Supplementary material

Article title: Effect of Oral Semaglutide on the Pharmacokinetics of Lisinopril, Warfarin, Digoxin, and Metformin in Healthy Subjects

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Supplementary table 1 Sampling time points

	Sampling schedule (h)																			
Treatments	**0**	**5 min**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**30**
Trial 1																					
Lisinopril	x							x			x		x	x	x	x	x	x		x	
Warfarin	x			x		x		x		x	x	x	x	x		x				x	
Semaglutide	x			x		x	x	x		x	x		x			x				x	
SNAC	x		x	x	x	x	x	x			x		x			x				x	
Trial 2																					
Digoxin	x			x		x	x	x	x	x	x		x	x		x		x		x	
Metformin	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Semaglutide	x			x		x	x	x	x	x	x		x			x				x	
SNAC	x	x	x	x	x	x	x	x			x		x			x				x	

	Sampling schedule (h)										
Treatments	**36**	**48**	**60**	**72**	**96**	**120**	**144**	**168**	**312**	**504**	**744–840**
Trial 1											
Lisinopril	x	x	x								
Warfarin	x	x		x	x	x	x	x			
Semaglutide	x[a]	x[a]			x[a]		x[a,b]		x[a]	x[a]	
SNAC							x[b]				
Trial 2											
Digoxin		x		x	x	x					
Metformin											
Semaglutide	x[a]	x[a]			x[a]		x[a]		x[a]	x[a]	x[a]
SNAC											

[a]Sampling at these time points only when oral semaglutide was given alone; [b]Sampling at 144 h only when given with warfarin

SNAC sodium N-(8-[2-hydroxybenzoyl] amino) caprylate

Supplementary table 2 Pharmacokinetic endpoints either alone or after co-administration with oral semaglutide or SNAC

a. Lisinopril (single dose)

Parameters	**Lisinopril alone (*N* = 52)**	**Lisinopril + oral semaglutide (*N* = 46)**	**Lisinopril + SNAC (*N* = 50)**
$AUC_{0–60h}$, ng·h/mL	930.01 (33.27)	983.10 (45.15)	863.91 (40.53)
C_{max}, ng/mL	62.61 (38.23)	59.74 (49.59)	55.38 (49.63)
t_{max}, h	6.0 (4.0, 8.0)	6.0 (4.0, 14.0)	6.0 (4.0, 10.0)
$t_{½}$, h	20 (30)	18 (28)	22 (29)

b. S-warfarin (single dose)

Parameters	**S-warfarin alone (*N* = 50)**	**S-warfarin + oral semaglutide (*N* = 46)**	**S-warfarin + SNAC (*N* = 49)**
$AUC_{0–168h}$, ng·h/mL	53454.44 (34.38)	57340.45 (39.57)	36590.44 (108.27)
C_{max}, ng/mL	1518.47 (25.50)	1339.37 (34.50)	943.51 (85.46)
t_{max}, h	1.0 (0.5, 7.9)	1.0 (0.5, 23.9)	1.0 (0.5, 35.2)
$t_{½}$, h	38 (27)	38 (27)	42 (28)

c. Digoxin (single dose)

Parameters	**Digoxin alone (*N* = 31)**	**Digoxin + oral semaglutide (*N* = 31)**	**Digoxin alone (*N* = 32)**	**Digoxin + SNAC (*N* = 32)**
$AUC_{0–120h}$, ng·h/mL	32.42 (26.1)	33.30 (34.9)	32.58 (25.8)	30.69 (26.1)
C_{max}, ng/mL	3.11 (33.4)	3.06 (36.2)	3.12 (32.9)	2.57 (35.1)
t_{max}, h	1.0 (0.5, 1.0)	1.0 (0.5, 1.6)	1.0 (0.5, 1.0)	1.0 (0.5, 1.1)
$t_{½}$, h	42 (11)	43 (13)	42 (11)	45 (13)

d. Metformin (steady state)

Parameters	Metformin alone (*N* = 31)	Metformin + oral semaglutide (*N* = 31)	Metformin alone (*N* = 32)	Metformin + SNAC (*N*=32)
AUC_{0-inf}, ng·h/mL	7873 (23.4)	10430 (26.5)	7895 (23.1)	8326 (27.3)
C_{max}, ng/mL	1690 (18.5)	1654 (32.5)	1683 (18.3)	1777 (27.2)
t_{max}, h	0.8 (0.5, 1.5)	1.0 (0.5, 6.0)	0.8 (0.5, 1.5)	0.8 (0.5, 1.5)
$t_{½}$, h	16 (58)	13 (72)	16 (57)	14 (52)

Data are geometric means (coefficient of variation) except for t_{max} where median (minimum, maximum) values are presented

AUC_{0-60h} area under the concentration–time curve from time 0 to 60 h, AUC_{0-120h} area under the concentration–time curve from time 0 to 120 h, AUC_{0-168h} area under the concentration–time curve from time 0 to 168 h, AUC_{0-inf} area under the concentration–time curve from time 0 to infinity, C_{max} maximum concentration, *SNAC* sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, $t_{1/2}$ terminal half-life, t_{max} time to reach maximum concentration

Supplementary table 3 Pharmacokinetic endpoints for SNAC

a. Trial 1

	Lisinopril + SNAC alone	**Warfarin + SNAC alone**	**Lisinopril + oral semaglutide**	**Warfarin + oral semaglutide**	**Oral semaglutide only**
$AUC_{0–24h}$, ng·h/mL, single dose	1154 (410)	1150 (385)	–	–	–
$AUC_{0–24h}$, ng·h/mL, steady state	–	–	1333 (590)	1369 (510)	1466 (596)
C_{max}, ng/mL, single dose	1519 (754)	1536 (825)	–	–	–
C_{max}, ng/mL, steady state	–	–	1448 (1029)	1460 (728)	1834 (1628)
t_{max}, h, single dose	0.5 (0.2, 1.0)	0.5 (0.2, 1.5)	–	–	–
t_{max}, h, steady state	–	–	0.8 (0.2, 4.0)	0.6 (0.2, 4.0)	0.7 (0.2, 1.5)

Data are mean (standard deviation) except for t_{max} where median (minimum, maximum) values are presented

b. Trial 2

	Digoxin + SNAC alone	**Metformin + SNAC alone**	**Digoxin + oral semaglutide**	**Metformin + oral semaglutide**	**Oral semaglutide only**
$AUC_{0–24h}$, ng·h/mL, single dose	1063 (29)	–	–	–	–
$AUC_{0–24h}$, ng·h/mL, 4 daily doses	–	1147 (26)	–	–	–
$AUC_{0–24h}$, ng·h/mL, steady state	–	–	1331 (28)	1323 (28)	1320 (25)
C_{max}, ng/mL, single dose	1318 (42)	–	–	–	–

C_{max}, ng/mL, 4 daily doses	–	1390 (46)	–	–	–
C_{max}, ng/mL, steady state	–	–	1163 (87)	1063 (81)	1157 (72)
t_{max}, h, single dose	0.5 (0.3, 1.0)	–	–	–	–
t_{max}, h, 4 daily doses	–	0.4 (0.2, 1.5)	–	–	–
t_{max}, h, steady state	–	–	0.8 (0.3, 1.0)	0.5 (0.1, 6.0)	0.7 (0.2, 6.0)

Data are geometric means (coefficient of variation) except for t_{max} where median (minimum, maximum) values are presented

$AUC_{0–24h}$ area under the concentration–time curve from time 0 to 24 h, *C_{max}* maximum concentration, *SNAC* sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, *t_{max}* time to reach maximum concentration

Supplementary table 4 Overview of treatment-emergent adverse events in healthy subjects by treatment

a. Trial 1

	Lisinopril ***n*** **(%) E**	**Warfarin** ***n*** **(%) E**	**Lisinopril + SNAC** ***n*** **(%) E**	**Warfarin + SNAC** ***n*** **(%) E**	**Lisinopril + oral semaglutide** ***n*** **(%) E**	**Warfarin + oral semaglutide** ***n*** **(%) E**	**Oral semaglutide only** ***n*** **(%) E**	**Oral semaglutide total** ***n*** **(%) E**	**Total** ***n*** **(%) E**
Number of subjects	52	50	50	49	46	46	49	49	52
Adverse events	9 (17.3) 15	6 (12.0) 7	10 (20.0) 15	19 (38.8) 29	18 (39.1) 46	10 (21.7) 19	34 (69.4) 163	36 (73.5) 228	44 (84.6) 294
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to withdrawal	1 (1.9) 1	0	1 (2.0) 1	0	0	0	1 (2.0) 1	1 (2.0) 1	3 (5.8) 3
Adverse events by organ class									
Gastrointestinal disorders	3 (5.8) 4	0	6 (12.0) 8	4 (8.2) 7	11 (23.9) 24	6 (13.0) 11	27 (55.1) 102	29 (59.2) 137	33 (63.5) 156
Nervous system disorders	3 (5.8) 4	3 (6.0) 3	2 (4.0) 2	3 (6.1) 3	9 (19.6) 10	4 (8.7) 4	9 (18.4) 13	17 (34.7) 27	22 (42.3) 39
General disorders & administration site conditions	2 (3.8) 2	1 (2.0) 1	1 (2.0) 1	3 (6.1) 3	5 (10.9) 5	1 (2.2) 1	14 (28.6) 23	19 (38.8) 29	22 (42.3) 36
Metabolism & nutrition disorders	0	1 (2.0) 1	0	1 (2.0) 1	2 (4.3) 2	1 (2.2) 1	13 (26.5) 15	14 (28.6) 18	14 (26.9) 20
Injury, poisoning & procedural complications	0	0	1 (2.0) 1	12 (24.5) 12	0	0	2 (4.1) 2	2 (4.1) 2	15 (28.8) 15
Respiratory, thoracic & mediastinal disorders	2 (3.8) 2	2 (4.0) 2	1 (2.0) 1	0	1 (2.2) 1	1 (2.2) 1	0	2 (4.1) 2	7 (13.5) 7
Infections & infestation	1 (1.9) 1	0	1 (2.0) 1	1 (2.0) 1	0	0	2 (4.1) 2	2 (4.1) 2	5 (9.6) 5
Musculoskeletal & connective tissue	1 (1.9) 1	0	0	0	1 (2.2) 1	0	2 (4.1) 2	2 (4.1) 3	2 (3.8) 4

disorders									
Eye disorders	1 (1.9) 1	0	0	1 (2.0) 1	1 (2.1) 1	0	0	1 (2.0) 1	2 (3.8) 3

b. Trial 2

	Digoxin *n* (%) E	**Metformin *n* (%) E**	**Digoxin + SNAC *n* (%) E**	**Metformin + SNAC *n* (%) E**	**Digoxin + oral semaglutide *n* (%) E**	**Metformin + oral semaglutide *n* (%) E**	**Oral semaglutide only *n* (%) E**	**Oral semaglutide total *n* (%) E**	**Total *n* (%) E**
Number of subjects	32	32	32	32	31	31	32	32	32
Adverse events	3 (9.4) 4	6 (18.8) 7	6 (18.8) 9	8 (25.0) 10	8 (25.8) 12	18 (58.1) 36	23 (71.9) 103	27 (84.4) 151	28 (87.5) 181
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to withdrawal	0	0	0	0	0	0	1 (3.1) 4	1 (3.1) 4	1 (3.1) 4
Adverse events by organ class									
Gastrointestinal disorders	1 (3.1) 1	5 (15.6) 5	1 (3.1) 2	6 (18.8) 7	5 (16.1) 7	15 (48.4) 24	15 (46.9) 50	23 (71.9) 81	24 (75.0) 96
Nervous system disorders	1 (3.1) 1	1 (3.1) 1	4 (12.5) 4	0	2 (6.5) 2	2 (6.5) 4	9 (28.1) 16	10 (31.3) 22	14 (43.8) 28
Metabolism & nutritional disorders	0	0	0	2 (6.3) 2	0	3 (9.7) 3	18 (56.3) 19	21 (65.6) 22	21 (65.6) 24
General disorders & administration site conditions	1 (3.1) 1	0	1 (3.1) 1	0	0	3 (9.7) 4	6 (18.8) 9	8 (25.0) 13	8 (25.0) 15
Infections & infestation	0	0	0	0	1 (3.2) 1	1 (3.2) 1	5 (15.6) 6	6 (18.8) 8	6 (18.8) 8
Eye disorders	0	0	1 (3.1) 1	0	0	0	1 (3.1) 1	1 (3.1) 1	2 (6.3) 2
Injury, poisoning & procedural	1 (3.1) 1	0	1 (3.1) 1	0	0	0	0	0	2 (6.3) 2

complications									
Psychiatric disorders	0	0	0	0	1 (3.2) 1	0	1 (3.1) 1	2 (6.3) 2	2 (6.3) 2
Respiratory, thoracic & mediastinal disorders	0	0	0	0	1 (3.2) 1	0	1 (3.1) 1	2 (6.3) 2	2 (6.3) 2
Musculoskeletal & connective tissue disorders	0	1 (3.1) 1	0	0	0	0	0	0	1 (3.1) 1
Skin & subcutaneous tissue disorders	0	0	0	1 (3.1) 1	0	0	0	0	1 (3.1) 1

E number of adverse events, *n* number of subjects with adverse event, *SNAC* sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, *%* proportion of subjects having an adverse event