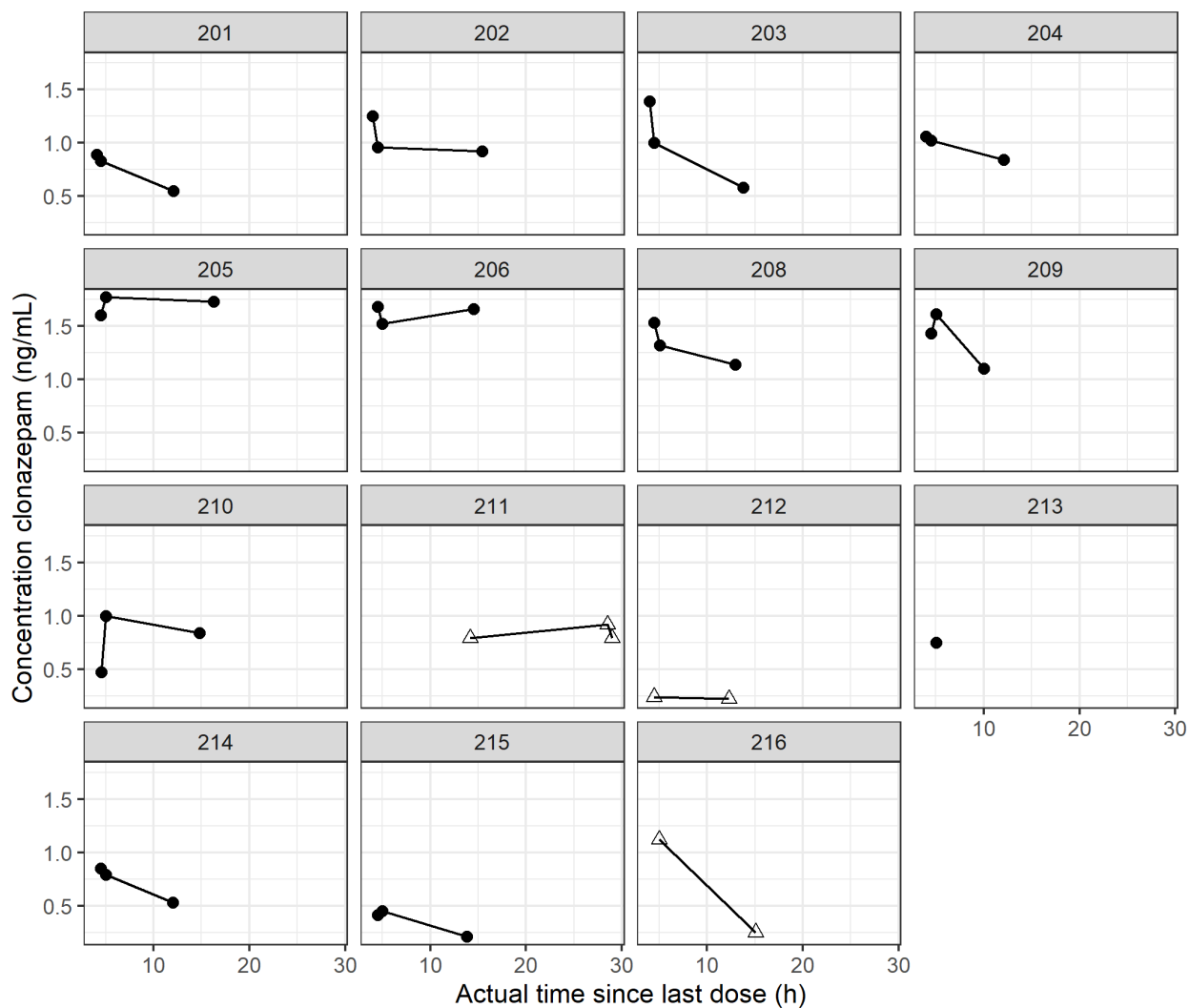
x = observation below the limit of quantification, Δ = excluded measurement due to missed dose

Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual – Dose 42-43 – Day 21-22



x = observation below the limit of quantification, Δ = excluded measurement due to missed dose

Concentrations of Clonazepam concentration in Saliva (ng/mL) – grouped per individual – Dose 42-43 – Day including line



x = observation below the limit of quantification, Δ = excluded measurement due to missed dose