Sheffield two-compound study

metformin (all results)

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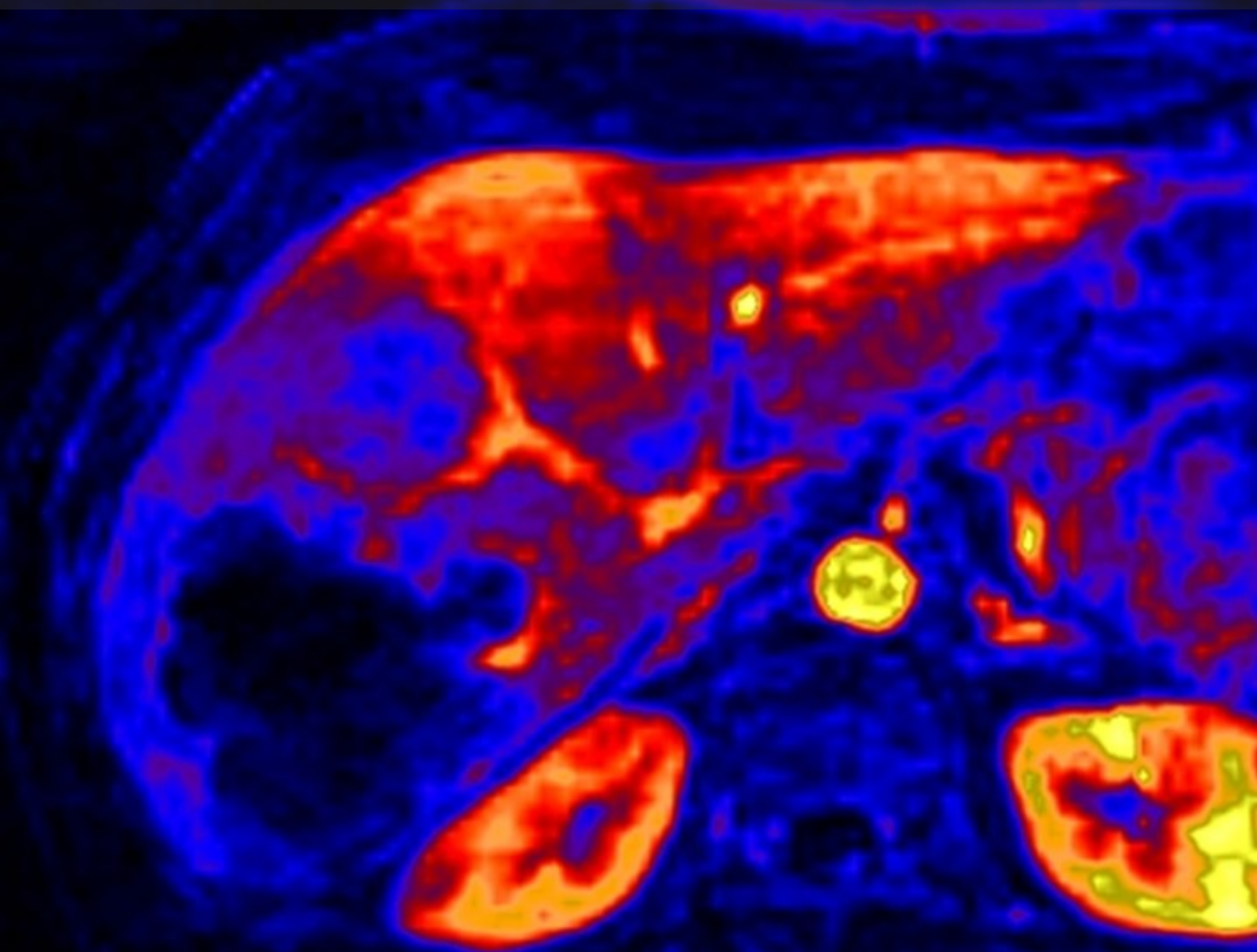

TRISTAN
TRANSLATIONAL IMAGING IN DRUG SAFETY ASSESSMENT

Sheffield two-compound study

metformin (all results)

by

miblab.org

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Date:	Friday 6th June, 2025

TRISTAN
TRANSLATIONAL IMAGING IN DRUG SAFETY ASSESSMENT

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Two-scan results

1.1. Data summary

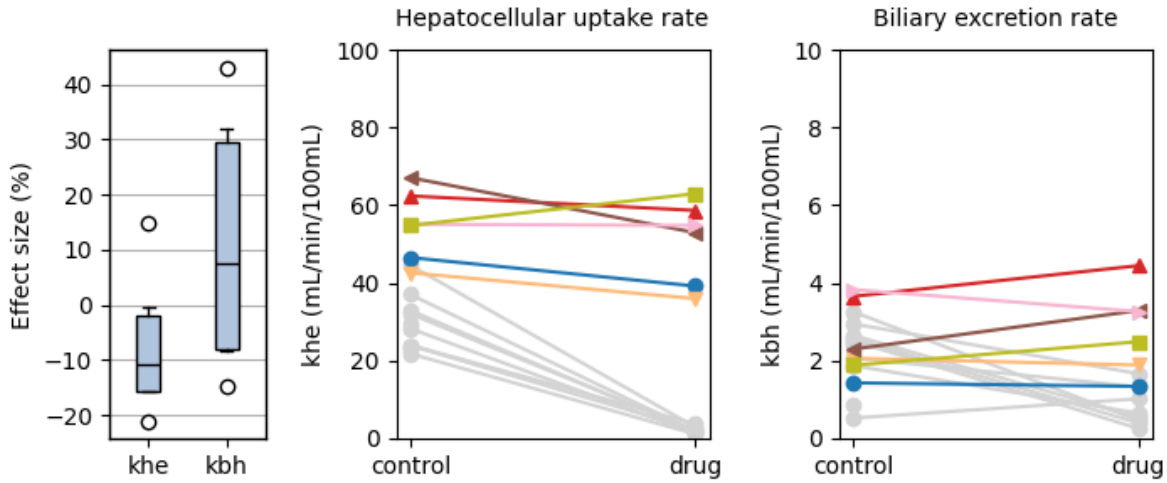

Figure 1.1: Effect size (%) on hepatocellular uptake (k_he, left) and biliary excretion (k_bh, right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_he, middle) and biliary excretion (k_bh, right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

parameter	count	mean	std	min	25%	50%	75%	max
khe effect size (%)	6.0	-7.3	13.2	-21.0	-15.7	-10.8	-1.9	14.9
khe control (mL/min/100cm3)	6.0	54.74	9.22	42.6	48.59	54.94	60.55	67.06
khe drug (mL/min/100cm3)	6.0	50.74	10.81	35.96	42.64	53.86	57.68	62.94
kbh effect size (%)	6.0	11.2	24.2	-14.7	-8.0	7.6	29.5	43.1
kbh control (mL/min/100cm3)	6.0	2.53	0.98	1.43	1.93	2.18	3.32	3.83
kbh drug (mL/min/100cm3)	6.0	2.78	1.12	1.34	2.04	2.88	3.28	4.44

Table 1.1: Effect size and absolute values of hepatocellular uptake (k_he) and biliary excretion (k_bh) of gadoxetate

1.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cl (0-35min)	0.76793	0.39	0.77
AUC for Cl (0-inf)	0.95528	0.37	1.06
Biliary excretion rate	0.35326	0.56	0.64
Biliary tissue excretion rate	0.7676	0.39	1.17
Extracellular dispersion	0.23017	0.72	4.19
Extracellular mean transit time	0.47682	0.47	2.41
Final biliary excretion rate	0.26405	0.66	0.45
Final hepatocellular uptake rate	0.68796	0.4	1.44
Hematocrit			
Hepatocellular mean transit time	0.83026	0.38	0.9
Hepatocellular tissue uptake rate	0.26673	0.66	0.28
Hepatocellular uptake rate	0.24898	0.69	2.06
Initial biliary excretion rate	0.8499	0.38	1.11
Initial hepatocellular uptake rate	0.59543	0.42	1.71
Liver T1-MOLLI at 45min	0.49899	0.46	0.65
Liver T1-MOLLI at baseline	0.46924	0.48	1.92
Liver T1-MOLLI at scan 2	0.37867	0.53	3.57
Liver blood clearance	0.22127	0.74	1.78
Liver extracellular volume fraction	0.05543	1.94	10.6
RE for R1l at 20min	0.88785	0.38	0.89
RE for Sl at 20min	0.63696	0.41	0.69

Table 1.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	192.0 (48.0)	199.0 (29.0)	14.3 (35.0)
AUC for Cl (0-inf)	mM*sec	681.0 (310.0)	671.0 (120.0)	47.4 (89.0)
Biliary excretion rate	mL/min/100cm3	2.53 (0.79)	2.78 (0.89)	11.2 (19.0)
Biliary tissue excretion rate	mL/min/100cm3	3.35 (0.98)	3.25 (0.84)	-0.0278 (19.0)
Extracellular dispersion	%	74.9 (4.2)	62.5 (17.0)	-16.1 (24.0)
Extracellular mean transit time	sec	23.8 (2.6)	20.0 (8.4)	-12.6 (41.0)
Final biliary excretion rate	mL/min/100cm3	2.22 (0.54)	2.62 (0.88)	16.6 (24.0)
Final hepatocellular uptake rate	mL/min/100cm3	62.2 (22.0)	57.9 (11.0)	1.59 (24.0)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	33.3 (9.3)	34.0 (9.7)	4.63 (19.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	223.0 (43.0)	598.0 (600.0)	156.0 (240.0)
Hepatocellular uptake rate	mL/min/100cm3	54.7 (7.4)	50.7 (8.6)	-7.34 (11.0)
Initial biliary excretion rate	mL/min/100cm3	3.07 (1.4)	2.99 (0.93)	6.3 (29.0)
Initial hepatocellular uptake rate	mL/min/100cm3	47.3 (12.0)	43.6 (6.8)	4.37 (42.0)
Liver T1-MOLLI at 45min	sec	0.445 (0.062)	0.47 (0.098)	5.58 (13.0)
Liver T1-MOLLI at baseline	sec	0.761 (0.025)	0.75 (0.023)	-1.31 (3.5)
Liver T1-MOLLI at scan 2	sec	0.621 (0.076)	0.568 (0.041)	-5.77 (18.0)
Liver blood clearance	L/min	0.538 (0.11)	0.49 (0.14)	-10.4 (12.0)
Liver extracellular volume fraction	mL/100cm3	25.1 (2.6)	16.1 (7.4)	-36.3 (27.0)
RE for R1l at 20min	%	72.0 (24.0)	73.4 (10.0)	27.3 (61.0)
RE for Sl at 20min	%	61.7 (21.0)	65.8 (9.4)	36.2 (70.0)

Table 1.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.31911	0.59	0.4
AUC for Cb (0-inf)	0.74479	0.39	0.7
Body extraction fraction	0.81785	0.38	1.36
Cardiac output	0.2283	0.73	1.53
Heart-lung dispersion	0.38416	0.53	2.74
Heart-lung mean transit time	0.93329	0.37	1.11
Organs blood mean transit time	0.3065	0.6	2.09
Organs extraction fraction	0.08979	1.37	0.28
Organs extravascular mean transit time	0.04821	2.14	8.42
RE for R1b at 20min	0.56233	0.44	0.58
RE for Sb at 20min	0.89265	0.38	1.15

Table 1.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	23.6 (6.0)	27.3 (5.9)	26.0 (40.0)
AUC for Cb (0-inf)	mM*sec	44.4 (19.0)	48.5 (13.0)	46.0 (83.0)
Body extraction fraction	%	5.44 (2.2)	5.05 (1.2)	19.4 (54.0)
Cardiac output	L/min	10.5 (3.5)	9.49 (3.2)	-9.24 (15.0)
Heart-lung dispersion	%	57.1 (14.0)	48.9 (8.4)	-8.09 (23.0)
Heart-lung mean transit time	sec	15.0 (4.2)	14.8 (3.7)	9.95 (46.0)
Organs blood mean transit time	sec	32.8 (9.8)	28.1 (8.4)	-10.2 (30.0)
Organs extraction fraction	%	17.2 (2.1)	19.1 (2.3)	11.8 (11.0)
Organs extravascular mean transit time	min	8.02 (0.89)	6.93 (0.57)	-12.6 (9.5)
RE for R1b at 20min	%	14.2 (4.5)	15.7 (3.4)	29.5 (56.0)
RE for Sb at 20min	%	13.2 (5.1)	12.8 (3.9)	20.5 (67.0)

Table 1.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.4. Comparison to reference values

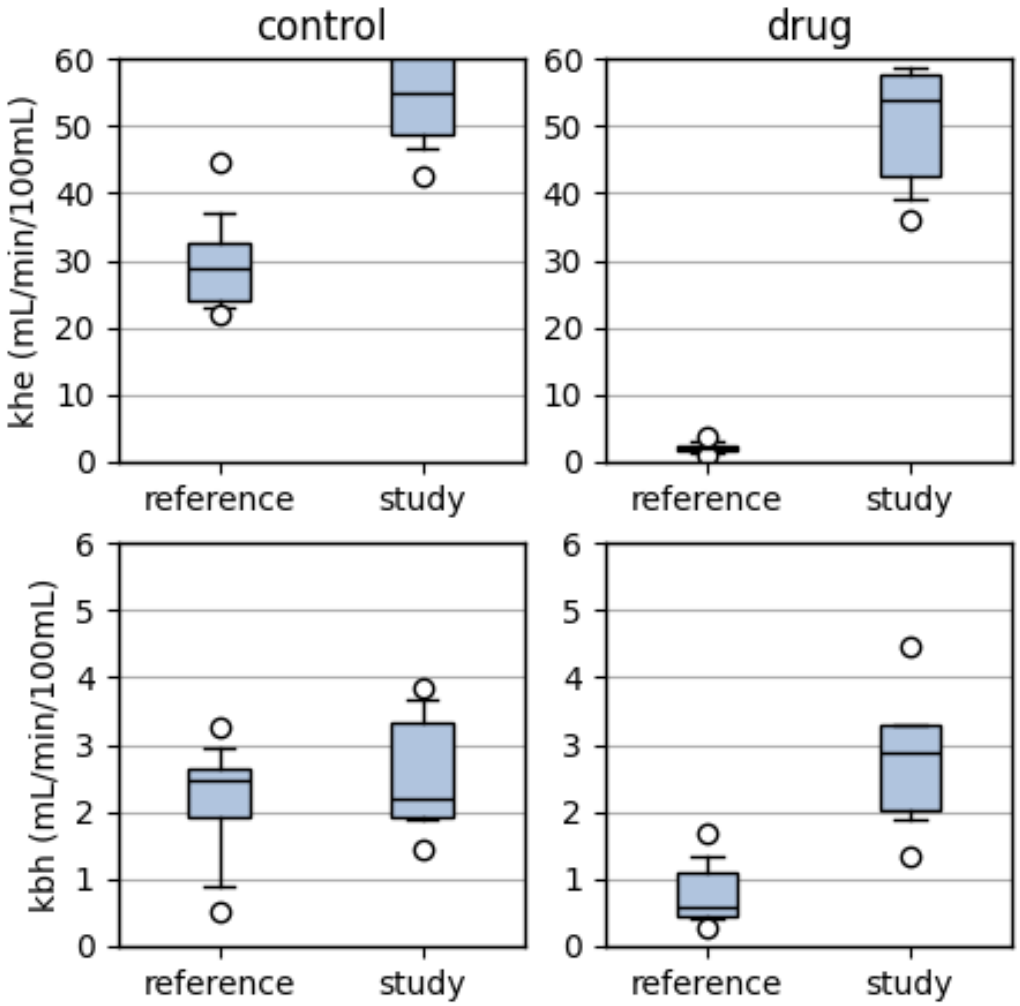

Figure 1.2: Comparison to reference values in healthy volunteers treated with the drug and under control conditions.

1.4.1. Control

Biomarker	Units	p-value	Bayes Factor	Power
Hepatocellular uptake rate	mL/min/100cm3	0.00034	302.74	1.0
Liver blood clearance	L/min	0.0035	77.29	1.0
Final hepatocellular uptake rate	mL/min/100cm3	0.02173	4.81	0.87
Extracellular mean transit time	sec	0.04575	2.06	0.38
Liver extracellular volume fraction	mL/100cm3	0.05762	1.68	0.35
Initial hepatocellular uptake rate	mL/min/100cm3	0.07059	1.75	0.64
Liver T1-MOLLI at baseline	sec	0.13425	0.97	0.26
Hepatocellular mean transit time	min	0.24708	0.71	0.15
Biliary tissue excretion rate	mL/min/100cm3	0.2742	0.68	0.2
Extracellular dispersion	%	0.32457	0.62	0.12
Liver T1-MOLLI at 45min	sec	0.3835	0.57	0.12
Hepatocellular tissue uptake rate	mL/min/100cm3	0.39344	0.57	0.1
Biliary excretion rate	mL/min/100cm3	0.4813	0.52	0.11
Initial biliary excretion rate	mL/min/100cm3	0.48333	0.52	0.12
RE for R1l at 20min	%	0.53742	0.5	0.08
Final biliary excretion rate	mL/min/100cm3	0.6057	0.48	0.07
RE for Sl at 20min	%	0.7892	0.45	0.06
AUC for Cl (0-35min)	mM*sec	0.81572	0.44	0.05
AUC for Cl (0-inf)	mM*sec	0.8925	0.44	0.05
Liver T1-MOLLI at scan 2	sec	0.8927	0.44	0.05
Hematocrit	%			

Table 1.6: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under control conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Organs extravascular mean transit time	min	0.01543	3.82	0.61
AUC for Cb (0-35min)	mM*sec	0.15453	0.92	0.21
Cardiac output	L/min	0.22484	0.76	0.26
RE for R1b at 20min	%	0.23558	0.72	0.16
Heart-lung dispersion	%	0.27216	0.68	0.22
Organs blood mean transit time	sec	0.40024	0.57	0.15
Body extraction fraction	%	0.41498	0.55	0.12
AUC for Cb (0-inf)	mM*sec	0.53138	0.5	0.08
Organs extraction fraction	%	0.55645	0.49	0.08
RE for Sb at 20min	%	0.69357	0.46	0.06
Heart-lung mean transit time	sec	0.84566	0.44	0.05

Table 1.7: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under control conditions.

1.4.2. Treatment

Biomarker	Units	p-value	Bayes Factor	Power
Liver T1-MOLLI at scan 2	sec	3e-05	650.24	1.0
RE for Sl at 20min	%	4e-05	156700.0	
RE for R1l at 20min	%	5e-05	169400.0	
AUC for Cl (0-35min)	mM*sec	6e-05	118500.0	1.0
Initial hepatocellular uptake rate	mL/min/100cm3	6e-05	145700.0	1.0
Hepatocellular uptake rate	mL/min/100cm3	0.0001	58150.0	
Final hepatocellular uptake rate	mL/min/100cm3	0.00017	20790.0	
AUC for Cl (0-inf)	mM*sec	0.00021	8393.48	
Liver blood clearance	L/min	0.00106	711.92	1.0
Biliary tissue excretion rate	mL/min/100cm3	0.00189	43.13	1.0
Extracellular mean transit time	sec	0.00219	17.16	0.95
Liver T1-MOLLI at 45min	sec	0.00229	51.28	1.0
Biliary excretion rate	mL/min/100cm3	0.00545	20.86	0.99
Hepatocellular mean transit time	min	0.01166	7.54	0.75
Final biliary excretion rate	mL/min/100cm3	0.03025	2.78	0.69
Liver T1-MOLLI at baseline	sec	0.0446	2.0	0.48
Hepatocellular tissue uptake rate	mL/min/100cm3	0.11287	1.35	0.54
Liver extracellular volume fraction	mL/100cm3	0.22882	0.78	0.27
Initial biliary excretion rate	mL/min/100cm3	0.25324	0.72	0.17
Extracellular dispersion	%	0.41888	0.57	0.15
Hematocrit	%			

Table 1.8: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under treatment conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Organs extraction fraction	%	0.02729	2.66	0.58
RE for R1b at 20min	%	0.06118	1.62	0.42
Body extraction fraction	%	0.06201	1.71	0.54
RE for Sb at 20min	%	0.10917	1.14	0.31
AUC for Cb (0-inf)	mM*sec	0.12406	1.04	0.3
AUC for Cb (0-35min)	mM*sec	0.14747	0.94	0.27
Cardiac output	L/min	0.33945	0.63	0.19
Organs blood mean transit time	sec	0.63242	0.49	0.07
Organs extravascular mean transit time	min	0.78145	0.46	0.06
Heart-lung dispersion	%	0.81322	0.46	0.06
Heart-lung mean transit time	sec	0.90028	0.45	0.05

Table 1.9: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under treatment conditions.

1.5. Case notes

1.5.1. Subject SHF-003

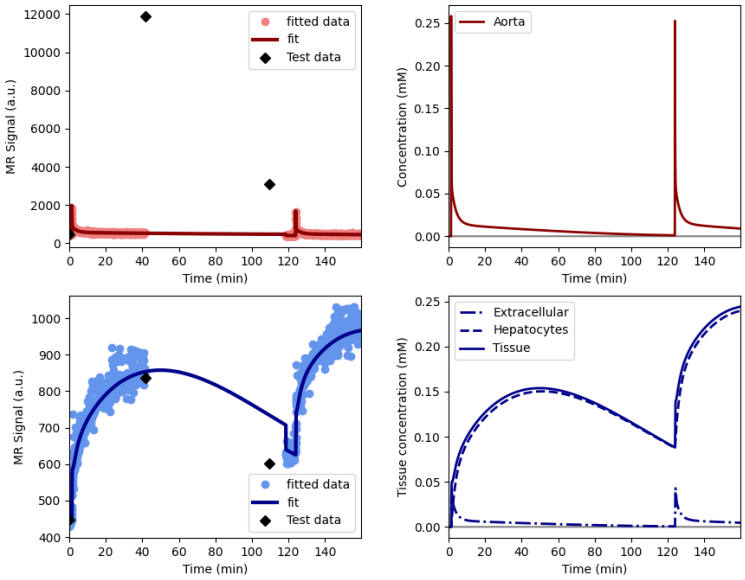

Figure 1.3: Signal-time curves for subject SHF-003 at the control visit.

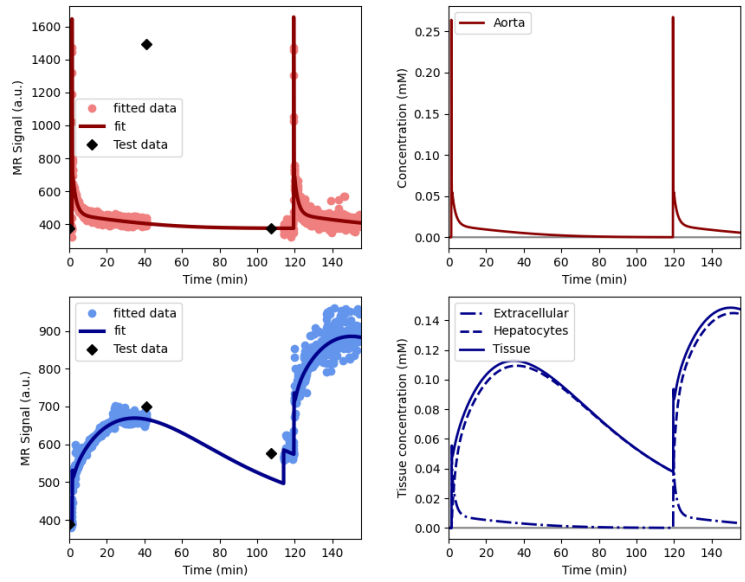

Figure 1.4: Signal-time curves for subject SHF-003 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	257.45	199.75	-22.41
AUC for Cl (0-inf)	mM*sec	1231.06	710.46	-42.29
Biliary excretion rate	mL/min/100cm3	1.43	1.34	-6.39
Biliary tissue excretion rate	mL/min/100cm3	1.98	1.94	-2.1
Extracellular dispersion	%	75.75	63.14	-16.64
Extracellular mean transit time	sec	20.21	19.49	-3.55
Final biliary excretion rate	mL/min/100cm3	1.27	1.24	-2.56
Final hepatocellular uptake rate	mL/min/100cm3	51.8	41.25	-20.36
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	50.54	51.63	2.15
Hepatocellular tissue uptake rate	mL/min/100cm3	167.72	126.85	-24.37
Hepatocellular uptake rate	mL/min/100cm3	46.52	39.2	-15.74
Initial biliary excretion rate	mL/min/100cm3	1.63	1.45	-10.86
Initial hepatocellular uptake rate	mL/min/100cm3	41.24	37.14	-9.94
Liver T1-MOLLI at 45min	sec	0.36	0.39	9.79
Liver T1-MOLLI at baseline	sec	0.72	0.76	4.8
Liver T1-MOLLI at scan 2	sec	0.47	0.59	26.68
Liver blood clearance	L/min	0.45	0.34	-23.31
Liver extracellular volume fraction	mL/100cm3	27.74	30.9	11.41
RE for R1l at 20min	%	91.79	78.01	-15.01
RE for Sl at 20min	%	79.87	69.67	-12.77

Table 1.10: Values for liver of subject SHF-003

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	31.23	26.48	-15.21
AUC for Cb (0-inf)	mM*sec	62.1	38.43	-38.11
Body extraction fraction	%	3.42	5.85	70.94
Cardiac output	L/min	12.36	12.08	-2.26
Heart-lung dispersion	%	84.6	40.47	-52.17
Heart-lung mean transit time	sec	9.48	19.35	104.08
Organs blood mean transit time	sec	26.38	17.4	-34.05
Organs extraction fraction	%	15.12	17.92	18.54
Organs extravascular mean transit time	min	8.81	6.3	-28.44
RE for R1b at 20min	%	18.1	15.04	-16.95
RE for Sb at 20min	%	20.31	11.57	-43.01

Table 1.11: Values for aorta of subject SHF-003

1.5.2. Subject SHF-008

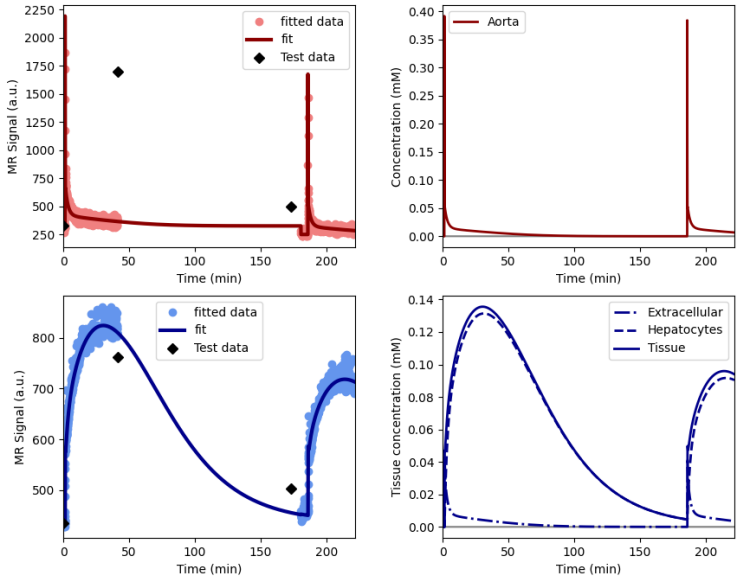

Figure 1.5: Signal-time curves for subject SHF-008 at the control visit.

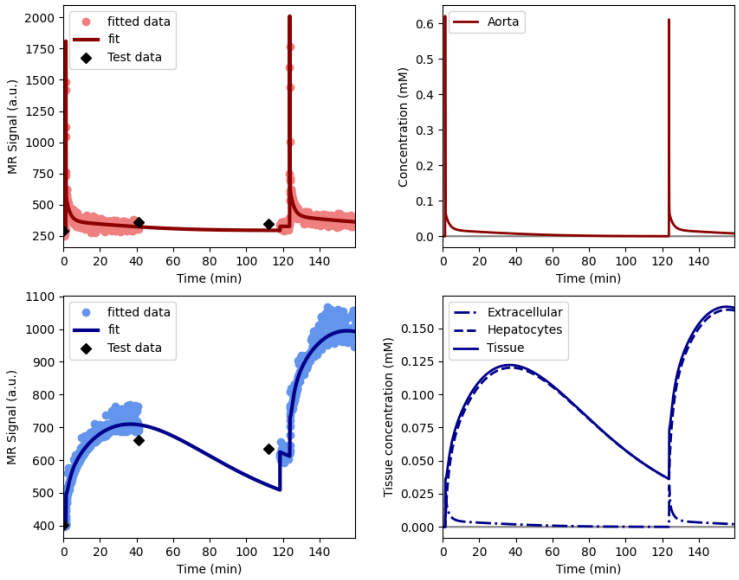

Figure 1.6: Signal-time curves for subject SHF-008 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	221.89	215.03	-3.09
AUC for Cl (0-inf)	mM*sec	745.22	774.22	3.89
Biliary excretion rate	mL/min/100cm3	2.06	1.89	-8.48
Biliary tissue excretion rate	mL/min/100cm3	2.91	2.2	-24.52
Extracellular dispersion	%	71.38	85.95	20.41
Extracellular mean transit time	sec	22.4	20.82	-7.06
Final biliary excretion rate	mL/min/100cm3	2.01	1.87	-7.25
Final hepatocellular uptake rate	mL/min/100cm3	32.37	40.37	24.73
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	34.38	45.56	32.49
Hepatocellular tissue uptake rate	mL/min/100cm3	146.48	256.76	75.29
Hepatocellular uptake rate	mL/min/100cm3	42.6	35.96	-15.58
Initial biliary excretion rate	mL/min/100cm3	2.11	1.91	-9.74
Initial hepatocellular uptake rate	mL/min/100cm3	52.83	31.55	-40.27
Liver T1-MOLLI at 45min	sec	0.42	0.43	1.39
Liver T1-MOLLI at baseline	sec	0.79	0.74	-5.76
Liver T1-MOLLI at scan 2	sec	0.67	0.56	-16.31
Liver blood clearance	L/min	0.36	0.28	-21.84
Liver extracellular volume fraction	mL/100cm3	29.08	14.01	-51.84
RE for R1l at 20min	%	100.43	81.05	-19.29
RE for Sl at 20min	%	85.95	71.98	-16.25

Table 1.12: Values for liver of subject SHF-008

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	27.45	34.7	26.41
AUC for Cb (0-inf)	mM*sec	43.95	53.33	21.34
Body extraction fraction	%	4.29	5.96	38.84
Cardiac output	L/min	7.17	4.26	-40.56
Heart-lung dispersion	%	37.19	41.47	11.49
Heart-lung mean transit time	sec	11.87	11.2	-5.65
Organs blood mean transit time	sec	20.91	32.2	54.0
Organs extraction fraction	%	15.76	19.42	23.26
Organs extravascular mean transit time	min	6.57	6.35	-3.37
RE for R1b at 20min	%	20.5	18.08	-11.79
RE for Sb at 20min	%	20.61	15.59	-24.36

Table 1.13: Values for aorta of subject SHF-008

1.5.3. Subject SHF-011

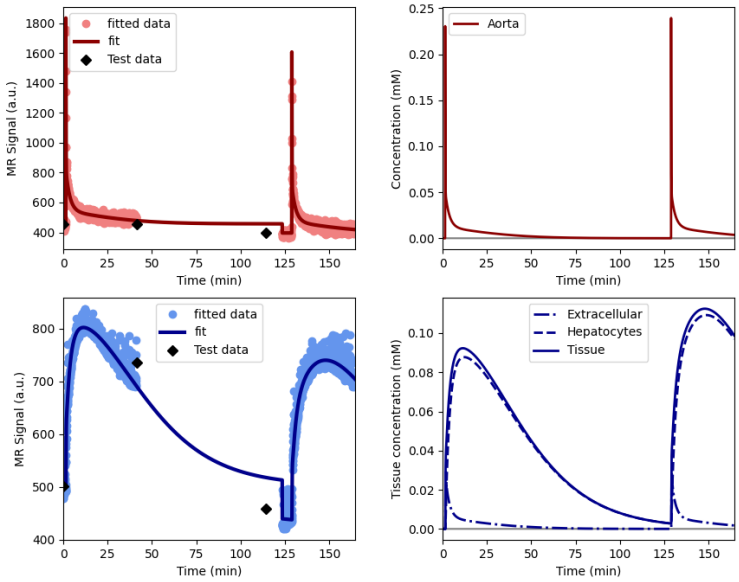

Figure 1.7: Signal-time curves for subject SHF-011 at the control visit.

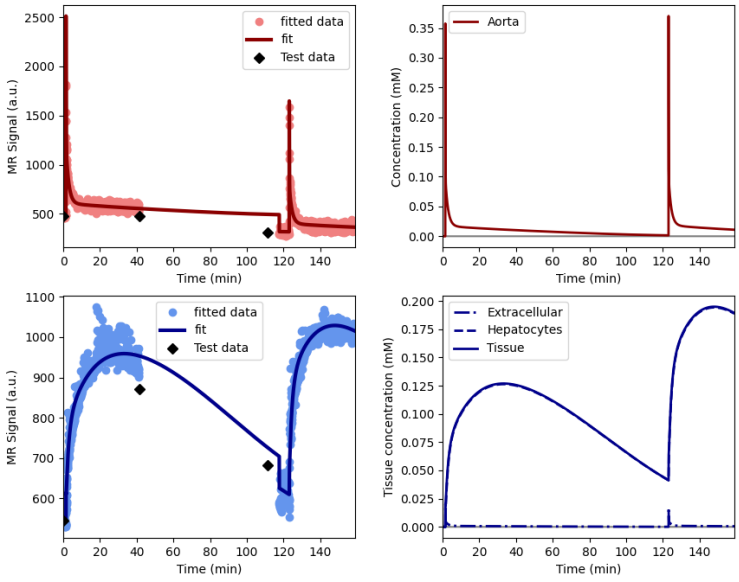

Figure 1.8: Signal-time curves for subject SHF-011 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	188.29	249.28	32.4
AUC for Cl (0-inf)	mM*sec	307.34	835.63	171.89
Biliary excretion rate	mL/min/100cm3	3.65	4.44	21.57
Biliary tissue excretion rate	mL/min/100cm3	4.91	4.57	-6.88
Extracellular dispersion	%	74.0	21.9	-70.41
Extracellular mean transit time	sec	24.99	1.75	-92.99
Final biliary excretion rate	mL/min/100cm3	2.67	4.45	66.89
Final hepatocellular uptake rate	mL/min/100cm3	58.91	70.85	20.28
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	20.38	21.88	7.39
Hepatocellular tissue uptake rate	mL/min/100cm3	244.29	2110.94	764.11
Hepatocellular uptake rate	mL/min/100cm3	62.37	58.64	-5.98
Initial biliary excretion rate	mL/min/100cm3	5.8	4.43	-23.58
Initial hepatocellular uptake rate	mL/min/100cm3	65.84	46.44	-29.47
Liver T1-MOLLI at 45min	sec	0.5	0.42	-14.81
Liver T1-MOLLI at baseline	sec	0.76	0.72	-5.54
Liver T1-MOLLI at scan 2	sec	0.71	0.49	-30.79
Liver blood clearance	L/min	0.5	0.46	-9.68
Liver extracellular volume fraction	mL/100cm3	25.53	2.78	-89.12
RE for R1l at 20min	%	63.32	85.31	34.72
RE for Sl at 20min	%	53.38	76.77	43.81

Table 1.14: Values for liver of subject SHF-011

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	21.65	35.48	63.85
AUC for Cb (0-inf)	mM*sec	28.48	73.96	159.71
Body extraction fraction	%	7.05	2.43	-65.54
Cardiac output	L/min	6.75	7.26	7.52
Heart-lung dispersion	%	49.87	64.61	29.57
Heart-lung mean transit time	sec	16.75	7.23	-56.84
Organs blood mean transit time	sec	24.14	12.58	-47.9
Organs extraction fraction	%	15.59	15.69	0.61
Organs extravascular mean transit time	min	6.82	7.04	3.13
RE for R1b at 20min	%	11.47	21.64	88.67
RE for Sb at 20min	%	11.66	19.1	63.72

Table 1.15: Values for aorta of subject SHF-011

1.5.4. Subject SHF-014

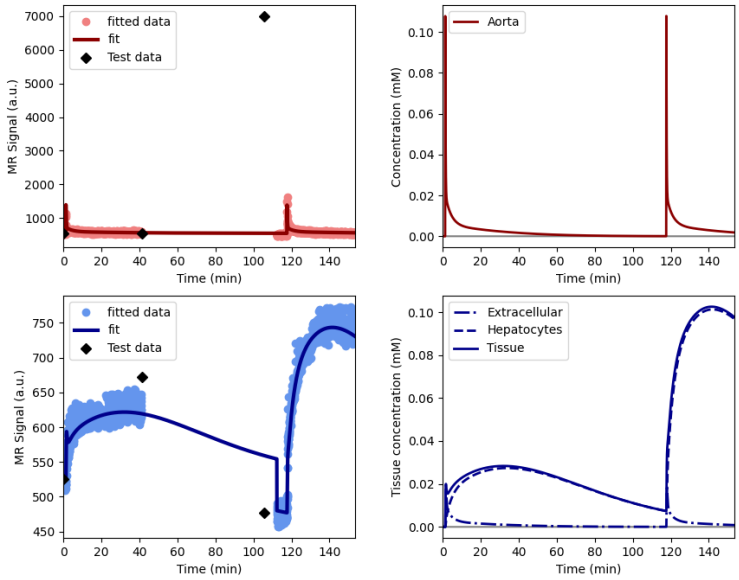

Figure 1.9: Signal-time curves for subject SHF-014 at the control visit.

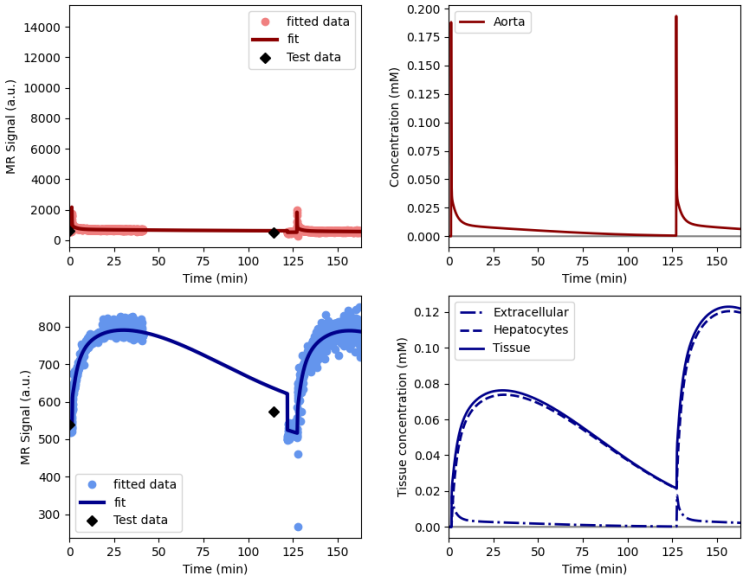

Figure 1.10: Signal-time curves for subject SHF-014 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	81.01	155.61	92.08
AUC for Cl (0-inf)	mM*sec	163.47	497.4	204.28
Biliary excretion rate	mL/min/100cm3	2.3	3.29	43.09
Biliary tissue excretion rate	mL/min/100cm3	3.05	4.07	33.3
Extracellular dispersion	%	82.02	67.32	-17.93
Extracellular mean transit time	sec	20.54	34.32	67.14
Final biliary excretion rate	mL/min/100cm3	2.17	2.89	33.33
Final hepatocellular uptake rate	mL/min/100cm3	112.77	62.16	-44.88
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	32.74	24.56	-24.98
Hepatocellular tissue uptake rate	mL/min/100cm3	270.86	275.26	1.63
Hepatocellular uptake rate	mL/min/100cm3	67.06	52.95	-21.04
Initial biliary excretion rate	mL/min/100cm3	2.44	3.81	55.93
Initial hepatocellular uptake rate	mL/min/100cm3	21.34	43.73	104.89
Liver T1-MOLLI at 45min	sec	0.56	0.72	29.04
Liver T1-MOLLI at baseline	sec	0.73	0.72	-1.47
Liver T1-MOLLI at scan 2	sec	0.69	0.56	-19.85
Liver blood clearance	L/min	0.75	0.62	-16.9
Liver extracellular volume fraction	mL/100cm3	24.76	19.23	-22.31
RE for R1l at 20min	%	18.91	52.24	176.22
RE for Sl at 20min	%	14.92	45.69	206.31

Table 1.16: Values for liver of subject SHF-014

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	10.79	22.18	105.55
AUC for Cb (0-inf)	mM*sec	14.87	43.51	192.65
Body extraction fraction	%	10.16	4.16	-59.1
Cardiac output	L/min	17.97	14.57	-18.91
Heart-lung dispersion	%	56.36	57.21	1.49
Heart-lung mean transit time	sec	24.5	16.09	-34.35
Organs blood mean transit time	sec	49.11	34.69	-29.36
Organs extraction fraction	%	18.44	17.15	-7.0
Organs extravascular mean transit time	min	8.83	8.11	-8.1
RE for R1b at 20min	%	5.38	13.14	144.34
RE for Sb at 20min	%	5.76	15.59	170.45

Table 1.17: Values for aorta of subject SHF-014

1.5.5. Subject SHF-021

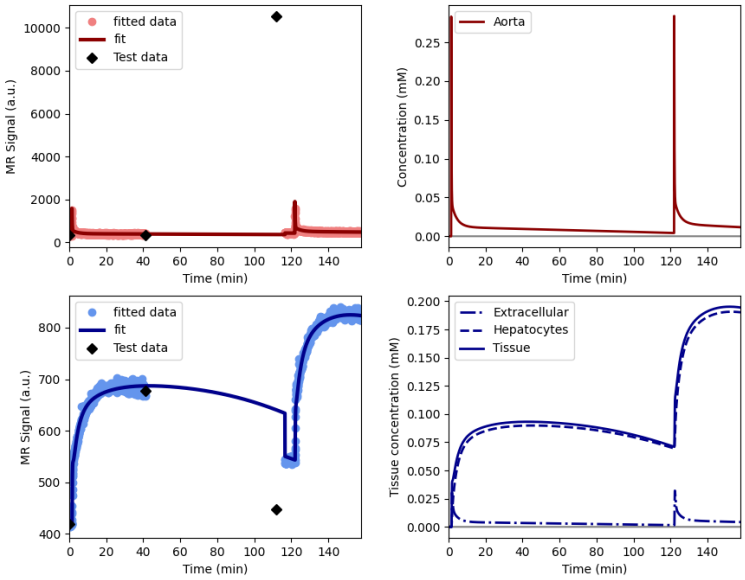

Figure 1.11: Signal-time curves for subject SHF-021 at the control visit.

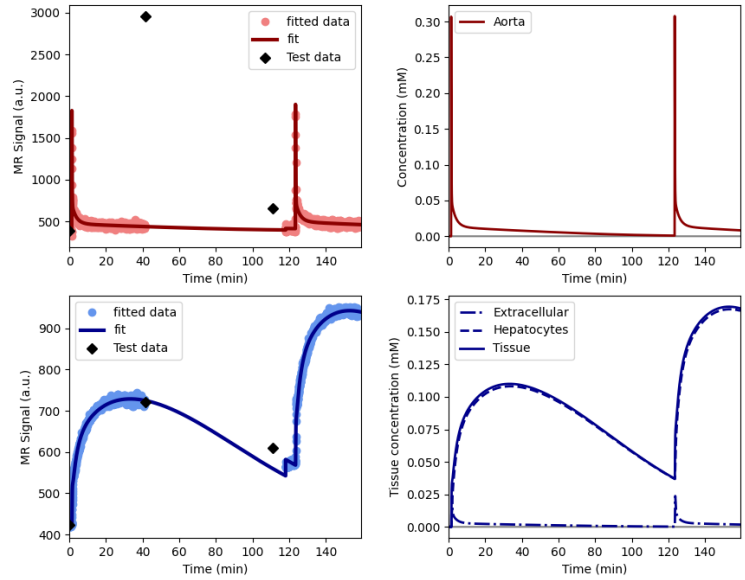

Figure 1.12: Signal-time curves for subject SHF-021 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	196.44	215.64	9.78
AUC for Cl (0-inf)	mM*sec	846.18	737.5	-12.84
Biliary excretion rate	mL/min/100cm3	3.83	3.26	-14.72
Biliary tissue excretion rate	mL/min/100cm3	4.79	3.7	-22.59
Extracellular dispersion	%	67.39	65.95	-2.14
Extracellular mean transit time	sec	28.16	20.19	-28.3
Final biliary excretion rate	mL/min/100cm3	3.26	2.95	-9.46
Final hepatocellular uptake rate	mL/min/100cm3	64.59	62.85	-2.7
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	20.9	26.99	29.18
Hepatocellular tissue uptake rate	mL/min/100cm3	275.07	460.55	67.43
Hepatocellular uptake rate	mL/min/100cm3	55.08	54.78	-0.55
Initial biliary excretion rate	mL/min/100cm3	4.63	3.65	-21.21
Initial hepatocellular uptake rate	mL/min/100cm3	45.57	46.71	2.5
Liver T1-MOLLI at 45min	sec	0.47	0.43	-8.89
Liver T1-MOLLI at baseline	sec	0.8	0.78	-2.93
Liver T1-MOLLI at scan 2	sec	0.64	0.56	-12.25
Liver blood clearance	L/min	0.54	0.49	-8.85
Liver extracellular volume fraction	mL/100cm3	20.02	11.89	-40.6
RE for R1l at 20min	%	70.04	80.28	14.63
RE for Sl at 20min	%	62.14	73.04	17.54

Table 1.18: Values for liver of subject SHF-021

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	29.36	28.68	-2.33
AUC for Cb (0-inf)	mM*sec	81.84	56.41	-31.06
Body extraction fraction	%	2.63	5.21	98.56
Cardiac output	L/min	7.26	6.7	-7.75
Heart-lung dispersion	%	71.75	50.95	-28.99
Heart-lung mean transit time	sec	13.29	18.64	40.26
Organs blood mean transit time	sec	47.32	39.06	-17.46
Organs extraction fraction	%	22.02	23.6	7.17
Organs extravascular mean transit time	min	9.17	7.34	-19.98
RE for R1b at 20min	%	17.56	16.75	-4.63
RE for Sb at 20min	%	7.03	7.09	0.96

Table 1.19: Values for aorta of subject SHF-021

1.5.6. Subject SHF-022

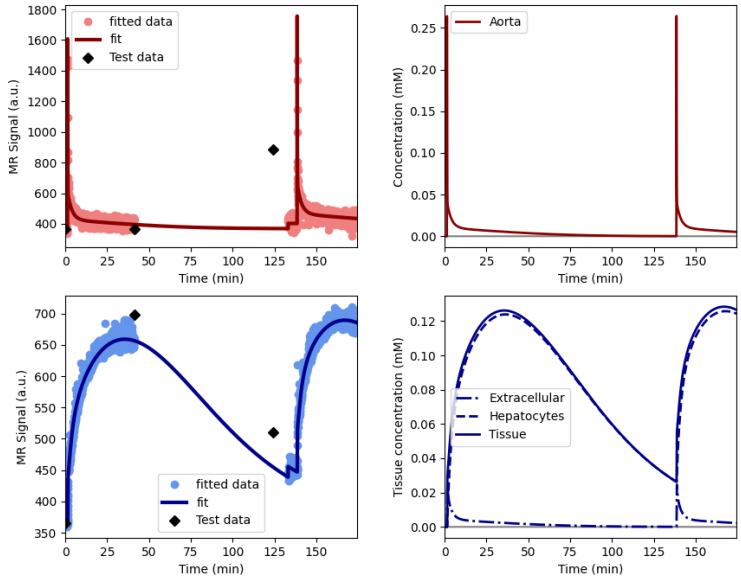

Figure 1.13: Signal-time curves for subject SHF-022 at the control visit.

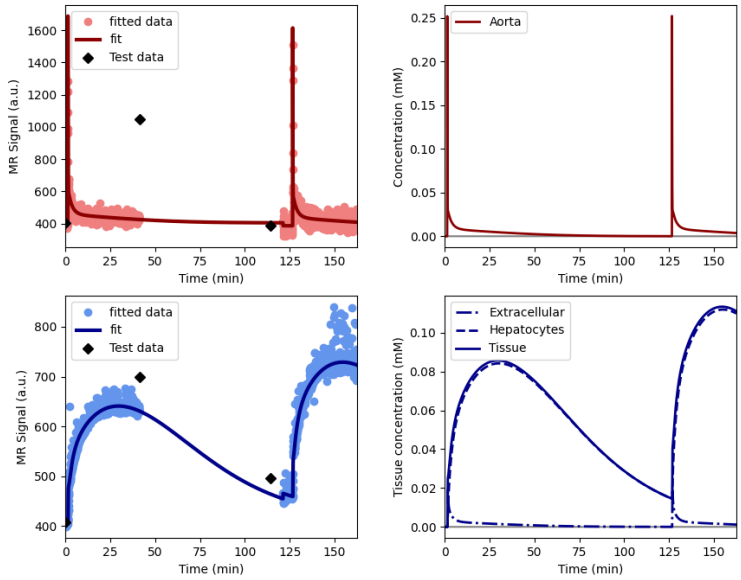

Figure 1.14: Signal-time curves for subject SHF-022 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	209.83	161.5	-23.03
AUC for Cl (0-inf)	mM*sec	791.04	472.25	-40.3
Biliary excretion rate	mL/min/100cm3	1.88	2.49	32.09
Biliary tissue excretion rate	mL/min/100cm3	2.46	3.02	22.63
Extracellular dispersion	%	78.72	70.94	-9.89
Extracellular mean transit time	sec	26.31	23.44	-10.91
Final biliary excretion rate	mL/min/100cm3	1.96	2.33	18.87
Final hepatocellular uptake rate	mL/min/100cm3	52.74	69.86	32.48
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	40.65	33.15	-18.45
Hepatocellular tissue uptake rate	mL/min/100cm3	233.65	358.7	53.52
Hepatocellular uptake rate	mL/min/100cm3	54.8	62.94	14.85
Initial biliary excretion rate	mL/min/100cm3	1.81	2.67	47.27
Initial hepatocellular uptake rate	mL/min/100cm3	56.86	56.01	-1.49
Liver T1-MOLLI at 45min	sec	0.37	0.43	16.95
Liver T1-MOLLI at baseline	sec	0.76	0.78	3.03
Liver T1-MOLLI at scan 2	sec	0.55	0.65	17.9
Liver blood clearance	L/min	0.62	0.74	18.32
Liver extracellular volume fraction	mL/100cm3	23.45	17.55	-25.19
RE for R1l at 20min	%	87.22	63.45	-27.26
RE for Sl at 20min	%	73.81	57.89	-21.57

Table 1.20: Values for liver of subject SHF-022

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	21.23	16.45	-22.55
AUC for Cb (0-inf)	mM*sec	35.15	25.11	-28.55
Body extraction fraction	%	5.06	6.71	32.64
Cardiac output	L/min	11.35	12.09	6.53
Heart-lung dispersion	%	42.66	38.42	-9.95
Heart-lung mean transit time	sec	14.3	16.04	12.21
Organs blood mean transit time	sec	28.66	32.62	13.82
Organs extraction fraction	%	16.34	20.95	28.25
Organs extravascular mean transit time	min	7.95	6.43	-19.11
RE for R1b at 20min	%	12.01	9.32	-22.39
RE for Sb at 20min	%	13.82	7.6	-45.02

Table 1.21: Values for aorta of subject SHF-022

2

One-scan results

2.1. Data summary

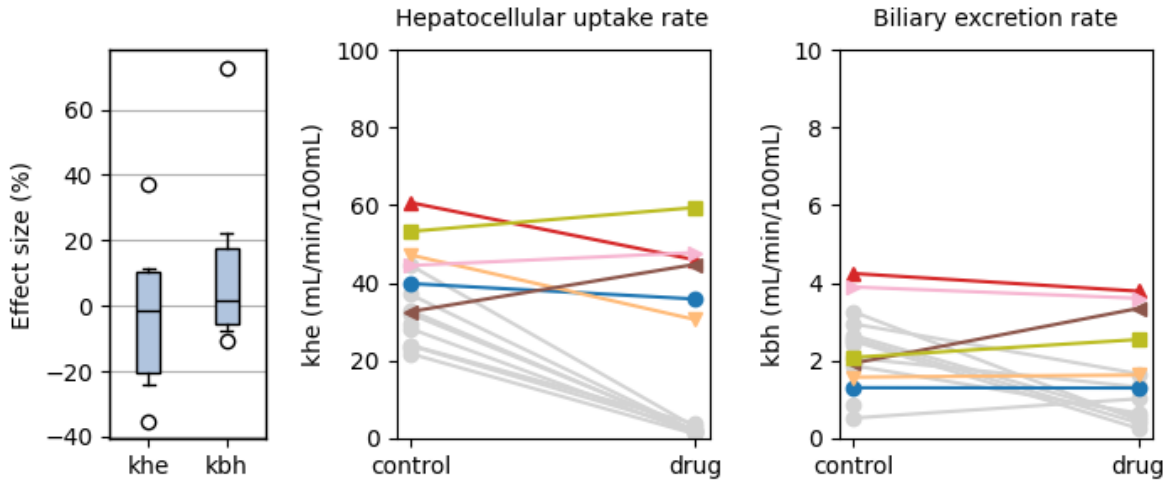

Figure 2.1: Effect size (%) on hepatocellular uptake (k_he, left) and biliary excretion (k_bh, right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_he, middle) and biliary excretion (k_bh, right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

parameter	count	mean	std	min	25%	50%	75%	max
khe effect size (%)	6.0	-2.2	26.3	-35.2	-20.7	-1.2	10.5	37.2
khe control (mL/min/100cm3)	6.0	46.34	9.87	32.62	41.0	45.84	51.72	60.66
khe drug (mL/min/100cm3)	6.0	44.06	10.01	30.6	38.09	45.35	47.34	59.38
kbh effect size (%)	6.0	13.3	31.4	-10.7	-5.7	1.5	17.4	72.9
kbh control (mL/min/100cm3)	6.0	2.51	1.25	1.3	1.67	2.01	3.44	4.24
kbh drug (mL/min/100cm3)	6.0	2.7	1.05	1.3	1.86	2.94	3.54	3.79

Table 2.1: Effect size and absolute values of hepatocellular uptake (k_he) and biliary excretion (k_bh) of gadoxetate

2.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cl (0-35min)	0.86209	0.38	0.86
AUC for Cl (0-inf)	0.80839	0.38	1.29
Biliary excretion rate	0.50816	0.46	0.74
Biliary tissue excretion rate	0.91801	0.38	1.06
Extracellular dispersion	0.58153	0.43	1.82
Extracellular mean transit time	0.17297	0.87	0.24
Hematocrit			
Hepatocellular mean transit time	0.66415	0.41	1.24
Hepatocellular tissue uptake rate	0.87198	0.38	0.86
Hepatocellular uptake rate	0.65042	0.41	1.52
Liver T1-MOLLI at 45min	0.49899	0.46	0.65
Liver T1-MOLLI at baseline	0.46924	0.48	1.92
Liver blood clearance	0.71944	0.4	1.31
Liver extracellular volume fraction	0.44276	0.49	2.45
RE for R1l at 20min	0.89461	0.38	0.9
RE for Sl at 20min	0.80594	0.38	0.8

Table 2.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	181.0 (57.0)	186.0 (26.0)	25.9 (58.0)
AUC for Cl (0-inf)	mM*sec	774.0 (370.0)	727.0 (100.0)	49.5 (100.0)
Biliary excretion rate	mL/min/100cm3	2.51 (1.0)	2.7 (0.84)	13.3 (25.0)
Biliary tissue excretion rate	mL/min/100cm3	3.57 (1.4)	3.52 (0.97)	6.09 (24.0)
Extracellular dispersion	%	85.5 (7.8)	82.0 (9.3)	-3.2 (13.0)
Extracellular mean transit time	sec	33.4 (11.0)	43.1 (8.5)	39.6 (35.0)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	33.8 (12.0)	32.1 (11.0)	0.599 (22.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	194.0 (95.0)	202.0 (71.0)	26.6 (55.0)
Hepatocellular uptake rate	mL/min/100cm3	46.3 (7.9)	44.1 (8.0)	-2.2 (21.0)
Liver T1-MOLLI at 45min	sec	0.445 (0.062)	0.47 (0.098)	5.58 (13.0)
Liver T1-MOLLI at baseline	sec	0.761 (0.025)	0.75 (0.023)	-1.31 (3.5)
Liver blood clearance	L/min	0.447 (0.072)	0.428 (0.13)	-4.58 (25.0)
Liver extracellular volume fraction	mL/100cm3	29.1 (8.9)	24.3 (6.7)	-0.278 (54.0)
RE for R1l at 20min	%	72.8 (23.0)	74.1 (10.0)	25.3 (57.0)
RE for Sl at 20min	%	62.7 (21.0)	65.2 (7.9)	35.9 (76.0)

Table 2.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.27329	0.65	0.36
AUC for Cb (0-inf)	0.61377	0.42	0.58
Body extraction fraction	0.73864	0.39	1.54
Cardiac output	0.37728	0.54	1.59
Heart-lung dispersion	0.04297	2.33	0.28
Heart-lung mean transit time	0.32374	0.58	3.45
Organs blood mean transit time	0.62147	0.42	0.67
Organs extraction fraction	0.86332	0.38	1.23
Organs extravascular mean transit time	0.54396	0.44	2.41
RE for R1b at 20min	0.42167	0.5	0.45
RE for Sb at 20min	0.96614	0.37	0.95

Table 2.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	24.1 (6.4)	28.6 (6.2)	32.8 (49.0)
AUC for Cb (0-inf)	mM*sec	51.9 (21.0)	58.6 (15.0)	56.4 (100.0)
Body extraction fraction	%	4.96 (2.2)	4.44 (1.0)	12.1 (43.0)
Cardiac output	L/min	9.57 (3.4)	8.49 (3.3)	-11.2 (25.0)
Heart-lung dispersion	%	54.1 (17.0)	67.3 (13.0)	30.3 (23.0)
Heart-lung mean transit time	sec	19.6 (4.9)	16.0 (3.5)	-10.9 (34.0)
Organs blood mean transit time	sec	33.9 (12.0)	36.6 (7.4)	22.2 (40.0)
Organs extraction fraction	%	24.1 (11.0)	22.9 (3.7)	16.2 (44.0)
Organs extravascular mean transit time	min	8.12 (2.9)	6.77 (1.3)	42.1 (140.0)
RE for R1b at 20min	%	14.6 (4.4)	16.9 (3.8)	32.8 (54.0)
RE for Sb at 20min	%	15.2 (8.1)	15.4 (3.1)	48.0 (81.0)

Table 2.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.4. Case notes

2.4.1. Subject SHF-003

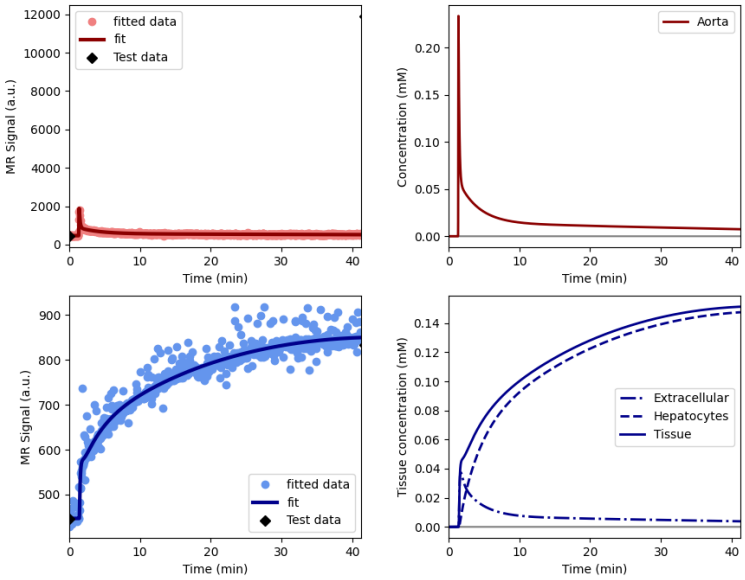

Figure 2.2: Signal-time curves for subject SHF-003 at the control visit.

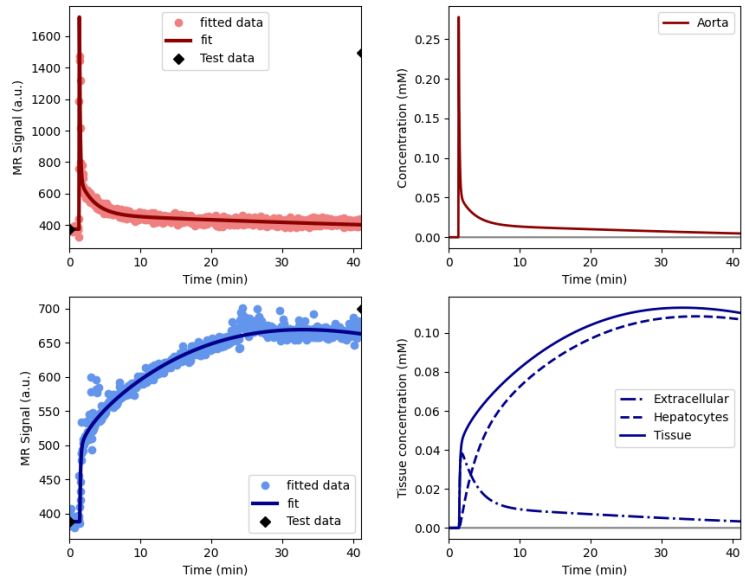

Figure 2.3: Signal-time curves for subject SHF-003 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	243.36	197.49	-18.85
AUC for Cl (0-inf)	mM*sec	1483.62	758.31	-48.89
Biliary excretion rate	mL/min/100cm3	1.3	1.3	-0.57
Biliary tissue excretion rate	mL/min/100cm3	1.81	2.08	14.45
Extracellular dispersion	%	82.13	87.0	5.93
Extracellular mean transit time	sec	24.28	39.76	63.74
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	55.14	48.18	-12.63
Hepatocellular tissue uptake rate	mL/min/100cm3	141.92	95.62	-32.62
Hepatocellular uptake rate	mL/min/100cm3	39.84	35.87	-9.96
Liver T1-MOLLI at 45min	sec	0.36	0.39	9.79
Liver T1-MOLLI at baseline	sec	0.72	0.76	4.8
Liver blood clearance	L/min	0.38	0.31	-18.05
Liver extracellular volume fraction	mL/100cm3	28.07	37.51	33.63
RE for R1l at 20min	%	93.17	79.19	-15.0
RE for Sl at 20min	%	85.61	67.73	-20.88

Table 2.6: Values for liver of subject SHF-003

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	31.94	28.49	-10.8
AUC for Cb (0-inf)	mM*sec	78.68	44.66	-43.24
Body extraction fraction	%	2.91	5.38	85.06
Cardiac output	L/min	10.12	11.26	11.3
Heart-lung dispersion	%	61.64	78.81	27.85
Heart-lung mean transit time	sec	18.08	9.97	-44.84
Organs blood mean transit time	sec	29.8	32.42	8.77
Organs extraction fraction	%	17.32	18.66	7.77
Organs extravascular mean transit time	min	10.83	6.2	-42.79
RE for R1b at 20min	%	18.42	16.56	-10.1
RE for Sb at 20min	%	20.51	14.52	-29.19

Table 2.7: Values for aorta of subject SHF-003

2.4.2. Subject SHF-008

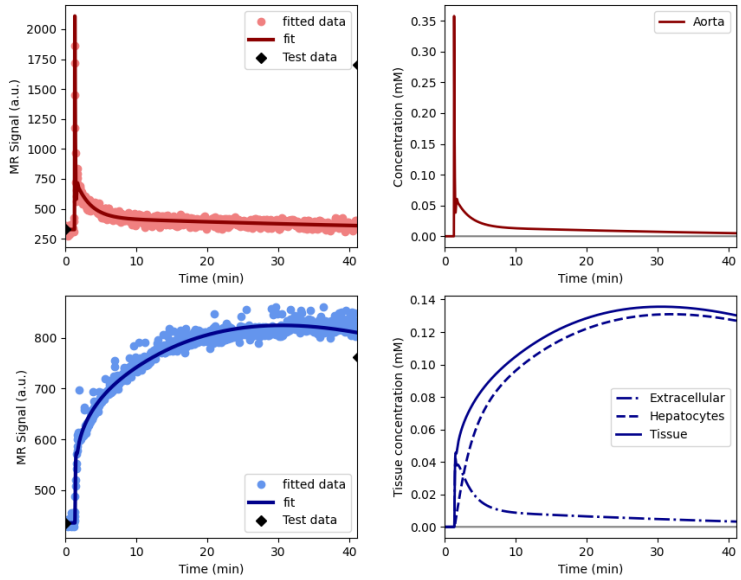

Figure 2.4: Signal-time curves for subject SHF-008 at the control visit.

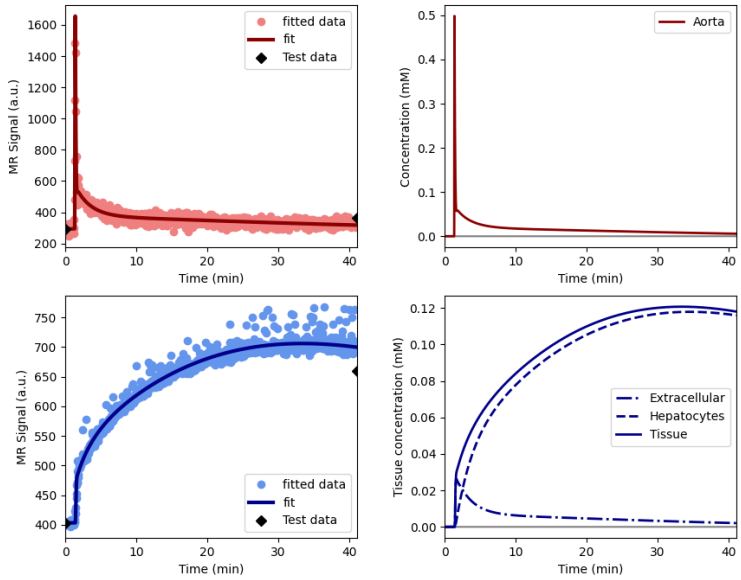

Figure 2.5: Signal-time curves for subject SHF-008 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	241.82	204.67	-15.37
AUC for Cl (0-inf)	mM*sec	883.79	790.64	-10.54
Biliary excretion rate	mL/min/100cm3	1.58	1.63	3.61
Biliary tissue excretion rate	mL/min/100cm3	2.47	2.02	-18.13
Extracellular dispersion	%	86.81	87.09	0.33
Extracellular mean transit time	sec	25.01	37.16	48.61
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	40.44	49.4	22.15
Hepatocellular tissue uptake rate	mL/min/100cm3	130.08	158.07	21.52
Hepatocellular uptake rate	mL/min/100cm3	47.19	30.6	-35.17
Liver T1-MOLLI at 45min	sec	0.42	0.43	1.39
Liver T1-MOLLI at baseline	sec	0.79	0.74	-5.76
Liver blood clearance	L/min	0.4	0.24	-39.98
Liver extracellular volume fraction	mL/100cm3	36.28	19.36	-46.65
RE for R1l at 20min	%	101.1	81.59	-19.3
RE for Sl at 20min	%	83.08	70.63	-14.98

Table 2.8: Values for liver of subject SHF-008

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	28.07	35.83	27.61
AUC for Cb (0-inf)	mM*sec	46.6	54.09	16.07
Body extraction fraction	%	4.07	5.86	44.03
Cardiac output	L/min	7.1	4.28	-39.66
Heart-lung dispersion	%	30.66	36.08	17.7
Heart-lung mean transit time	sec	15.39	15.96	3.67
Organs blood mean transit time	sec	15.1	30.41	101.31
Organs extraction fraction	%	14.9	19.65	31.82
Organs extravascular mean transit time	min	7.47	5.64	-24.59
RE for R1b at 20min	%	20.72	19.09	-7.86
RE for Sb at 20min	%	32.13	13.47	-58.08

Table 2.9: Values for aorta of subject SHF-008

2.4.3. Subject SHF-011

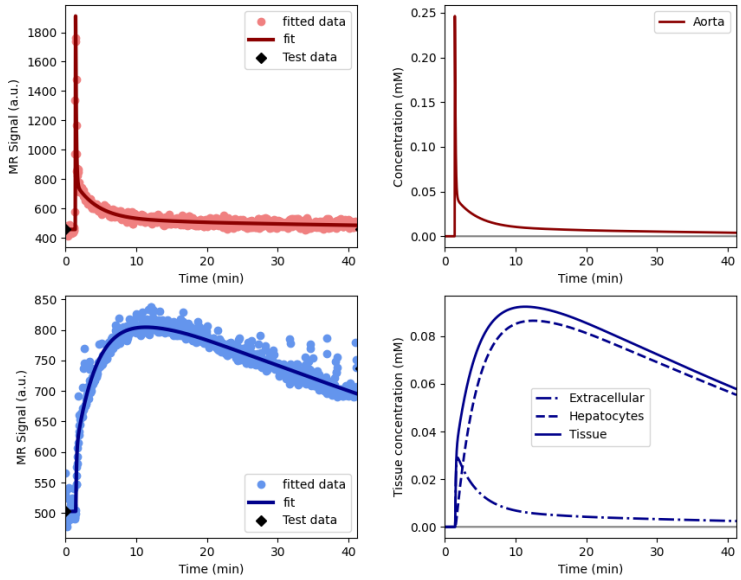

Figure 2.6: Signal-time curves for subject SHF-011 at the control visit.

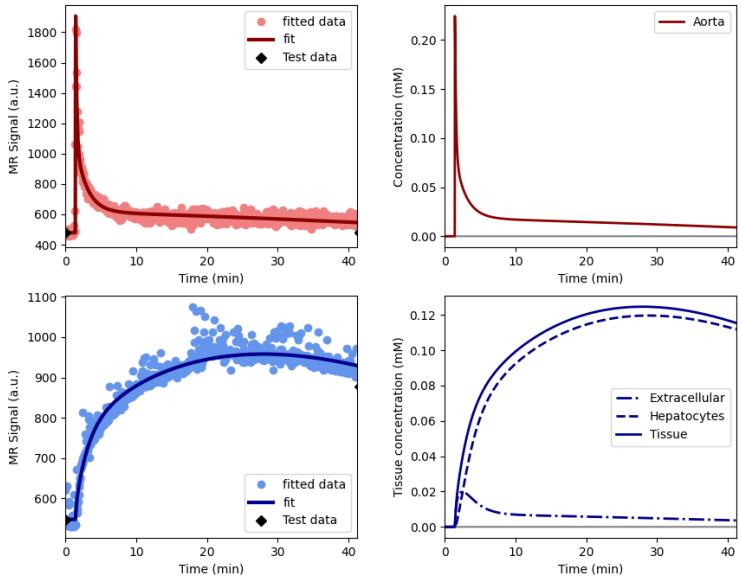

Figure 2.7: Signal-time curves for subject SHF-011 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	164.55	223.12	35.59
AUC for Cl (0-inf)	mM*sec	403.29	771.9	91.4
Biliary excretion rate	mL/min/100cm3	4.24	3.79	-10.69
Biliary tissue excretion rate	mL/min/100cm3	6.43	4.84	-24.82
Extracellular dispersion	%	90.48	100.0	10.52
Extracellular mean transit time	sec	35.27	59.99	70.08
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	15.54	20.67	33.02
Hepatocellular tissue uptake rate	mL/min/100cm3	177.99	211.83	19.01
Hepatocellular uptake rate	mL/min/100cm3	60.66	45.95	-24.26
Liver T1-MOLLI at 45min	sec	0.5	0.42	-14.81
Liver T1-MOLLI at baseline	sec	0.76	0.72	-5.54
Liver blood clearance	L/min	0.49	0.36	-27.25
Liver extracellular volume fraction	mL/100cm3	34.08	21.69	-36.36
RE for R1l at 20min	%	63.32	85.86	35.61
RE for Sl at 20min	%	53.57	75.81	41.51

Table 2.10: Values for liver of subject SHF-011

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	22.11	37.38	69.05
AUC for Cb (0-inf)	mM*sec	40.52	79.65	96.54
Body extraction fraction	%	4.86	4.26	-12.29
Cardiac output	L/min	6.69	3.86	-42.26
Heart-lung dispersion	%	56.4	70.1	24.29
Heart-lung mean transit time	sec	14.01	23.35	66.67
Organs blood mean transit time	sec	32.89	23.51	-28.51
Organs extraction fraction	%	14.36	30.03	109.11
Organs extravascular mean transit time	min	12.3	4.88	-60.3
RE for R1b at 20min	%	11.42	23.66	107.18
RE for Sb at 20min	%	16.33	21.43	31.26

Table 2.11: Values for aorta of subject SHF-011

2.4.4. Subject SHF-014

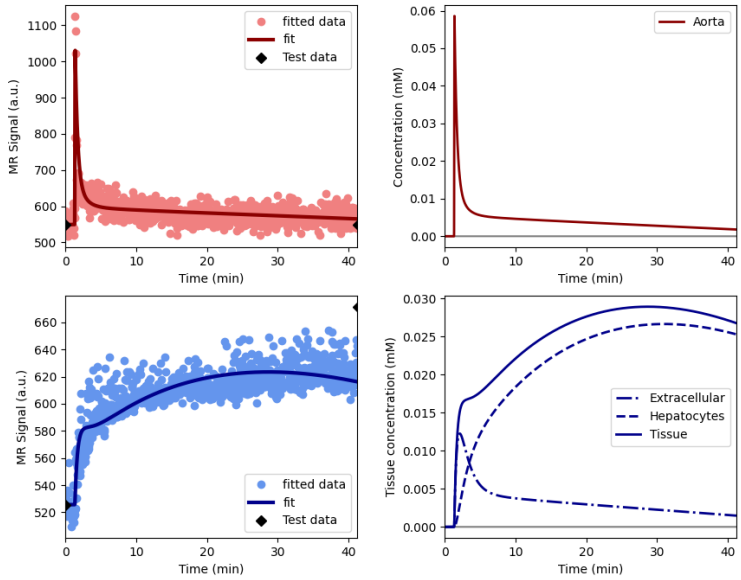

Figure 2.8: Signal-time curves for subject SHF-014 at the control visit.

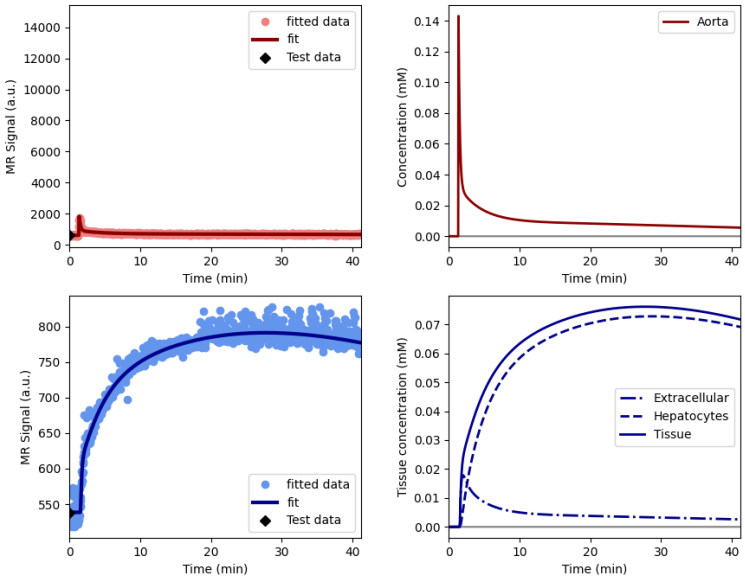

Figure 2.9: Signal-time curves for subject SHF-014 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	52.2	139.2	166.68
AUC for Cl (0-inf)	mM*sec	151.81	592.34	290.19
Biliary excretion rate	mL/min/100cm3	1.93	3.34	72.88
Biliary tissue excretion rate	mL/min/100cm3	3.41	4.46	30.73
Extracellular dispersion	%	100.0	71.95	-28.05
Extracellular mean transit time	sec	60.0	45.17	-24.72
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	29.32	22.43	-23.51
Hepatocellular tissue uptake rate	mL/min/100cm3	75.34	178.89	137.46
Hepatocellular uptake rate	mL/min/100cm3	32.62	44.76	37.2
Liver T1-MOLLI at 45min	sec	0.56	0.72	29.04
Liver T1-MOLLI at baseline	sec	0.73	0.72	-1.47
Liver blood clearance	L/min	0.36	0.53	44.4
Liver extracellular volume fraction	mL/100cm3	43.3	25.02	-42.22
RE for R1l at 20min	%	20.01	52.78	163.74
RE for Sl at 20min	%	15.81	50.99	222.55

Table 2.12: Values for liver of subject SHF-014

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	9.57	22.58	136.03
AUC for Cb (0-inf)	mM*sec	14.81	59.48	301.49
Body extraction fraction	%	10.19	2.71	-73.39
Cardiac output	L/min	18.0	13.79	-23.37
Heart-lung dispersion	%	89.04	83.32	-6.43
Heart-lung mean transit time	sec	30.0	16.23	-45.89
Organs blood mean transit time	sec	60.0	44.6	-25.67
Organs extraction fraction	%	50.0	18.74	-62.52
Organs extravascular mean transit time	min	1.88	9.44	401.16
RE for R1b at 20min	%	5.88	13.56	130.72
RE for Sb at 20min	%	4.33	14.3	230.14

Table 2.13: Values for aorta of subject SHF-014

2.4.5. Subject SHF-021

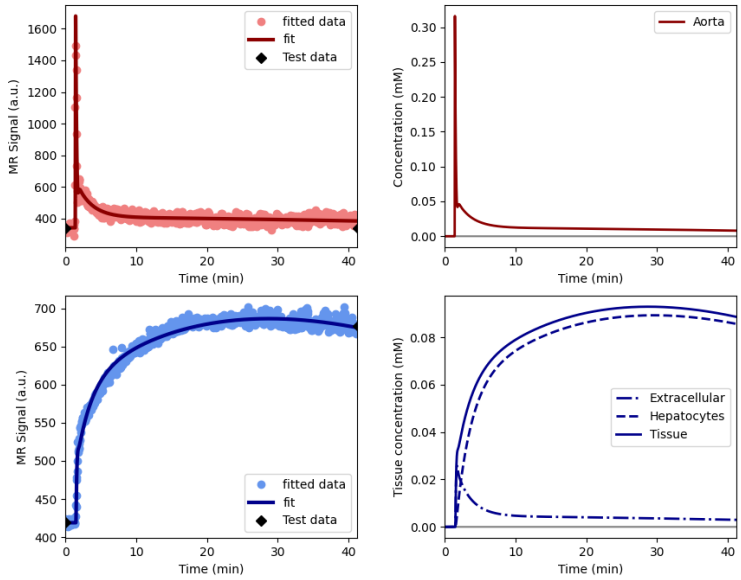

Figure 2.10: Signal-time curves for subject SHF-021 at the control visit.

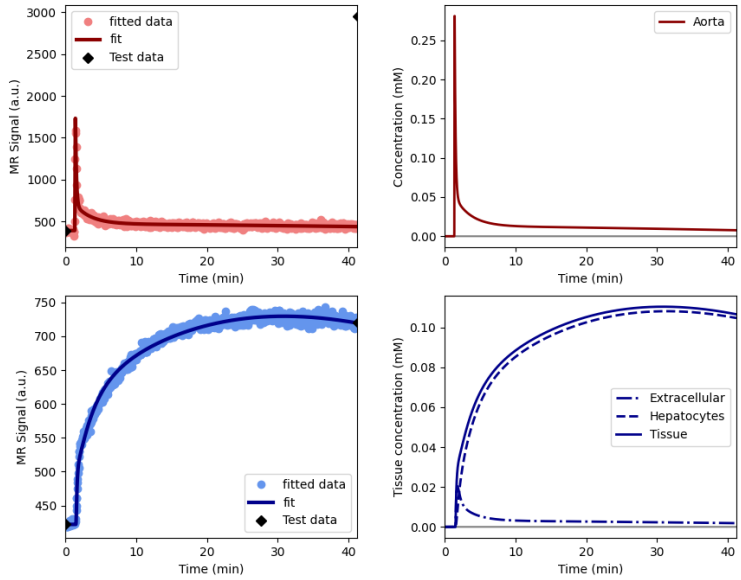

Figure 2.11: Signal-time curves for subject SHF-021 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	171.11	198.52	16.02
AUC for Cl (0-inf)	mM*sec	760.93	886.57	16.51
Biliary excretion rate	mL/min/100cm3	3.9	3.61	-7.46
Biliary tissue excretion rate	mL/min/100cm3	4.88	4.15	-14.95
Extracellular dispersion	%	83.46	68.81	-17.56
Extracellular mean transit time	sec	29.73	28.87	-2.89
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	20.48	24.08	17.57
Hepatocellular tissue uptake rate	mL/min/100cm3	219.98	362.28	64.69
Hepatocellular uptake rate	mL/min/100cm3	44.48	47.8	7.47
Liver T1-MOLLI at 45min	sec	0.47	0.43	-8.89
Liver T1-MOLLI at baseline	sec	0.8	0.78	-2.93
Liver blood clearance	L/min	0.44	0.43	-1.5
Liver extracellular volume fraction	mL/100cm3	20.22	13.2	-34.75
RE for R1l at 20min	%	71.71	81.45	13.57
RE for Sl at 20min	%	61.55	70.98	15.32

Table 2.14: Values for liver of subject SHF-021

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	29.39	30.12	2.48
AUC for Cb (0-inf)	mM*sec	84.84	79.97	-5.74
Body extraction fraction	%	2.43	3.13	28.83
Cardiac output	L/min	7.4	6.68	-9.79
Heart-lung dispersion	%	36.23	64.88	79.07
Heart-lung mean transit time	sec	23.51	16.15	-31.33
Organs blood mean transit time	sec	26.6	41.38	55.55
Organs extraction fraction	%	25.75	26.21	1.81
Organs extravascular mean transit time	min	7.83	7.54	-3.65
RE for R1b at 20min	%	18.09	18.28	1.04
RE for Sb at 20min	%	10.22	18.15	77.6

Table 2.15: Values for aorta of subject SHF-021

2.4.6. Subject SHF-022

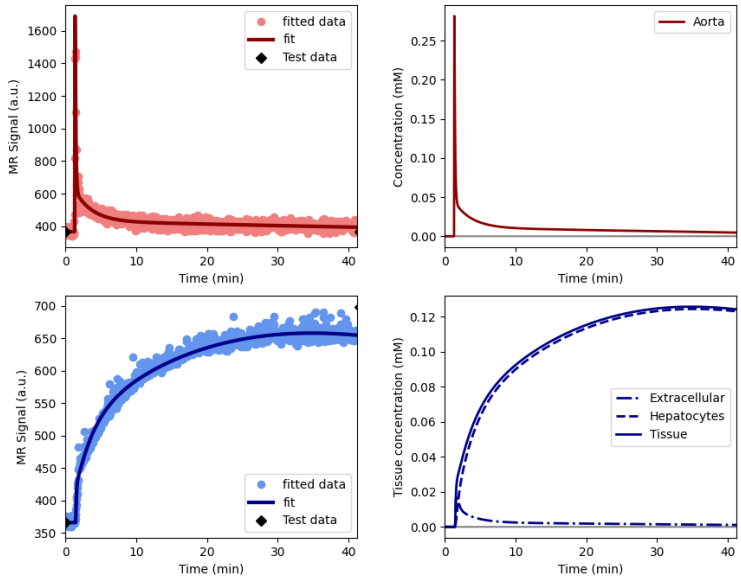

Figure 2.12: Signal-time curves for subject SHF-022 at the control visit.

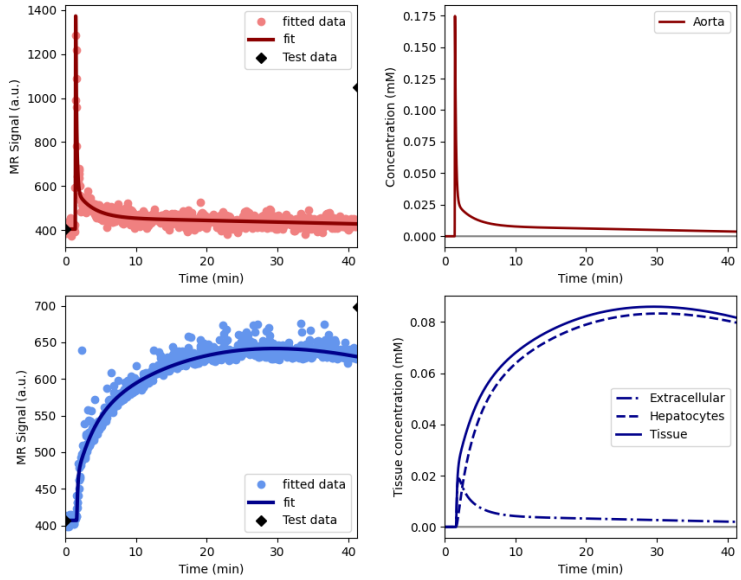

Figure 2.13: Signal-time curves for subject SHF-022 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	215.87	153.52	-28.88
AUC for Cl (0-inf)	mM*sec	961.65	561.47	-41.61
Biliary excretion rate	mL/min/100cm3	2.09	2.54	21.95
Biliary tissue excretion rate	mL/min/100cm3	2.39	3.57	49.28
Extracellular dispersion	%	70.38	77.14	9.61
Extracellular mean transit time	sec	26.08	47.62	82.59
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	41.79	28.0	-33.01
Hepatocellular tissue uptake rate	mL/min/100cm3	415.77	206.41	-50.35
Hepatocellular uptake rate	mL/min/100cm3	53.23	59.38	11.54
Liver T1-MOLLI at 45min	sec	0.37	0.43	16.95
Liver T1-MOLLI at baseline	sec	0.76	0.78	3.03
Liver blood clearance	L/min	0.61	0.7	14.91
Liver extracellular volume fraction	mL/100cm3	12.8	28.77	124.67
RE for R1l at 20min	%	87.4	63.91	-26.87
RE for Sl at 20min	%	76.62	54.92	-28.33

Table 2.16: Values for liver of subject SHF-022

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	23.42	16.95	-27.62
AUC for Cb (0-inf)	mM*sec	46.01	33.77	-26.59
Body extraction fraction	%	5.28	5.29	0.19
Cardiac output	L/min	8.12	11.08	36.42
Heart-lung dispersion	%	50.76	70.78	39.45
Heart-lung mean transit time	sec	16.56	14.3	-13.62
Organs blood mean transit time	sec	38.74	47.24	21.95
Organs extraction fraction	%	22.14	24.18	9.2
Organs extravascular mean transit time	min	8.38	6.92	-17.37
RE for R1b at 20min	%	13.28	10.06	-24.26
RE for Sb at 20min	%	7.78	10.6	36.26

Table 2.17: Values for aorta of subject SHF-022

3

Secondary results

3.1. Diurnal variation

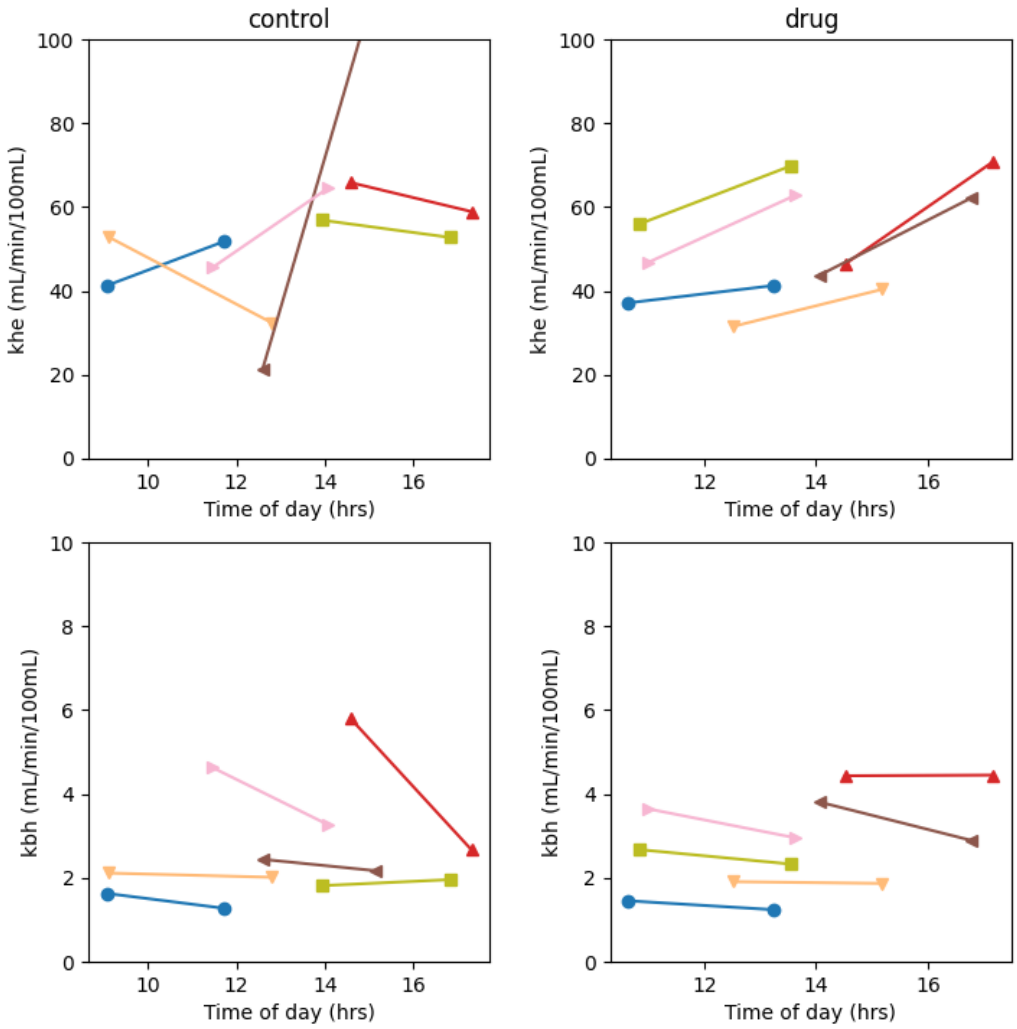

Figure 3.1: Intra-day changes in hepatocellular uptake (k_he, top row) and biliary excretion (k_bh, bottom row) of gadoxetate at for the control (left column) and treatment (right column). Full lines connect values taken in the same subject at the same day.