

Supporting information 2

Evaluation of Age-Related Changes in Teneligliptin Pharmacokinetics in Japanese and Caucasian Subjects Using a Physiologically Based Pharmacokinetic Model

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Supplementary Table 1. Summary of patient characteristics and pharmacokinetic parameters

Supplementary Table 1. Summary of patient characteristics and PK parameters

Name in Simcyp Population library	Age-group (years)		Population background													PK parameters (single dose)				PK parameters (multiple dose)				
			Age (years)	Weight (kg)	Height (cm)	BSA (m ²)	Brain weight (g)	Kidney weight (g)	Liver weight (g)	BMI (kg/m ²)	Cardiac output (L/h)	Haematocrit (%)	HSA (g/L)	AGP (g/L)	Serum creatinine (μmol/L)	GFR (mL/min/1.73m ²)	CYP3A4 (pmol P450/liver)	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	AUC _{0-24h} (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)
Sim-Japanese	≥20 to <25	Mean	22.4	60.0	164.2	1.65	1404	289	1415	22.2	311	39.9	46.8	0.633	63.6	133.5	5908648	1884.73	162.16	1.66	18.12	1876.93	200.55	1.60
		SD	1.5	11.6	9.0	0.18	239	48	240	3.7	34	3.3	4.7	0.128	12.4	21.9	4095401	778.41	130.66	0.59	6.05	773.44	133.73	0.53
		Median	22.2	58.5	163.6	1.62	1366	283	1377	21.8	305	39.8	46.8	0.610	64.0	130.9	4801865	1856.04	131.29	1.70	17.01	1856.23	170.93	1.64
		Min	20.0	42.0	145.7	1.35	1056	185	879	16.4	253	32.9	35.3	0.417	41.0	95.9	884551	573.16	21.05	0.50	8.84	570.42	37.71	0.51
		Max	25.0	104.8	182.8	2.13	2058	426	2111	37.0	400	49.1	59.1	0.974	90.4	199.6	22099754	3913.61	760.18	3.35	45.84	3896.17	799.65	2.81
Sim-Japanese	≥25 to <30	Mean	27.7	59.7	164.9	1.65	1347	276	1395	22.0	289	40.6	47.1	0.635	62.6	129.9	5871422	1899.77	165.15	1.69	17.82	1891.75	203.03	1.63
		SD	1.4	10.4	9.0	0.16	229	43	232	3.4	29	4.0	4.6	0.122	11.9	19.7	3299296	691.81	125.59	0.61	4.84	688.65	127.26	0.56
		Median	27.9	58.9	164.5	1.65	1295	280	1378	21.4	288	40.4	47.0	0.636	63.2	127.6	5235271	1852.18	134.53	1.69	16.90	1846.56	168.27	1.64
		Min	25.1	39.8	142.6	1.32	1042	184	944	16.3	234	30.7	36.1	0.405	40.5	93.9	808427	281.20	19.24	0.45	7.80	278.94	31.78	0.45
		Max	30.0	90.0	185.7	2.03	1995	407	2022	32.4	358	48.5	59.2	0.907	85.4	185.2	19344070	3654.00	734.36	3.66	31.43	3656.24	777.47	3.26
Sim-Japanese	≥30 to <35	Mean	32.6	60.8	165.2	1.67	1392	280	1431	22.2	287	40.6	45.9	0.650	63.5	123.8	6114959	1944.23	166.19	1.67	18.75	1935.18	206.57	1.61
		SD	1.4	11.7	9.1	0.18	223	55	275	3.2	32	3.7	4.5	0.133	12.3	18.8	4195693	928.12	136.17	0.65	6.23	922.40	141.62	0.58
		Median	32.5	58.7	165.8	1.65	1370	270	1400	22.2	285	40.3	45.9	0.636	66.4	121.1	4957817	1685.99	124.11	1.56	18.20	1683.15	171.44	1.56
		Min	30.0	39.3	148.5	1.33	1040	172	958	16.2	228	33.1	37.4	0.374	40.2	85.4	739992	511.78	23.86	0.45	9.86	498.34	42.24	0.47
		Max	35.0	99.0	185.5	2.17	2032	469	2174	31.3	373	52.1	60.1	1.041	87.5	179.7	26654412	4998.04	755.95	3.70	43.76	4901.38	824.50	3.10
Sim-Japanese	≥35 to <40	Mean	37.5	60.4	165.4	1.66	1374	280	1448	22.0	282	40.7	46.3	0.643	62.8	118.3	5936947	1881.31	150.49	1.74	18.63	1874.84	189.85	1.68
		SD	1.4	11.5	8.7	0.18	218	48	240	3.2	30	3.3	5.2	0.127	11.0	13.7	3324064	714.92	113.74	0.65	5.47	708.85	113.97	0.58
		Median	37.6	58.0	164.7	1.64	1359	274	1437	22.0	278	41.0	45.9	0.634	64.5	116.9	4748343	1807.01	126.34	1.74	17.79	1804.38	160.73	1.70
		Min	35.0	41.5	149.1	1.35	1040	193	1008	16.5	228	33.7	35.1	0.371	40.3	83.3	1755864	276.35	25.28	0.50	9.51	269.98	30.66	0.47
		Max	40.0	91.1	187.9	2.10	2042	456	1992	29.6	356	48.7	59.7	0.945	86.0	171.8	16444821	3999.74	766.92	3.66	33.74	3967.90	792.48	3.30
Sim-Japanese	≥40 to <45	Mean	42.2	60.0	164.1	1.65	1395	289	1414	22.2	275	39.9	45.9	0.642	74.0	117.0	5579253	2005.98	157.07	1.69	19.77	1989.81	200.30	1.63
		SD	1.5	11.5	8.7	0.17	249	48	237	3.7	29	3.3	4.7	0.139	38.4	57.4	3840118	921.91	129.89	0.61	7.76	910.12	136.78	0.54
		Median	41.7	58.5	163.8	1.62	1366	282	1378	21.9	270	39.8	45.9	0.612	66.0	101.4	4549394	1916.80	124.89	1.72	18.31	1934.40	173.43	1.66
		Min	40.0	42.0	146.3	1.36	1041	186	882	16.5	226	32.9	34.9	0.417	23.2	37.7	824979	610.66	19.17	0.50	9.47	598.48	35.20	0.51
		Max	44.9	104.5	182.2	2.12	2058	426	2108	37.1	353	49.1	57.7	1.059	215.8	288.6	20102210	4682.86	748.14	3.61	60.50	4682.32	792.60	2.90
Sim-Japanese	≥45 to <50	Mean	47.4	59.4	163.7	1.64	1356	273	1383	22.2	268	40.6	45.7	0.637	63.1	127.5	5162242	2035.84	164.43	1.71	19.13	2020.88	207.06	1.66
		SD	1.4	10.3	8.7	0.16	229	43	229	3.5	26	4.0	4.5	0.117	30.0	61.4	2905650	857.30	129.22	0.62	5.91	843.60	134.38	0.56
		Median	47.4	58.9	163.4	1.64	1308	278	1368	21.6	268	40.4	45.6	0.640	55.7	113.7	4625776	1904.79	130.01	1.70	18.33	1890.83	170.01	1.66
		Min	45.0	39.7	141.6	1.32	1042	183	937	16.5	217	30.7	35.4	0.405	22.3	35.2	707994	487.99	18.45	0.45	8.85	483.56	36.38	0.46
		Max	50.0	89.3	184.2	2.01	1995	404	2012	32.7	326	48.5	57.7	0.907	157.4	311.4	17092724	5075.22	752.61	3.56	47.81	5051.56	813.71	3.25
Sim-Japanese	≥50 to <55	Mean	52.4	60.3	163.0	1.64	1382	275	1408	22.6	264	40.6	45.1	0.647	67.2	111.8	5094971	2169.72	160.92	1.72	21.36	2145.02	209.57	1.64
		SD	1.3	11.4	8.9	0.18	227	54	269	3.3	29	3.7	4.6	0.132	31.4	46.5	3532744	1040.58	131.33	0.68	7.67	1022.86	139.14	0.60
		Median	52.3	58.2	163.7	1.63	1361	265	1376	22.7	263	40.3	45.0	0.642	61.5	104.3	4072848	1942.11	119.84	1.61	19.83	1933.99	170.18	1.56
		Min	50.1	39.1	146.4	1.31	1040	170	943	16.6	210	33.1	35.7	0.374	21.7	33.7	615293	520.68	23.20	0.45	9.88	505.86	41.85	0.47
		Max	54.9	97.9	182.5	2.14	2032	460	2130	31.8	344	52.1	58.4	1.003	180.0	268.8	22604176	4650.59	693.61	3.81	43.11	4587.30	744.53	3.16
Sim-Japanese	≥55 to <60	Mean	57.4	59.5	162.1	1.63	1364	272	1413	22.6	256	40.8	45.6	0.644	60.4	115.1	4757203	2193.40	152.88	1.78	20.93	2174.46	202.40	1.71
		SD	1.4	11.4	8.6	0.18	219	47	236	3.3	28	3.3	4.8	0.126	26.5	51.8	2721684	898.86	118.20	0.66	6.77	883.44	120.31	0.59
		Median	57.3	57.7	161.7	1.61	1320	267	1405	22.5	253	41.0	45.3	0.636	55.4	106.3	3783373	2099.46	124.76	1.79	19.81	2099.41	178.81	1.71
		Min	55.0	38.4	145.5	1.29	1040	188	990	16.6	202	33.7	34.2	0.371	14.8	43.8	1144624	252.14	24.32	0.50	10.73	247.08	29.09	0.48
		Max	60.0	89.7	184.0	2.06	2042	444	1934	30.4	326	48.7	56.9	0.945	163.8	388.0	13329719	4339.63	820.74	3.47	42.93	4265.37	857.34	3.19
Sim-Japanese	≥60 to <65	Mean	62.2	58.9	159.7	1.60	1398	279	1369	23.1	248	40.0	44.7	0.648	74.1	93.5	4434464	2469.63	161.98	1.73	23.32	2427.33	219.97	1.66
		SD	1.4	11.4	8.6	0.17	250	46	231	3.9	26	3.3	4.6	0.137	38.3	45.7	3049060	1150.87	133.02	0.62	9.51	1115.12	144.73	0.55
		Median	62.0	57.7	159.2	1.58	1393	273	1337	22.5	245	39.8	44.7	0.632	66.0	81.1	3633326	2270.80	122.15	1.77	21.79	2243.19	191.69	1.71
		Min	60.0	35.6	141.9	1.22	1040	179	853	16.4	190	32.9	34.1	0.417	23.2	31.4	668904	741.27	19.13	0.55	10.67	710.67	39.52	0.52
		Max	64.9	102.1	178.1	2.06	2075	413	2030	38.5	316	49.1	55.3	1.059	215.8	230.7	16579588	6302.36	784.03	3.75	72.95	6237.64	846.84	3.01
Sim-Japanese	≥65 to ≤70	Mean	67.5	58.3	158.2	1.59	1348	250	1271	23.3	240	40.6	43.3	0.642	63.1	101.2	3837155	2537.81	168.64	1.77	23.01	2500.07	227.83	1.69
		SD	1.4	9.9	8.7	0.15	232	40	214	3.7	23	4.0	4.6	0.114	30.0	48.5	20							

Sim-NEurCaucasian	≥40 to <45	Mean	42.7	75.7	168.1	1.85	1331	312	1627	26.7	307	40.7	45.2	0.745	64.6	122.3	8107232	1722.88	129.59	1.82	21.84	1718.96	167.88	1.76
		SD	1.4	17.8	8.6	0.22	207	99	284	5.6	37	4.0	4.0	0.170	13.3	23.4	4462887	753.16	100.23	0.66	6.28	747.41	104.28	0.59
		Median	42.7	75.6	167.1	1.84	1301	299	1627	26.0	306	40.3	45.1	0.723	64.9	121.5	7181769	1552.03	98.23	1.80	20.38	1573.41	137.50	1.74
		Min	40.1	40.3	150.8	1.31	1040	168	979	17.4	218	31.0	35.2	0.385	36.3	76.8	2800286	449.15	20.79	0.60	10.02	445.88	33.84	0.58
Sim-NEurCaucasian	≥45 to <50	Max	45.0	130.0	191.9	2.47	1937	654	2406	46.2	408	49.6	54.7	1.354	102.3	218.1	25520308	3699.57	534.50	4.05	41.37	3668.94	575.96	3.46
		Mean	47.3	78.2	170.6	1.90	1323	330	1664	26.6	310	40.7	44.7	0.737	66.4	115.5	7851152	1736.53	137.28	1.75	23.48	1722.56	175.45	1.68
		SD	1.3	17.0	10.1	0.24	189	86	302	4.3	39	3.8	4.3	0.153	14.0	21.3	3479684	747.21	119.40	0.60	13.36	751.37	122.26	0.54
		Median	47.2	77.1	171.5	1.90	1311	322	1654	26.5	311	40.7	44.8	0.755	66.2	113.4	7120629	1684.31	109.65	1.75	21.13	1668.86	145.63	1.66
Sim-NEurCaucasian	≥50 to <55	Min	45.0	43.6	145.4	1.32	1040	149	1099	19.2	216	32.5	35.2	0.412	42.5	76.3	2634982	335.54	6.23	0.50	11.95	330.41	24.84	0.47
		Max	49.9	115.6	197.3	2.42	1865	623	2653	36.7	397	50.1	60.3	1.124	101.7	178.2	21907504	4509.83	761.38	3.36	137.58	4397.39	789.31	2.90
		Mean	52.4	75.7	168.6	1.85	1431	312	1597	26.5	297	40.0	45.7	0.777	70.7	102.2	7981661	1907.46	142.95	1.83	23.91	1890.71	186.72	1.74
		SD	1.5	16.6	9.7	0.23	215	94	284	4.7	37	3.7	4.3	0.159	14.9	21.6	4572337	869.92	132.06	0.66	7.55	857.97	135.45	0.58
Sim-NEurCaucasian	≥55 to <60	Median	52.6	76.0	168.1	1.86	1388	309	1594	25.9	299	39.8	45.4	0.778	69.7	98.7	6781272	1824.46	100.22	1.80	22.87	1807.41	148.46	1.76
		Min	50.1	44.0	145.7	1.40	1040	153	1068	17.2	224	32.9	35.9	0.409	35.4	68.7	1790388	460.01	21.39	0.50	11.49	442.95	32.54	0.49
		Max	54.9	120.3	189.1	2.46	2031	698	2173	39.9	394	48.3	56.9	1.262	109.2	173.8	22935982	4629.72	764.99	3.66	45.68	4554.27	794.43	3.07
		Mean	57.5	78.9	168.5	1.88	1371	327	1623	27.7	297	41.1	44.6	0.772	74.1	95.4	7173600	2046.60	132.62	1.93	25.63	2023.51	180.91	1.84
Sim-NEurCaucasian	≥60 to <65	SD	1.5	17.3	8.8	0.22	236	89	327	5.5	34	3.6	4.8	0.181	16.6	22.7	3657621	831.16	107.20	0.66	9.14	815.65	111.94	0.58
		Median	57.4	78.4	169.4	1.88	1310	322	1599	27.3	296	41.4	44.2	0.748	72.5	92.4	6509702	1919.85	105.57	1.90	24.81	1857.48	146.70	1.84
		Min	55.0	42.3	148.5	1.33	1060	170	1008	17.0	211	32.1	35.9	0.467	42.3	49.5	718159	340.00	13.17	0.61	11.07	342.63	24.05	0.57
		Max	60.0	128.0	185.4	2.39	2044	664	2639	45.4	376	51.6	60.2	1.180	122.1	164.1	20582508	4035.42	666.64	3.76	71.13	3870.20	721.03	3.31
Sim-NEurCaucasian	≥65 to <70	Mean	62.7	73.8	165.4	1.81	1331	304	1584	26.9	279	40.7	44.2	0.745	71.8	87.7	6411001	2199.15	133.97	1.88	26.36	2163.12	187.49	1.80
		SD	1.4	17.2	8.5	0.22	207	96	276	5.6	34	4.0	3.9	0.170	15.3	18.2	3528949	986.78	105.26	0.68	8.23	959.02	112.89	0.60
		Median	62.7	74.1	164.5	1.80	1301	291	1583	26.2	278	40.3	44.0	0.723	72.7	88.1	5681110	2012.13	100.34	1.86	24.56	1959.54	153.43	1.80
		Min	60.1	39.5	148.3	1.29	1040	164	955	17.6	198	31.0	34.6	0.385	39.9	50.8	2210817	544.66	20.71	0.60	11.83	535.33	37.25	0.60
Sim-Geriatric NEC	≥70 to <75	Max	65.0	126.1	188.6	2.40	1937	634	2339	46.7	369	49.6	53.3	1.354	130.5	154.0	20125650	4712.26	558.98	4.20	50.23	4534.55	617.37	3.55
		Mean	67.5	78.7	167.1	1.87	1369	317	1578	28.1	284	40.6	43.9	0.738	73.7	84.9	6230268	2087.14	127.33	1.84	28.06	2046.14	178.63	1.76
		SD	1.4	15.3	9.3	0.21	201	92	283	4.3	32	3.9	4.1	0.176	18.1	20.3	3397248	889.82	109.73	0.63	8.76	868.36	115.69	0.56
		Median	67.5	79.2	168.9	1.89	1352	305	1566	27.9	286	40.3	43.7	0.714	71.7	83.3	5673953	1921.02	95.89	1.86	26.13	1874.02	141.79	1.81
Sim-Geriatric NEC	≥75 to <80	Min	65.0	35.4	140.2	1.18	1040	138	816	18.0	177	33.5	35.4	0.339	36.8	44.3	4132888	426.79	11.11	0.51	9.25	425.72	29.48	0.50
		Max	70.0	117.8	189.9	2.36	1945	585	2400	40.6	359	50.1	55.1	1.177	128.7	146.7	20818710	4552.82	595.22	3.31	60.28	4423.77	642.71	2.85
		Mean	72.6	74.2	165.1	1.81	1420	286	1382	27.1	269	40.7	44.9	0.764	75.2	76.3	5121302	2856.97	152.83	1.88	31.81	2745.42	225.20	1.79
		SD	1.6	14.9	8.8	0.20	241	75	232	4.8	30	3.8	4.2	0.180	19.4	21.2	2803636	1256.26	118.55	0.73	14.63	1167.48	129.11	0.63
Sim-Geriatric NEC	≥80 to <85	Median	72.8	73.8	165.2	1.82	1393	284	1380	27.4	272	40.6	44.2	0.759	73.2	74.8	4165507	2652.32	118.37	1.83	30.63	2585.93	193.44	1.80
		Min	70.0	42.5	142.6	1.36	1040	131	897	17.4	200	32.3	34.6	0.335	35.4	42.5	1172529	719.30	22.95	0.60	11.20	725.23	51.83	0.60
		Max	75.0	108.4	184.7	2.18	1937	502	1831	43.3	325	49.2	56.1	1.303	140.4	134.8	16222883	8816.84	570.79	3.81	140.79	8463.50	650.94	3.40
		Mean	77.4	75.7	163.7	1.82	1395	280	1257	28.2	264	41.0	43.1	0.746	80.1	67.3	4550883	2905.86	129.24	1.97	34.91	2760.12	205.37	1.87
Sim-Geriatric NEC	≥85 to <90	SD	1.4	14.3	9.3	0.20	225	77	235	4.2	29	3.8	4.4	0.166	20.3	15.4	2521383	1205.78	90.03	0.67	13.15	1088.27	98.93	0.58
		Median	77.3	74.4	164.0	1.80	1368	272	1259	27.8	263	40.8	43.0	0.735	75.4	67.8	3862718	2769.18	108.41	2.01	32.65	2685.37	185.67	1.93
		Min	75.0	45.7	140.1	1.46	1040	137	809	16.5	212	32.6	32.0	0.433	48.5	31.3	839577	838.26	16.30	0.45	16.70	765.26	39.68	0.46
		Max	80.0	117.0	191.6	2.37	1931	497	2186	38.8	348	51.0	55.1	1.183	139.5	103.0	14052681	7340.68	465.33	3.90	117.74	6199.78	560.85	3.40
Sim-Geriatric NEC	≥90 to <94	Mean	82.1	72.2	161.8	1.76	1370	259	1130	27.4	252	40.5	42.8	0.758	86.4	57.0	4071194	3295.47	149.07	1.95	36.66	3110.93	235.62	1.84
		SD	1.3	15.3	9.8	0.22	226	68	200	4.6	32	4.0	4.3	0.215	24.0	16.7	2020505	1261.36	123.17	0.75	13.84	1133.85	129.48	0.65
		Median	81.8	72.7	161.8	1.77	1314	254	1144	27.1	252	40.9	42.9	0.732	83.7	57.5	3668990	3097.93	103.05	1.91	34.77	3013.01	200.17	1.85
		Min	80.0	37.0	137.0	1.22	1045	137	760	17.2	174	32.3	34.2	0.349	36.6	23.6	995417	1031.67	17.85	0.50	15.84	951.52	51.88	0.50
Sim-Geriatric NEC	≥94 to <98	Max	84.8	113.4	184.5	2.26	1980	461	1612	41.2	324	49.3	55.8	1.395	157.4	116.0	10510347	6904.24	697.77	4.41	88.94	6411.36	772.28	3.86
		Mean	87.2	72.2	161.2	1.76	1374	264	1047	27.6	246	40.7	43.2	0.761	80.4	55.8	4156337	3342.19	145.57	1.87	38.20	3129.47	233.58	1.78
		SD	1.3	14.9	8.9	0.21	218	92	206	4.3	29	3.2	4.2	0.205	19.9	15.2	2433109	1359.05	114.19	0.62	18.02	1249.09	128.08	0.55
		Median	87.1	71.5	162.1	1.76	1334	258	1052	27.3	246	40.7	43.2	0.738	77.8	55.0	3612378	3146.95	115.92	1.87	34.73	3028.59	201.52	1.80
Sim-Geriatric NEC	≥98 to <100	Min	85.0	38.8	137.7	1.26	1040	104	679	18.1	176	33.6	32.9	0.339	42.4	24.9	924170	828.37	12.97	0.45	15.74	724.86	51.14	