

## SUPPLEMENTARY APPENDIX

Supplement to: Heerspink HJL Arihiro Kiyosue, David C Wheeler et al. Zibotentan in combination with dapagliflozin compared to dapagliflozin alone in patients with chronic kidney disease: A randomised active-controlled clinical trial

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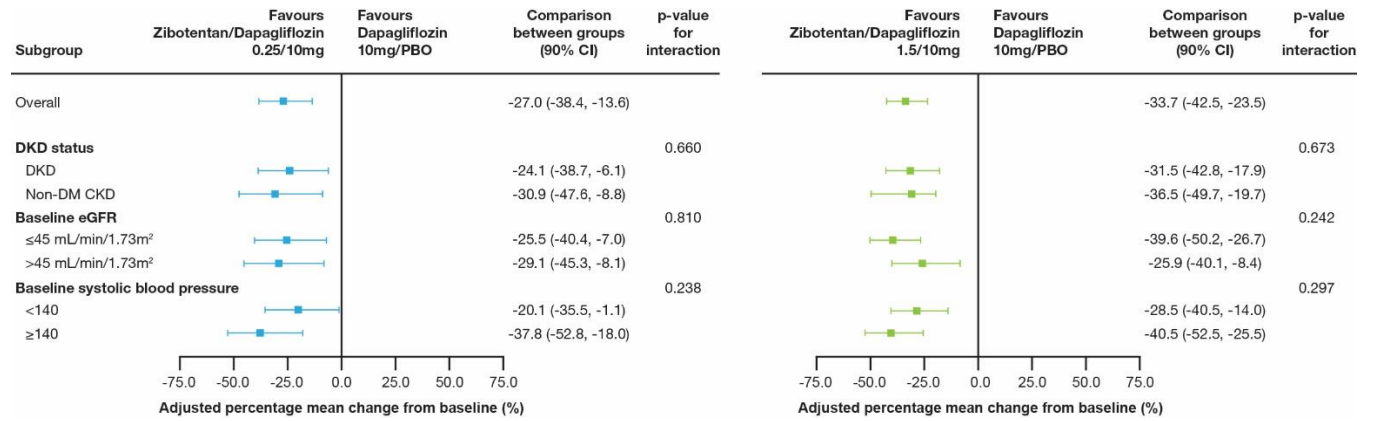
**Supplementary Table 1: Laboratory assessments**

Variable	Time	Dapagliflozin /placebo		Zibotentan 0.25 mg/day / Dapagliflozin		Zibotentan 1.5 mg/day / Dapagliflozin	
	Week	<i>n</i>	Mean (SD) or median	<i>n</i>	Mean (SD) or median	<i>n</i>	Mean (SD) or median
UACR, median, mg/g	Baseline	177	577.0	91	526.7	178	566.8
	3	147	461.0	84	251.9	157	271.1
	6	149	464.5	82	325.3	148	232.2
	12	143	445.5	73	342.5	134	289.1
	Follow-up	142	570.6	74	506.0	134	527.9
SBP, mmHg	Baseline	177	137.6 (17.59)	91	136.5 (17.76)	179	136.4 (16.13)
	3	168	133.2 (17.16)	87	129.2 (15.15)	166	131.2 (17.13)
	6	163	133.0 (15.76)	87	129.8 (18.60)	158	129.0 (15.45)
	12	150	133.5 (14.74)	77	131.2 (16.51)	139	128.2 (17.05)
	Follow-up	152	137.3 (17.48)	74	136.4 (18.05)	141	134.6 (17.93)
DBP, mmHg	Baseline	177	79.9 (9.78)	91	79.6 (10.51)	179	78.9 (9.37)
	3	168	77.8 (9.20)	87	75.7 (9.91)	166	73.8 (10.36)
	6	163	78.0 (9.79)	87	75.9 (10.66)	158	72.6 (10.09)
	12	150	78.2 (8.75)	77	75.4 (10.25)	139	73.5 (10.45)
	Follow-up	152	79.3 (9.34)	74	78.9 (8.96)	141	77.4 (10.16)
LDL cholesterol, mmol/L	Baseline	169	2.45 (1.1)	88	2.29 (1.0)	173	2.37 (1.1)
	12	127	2.42 (1.1)	65	2.06 (0.9)	129	2.11 (1.0)
	Follow-up	137	2.35 (0.9)	64	2.10 (1.0)	124	2.29 (1.0)
GFR, ml/min/1.73 m <sup>2</sup>	Baseline	177	45.2 (20.71)	91	48.4 (23.49)	179	47.4 (23.38)
	3	165	43.3 (20.55)	85	46.5 (23.77)	166	43.7 (22.78)
	6	160	43.2 (21.03)	84	45.4 (22.45)	152	44.0 (22.34)
	12	148	44.0 (21.33)	76	44.7 (21.32)	138	44.8 (22.88)
	Follow-up	149	45.8 (21.65)	74	46.6 (21.99)	137	46.7 (22.80)
HbA1C, %	Baseline	177	6.9 (1.45)	91	6.8 (1.53)	179	6.8 (1.39)
	12	139	6.8 (1.43)	74	6.6 (1.27)	134	6.5 (1.12)
	Follow-up	147	6.8 (1.46)	73	6.7 (1.33)	138	6.6 (1.27)
Hemoglobin, g/L	Baseline	176	132.0 (16.69)	91	131.7 (16.46)	179	130.3 (16.18)
	3	158	132.6 (16.54)	82	127.9 (15.57)	154	121.4 (16.54)
	6	154	133.7 (17.61)	82	129.1 (16.08)	133	122.8 (16.14)
	12	140	134.3 (18.62)	72	129.9 (17.68)	132	124.6 (16.56)
	Follow-up	147	132.6 (18.50)	71	131.6 (18.44)	132	130.4 (17.27)
Hematocrit, ratio	Baseline	176	0.396 (0.0495)	90	0.398 (0.0473)	179	0.391 (0.0465)

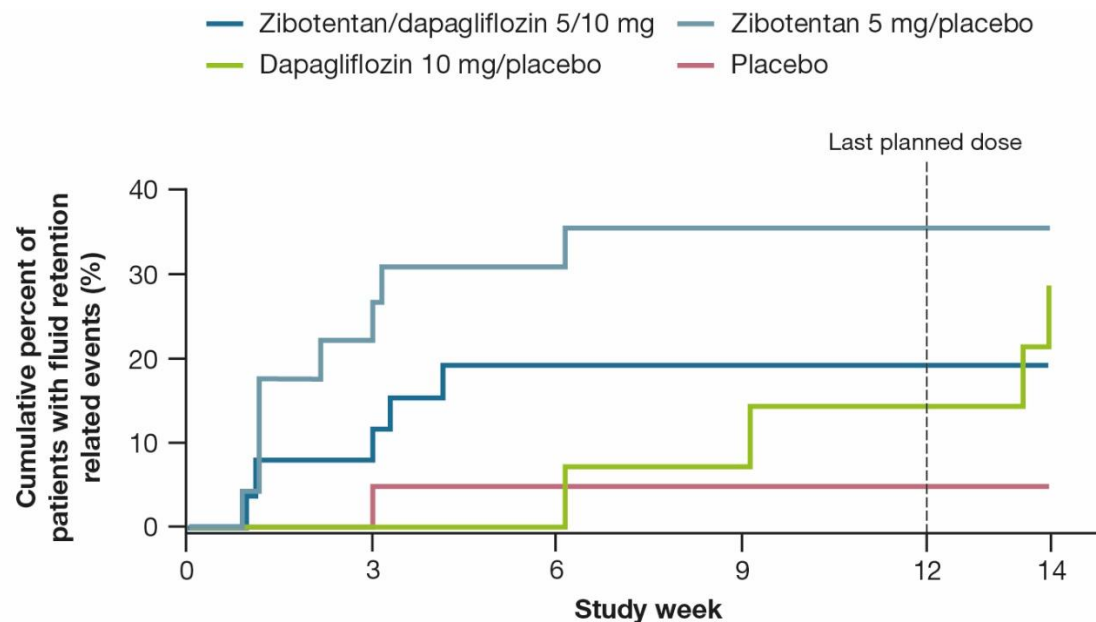
	3	157	0.399 (0.0501)	81	0.386 (0.0438)	150	0.367 (0.0489)
	6	151	0.405 (0.0520)	81	0.393 (0.0485)	131	0.374 (0.0493)
	12	139	0.408 (0.0576)	72	0.396 (0.0532)	131	0.378 (0.0495)
	Follow-up	146	0.402 (0.0540)	70	0.400 (0.0506)	130	0.394 (0.0502)
BNP, pg/mL	Baseline	177	59.0 (72.44)	91	63.5 (75.56)	177	59.5 (75.53)
	3	161	55.1 (70.05)	84	56.5 (59.11)	164	58.8 (60.71)
	6	161	51.7 (57.13)	84	55.9 (67.42)	146	60.5 (66.57)
	12	146	58.5 (83.34)	76	57.2 (65.02)	135	55.1 (53.45)
	Follow-up	147	64.2 (62.47)	73	69.3 (93.21)	137	54.8 (56.06)
Weight, kg	Baseline	177	85.51 (18.197)	91	83.80 (16.476)	179	85.88 (16.904)
	3	168	83.96 (17.360)	86	83.02 (15.340)	166	86.45 (17.201)
	6	163	84.20 (17.277)	86	83.09 (16.056)	158	85.65 (17.413)
	12	150	84.29 (17.713)	77	83.29 (16.784)	139	85.54 (16.908)
	Follow-up	152	84.18 (17.899)	74	83.73 (16.801)	140	85.72 (16.777)
Uric acid, umol/L	Baseline	177	403.08 (103.739)	91	410.50 (105.536)	179	392.21 (98.455)
	12	148	381.75 (96.142)	76	371.76 (101.004)	137	370.94 (94.492)
	Follow-up	150	387.77 (100.277)	74	388.89 (92.582)	138	374.22 (87.838)

BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HbA1C, haemoglobin A1C; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio

**Supplementary figure 1:** Forest plot showing adjusted percentage mean change from baseline (90%CI) overall, by type 2 diabetes status and by baseline eGFR for Zibotentan 0.25 mg/dapagliflozin 10 mg and Zibotentan 1.5 mg/dapagliflozin 10 mg



**Supplementary figure 2** Kaplan Meier curve of fluid related events by treatment group in part A of the study. Changes from baseline in mean body weight and median BNP are presented by treatment group below the Kaplan Meier curve.



		n at risk					
Zibotentan/dapagliflozin 5/10 mg (N=21)	21	19	16	16	16	16	
Placebo (N=22)	21	21	20	20	19	19	
Dapagliflozin 10 mg/placebo (N=14)	14	14	14	13	12	11	
Zibotentan 5 mg (N=19)	19	13	11	10	10	10	

	Mean (SD) change from baseline in body weight (kg)				Median (25 <sup>th</sup> 75 <sup>th</sup> Percentile) change from baseline in BNP, ng/L			
	Placebo	5 mg Zibotentan / placebo	Dapagliflozin / placebo	5 mg Zibotentan / dapagliflozin	Placebo	5 mg Zibotentan / placebo	Dapagliflozin / placebo	5 mg Zibotentan / dapagliflozin
Week 1	-0.1 (1.2)	2.1 (1.4)	-0.6 (1.8)	0.8 (1.4)	-1.0 [-29, 10]	9.0 [2, 28]	-18.0 [-37, -7]	2.5 [-15, 37]
Week 6	0.0 (1.5)	0.6 (1.4)	-0.7 (3.5)	-0.1 (0.5)	-0.5 [-24, 10]	38.0 [4, 70]	-8.5 [-23, 35]	8.0 [-5, 16]
Week 12	-0.3 (1.6)	0.1 (2.8)	-0.2 (6.0)	-0.3 (1.8)	-14.0 [-49, 47]	-1.0 [-19.0, 20]	-7.0 [-34, 9]	13 [0, 26]

**Supplementary figure 3:** Scatterplot showing log of the ratio to baseline in UACR and change from baseline in systolic blood pressure at week 12, by treatment group. There was no correlation between changes from week 12 in UACR and SBP during the wash-out period at week 14. There was also no correlation between changes from baseline in diastolic blood pressure and UACR at week 12.

