ONLINE SUPPLEMENT

Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial

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SUPPLEMENTARY FIGURES

Figure S1. Individual changes in 24-hour ambulatory systolic blood pressure (BP) from baseline to 12 weeks.

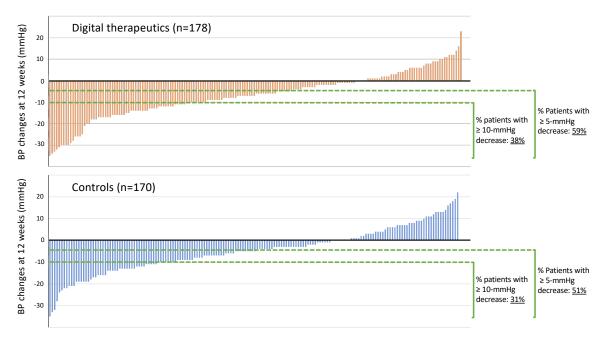


Figure S2. Changes from baseline to 12 weeks in 24-hour, daytime and nighttime diastolic blood pressure (DBP) based on ambulatory blood pressure monitoring (ABPM), morning and evening home DBP, and office DBP. Values are reported as mean [95% confidence interval].

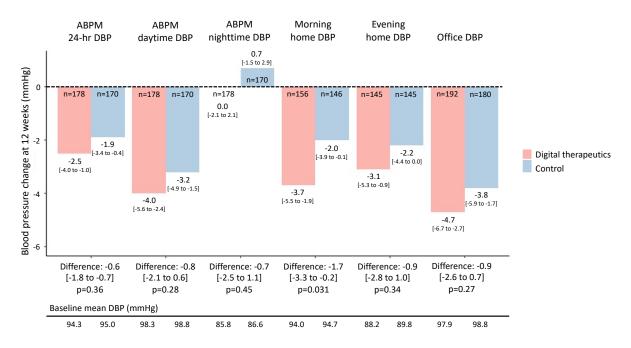


Figure S3. Changes from baseline to 12 weeks in 24-hour, daytime and nighttime heart rate (HR) based on ambulatory blood pressure monitoring (ABPM), morning and evening home HR, and office HR. Values are reported as mean [95% confidence interval].

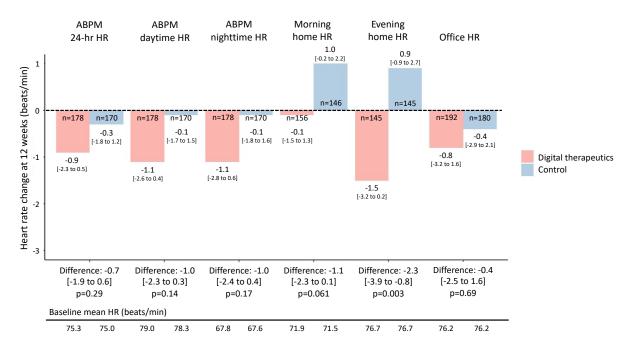


Figure S4. Change in morning home diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

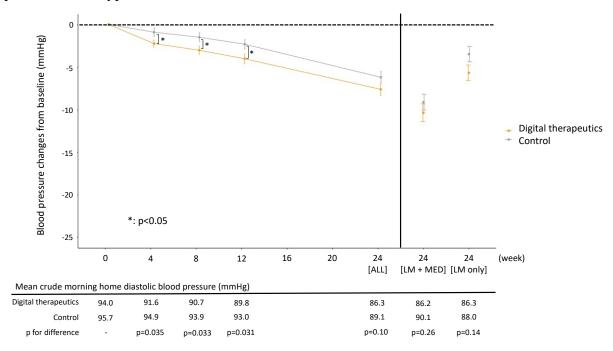


Figure S5. Change in evening home systolic blood pressure (SBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

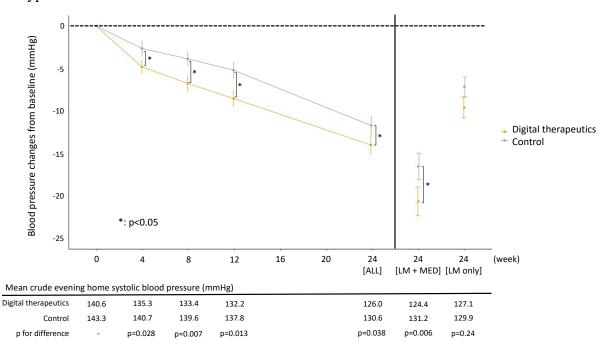


Figure S6. Change in evening home diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

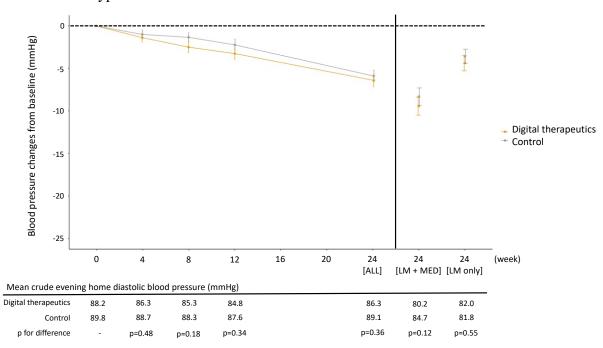


Figure S7. Change in office systolic blood pressure (SBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

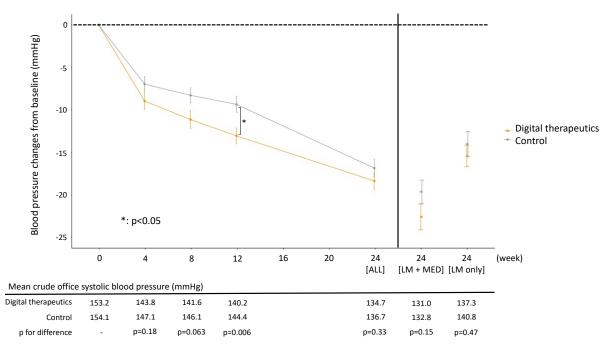


Figure S8. Change in office diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

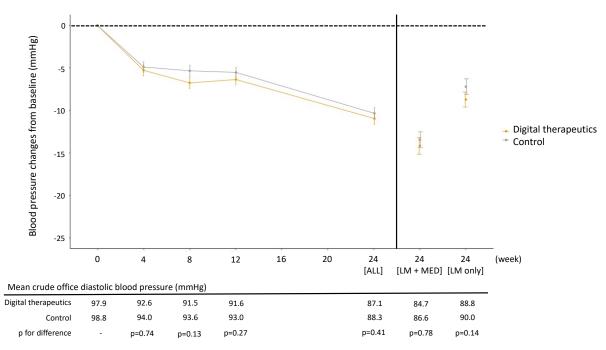


Figure S9. Change in body weight from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

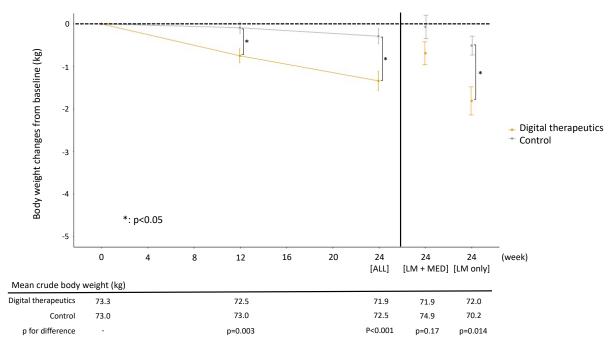


Figure S10. Change in body mass index from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

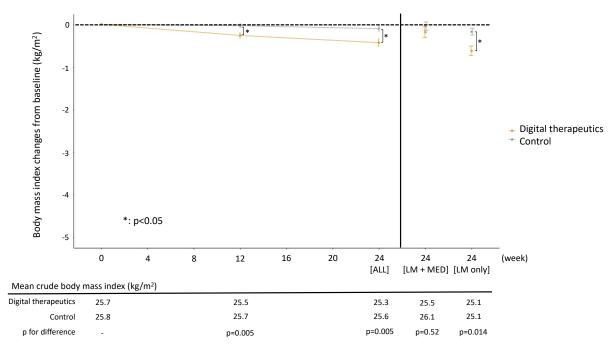


Figure S11. Change in salt intake from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

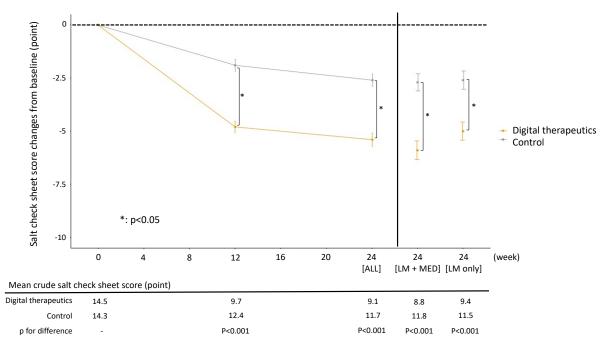


Figure S12. Change in urinary sodium corrected for urinary creatinine from baseline to 24 weeks. Urinary creatinine-corrected urinary sodium was calculated as the urinary sodium level divided by the urinary creatinine level. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.

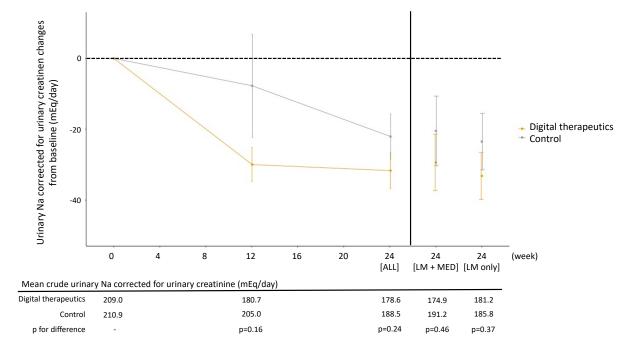
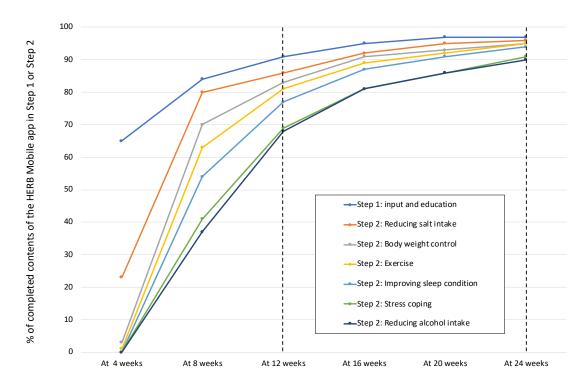


Figure S13. Progress of app-supported lifestyle modification. Completion of Step 1 was defined as receiving all 14 interactive education chapters, and completion of Step 2 was defined as the app user having successfully experienced and achieved three consecutive recommended goals in each category.



SUPPLEMENTARY TABLES

Table S1. (A) Research organization and roles (each team and committee was independently organised and responsible for their own work. (B) Study sites, principal investigators (PI) and center personnel.

А

Role	Investigators and personnel	Institute
Steering Committee		
Chairman, Coordinating investigator	Kazuomi Kario MD, PhD	Jichi Medical University, Tochigi
Medical expert	Akihiro Nomura, MD, PhD	Kanazawa University, Kanazawa
Coordinator	Noriko Harada, BE	Jichi Medical University, Tochigi
,Coordinator	Ayako Okura, BA	Jichi Medical University, Tochigi
Biostatistical Committee		
Director of biostatistical analysis	Eisuke Hida, PhD	Osaka University, Osaka
Biostatistical analysis	Kunitake Komatsu, BSc	Intage Healthcare Inc., Tokyo
Data management	Ryoichi Muraoka, DVM	Intage Healthcare Inc., Tokyo
Clinical Trial Management		
Assignment manager	Ryoichi Muraoka, DVM	Intage Healthcare Inc., Tokyo
Manager, Contact for public queries	Kiyose Nakagawa, MPharm	CureApp, Inc., Tokyo
Safety information management	Katsunori Sakai, BSc	CureApp, Inc., Tokyo
Medical expert	Tomoyuki Tanigawa, MD, MPH	CureApp, Inc., Tokyo
Data Safety Monitoring Board		
Monitoring	Wataru Muto, BPharm	Intage Healthcare Inc., Tokyo
Audit	Susumu Kato, MPharm	Intage Healthcare Inc., Tokyo
Clinical trial sponsor	Kota Satake, MD, MBA, MPH	CureApp, Inc., Tokyo

B

Site, prefecture	Investigators and personnel
Hatori Clinic, Kanagawa	PI: Yutaka Hatori
Jichi Medical University Hospital, Tochigi	PI: Kazuomi Kario
Kita Shin-yokohama Internal Medicine Clinic, Kanagawa	PI: Uguri Kamiya
Kyosokai AMC NISHI-UMEDA Clinic, Osaka	PI: Yoshimitsu Yamasaki
Maekawa Medical Clinic, Kanagawa	PI: Hiromitsu Maekawa
Medical corporation Shirayurikai Swing Nozaki Clinic, Tokyo	PI: Minoru Nozaki
Sasaki Clinic, Hyogo	PI: Ryotaro Sasaki
Shimokitazawa Tomo Clinic, Tokyo	PI: Tomofumi Murakami
Sone Clinic Shinjuku, Tokyo	PI: Masayoshi Sone
Tokyo Center Clinic, Tokyo	PI: Hirotaka Nagashima
Tokyo-Eki Center-building Clinic, Tokyo	PI: Arihiro Kiyosue
Yotsuya Internal Medicine Clinic, Tokyo	PI: Takahiro Yokoyama

Prescribed medications, n (%)	Control (n=180)	Digital therapeutics (n=192)
Prescribed antihypertensive drugs	87 (48.3)	78 (40.6)
Calcium channel blocker	74 (41.1)	68 (35.4)
Angiotensin-2 receptor blocker	22 (12.2)	12 (6.3)
Diuretics	2 (1.1)	2 (1.0)

Table S2. List of prescribed medications at 3 months after registration.

Table S3. Differences in change from baseline to 12 and 24 weeks between the digitaltherapeutics and control groups in 24-hour systolic and diastolic blood pressure (mmHg), and24-hour heart rate (beats/min) based on ambulatory blood pressure monitoring.

	At 12 we	eks		At 24 weeks				
	Difference	95% CI	p-value	Medication-use evaluation at 12 weeks	Difference	95% CI	p-value	
				All	-1.8	-4.1 to 0.5	0.12	
24-hour SBP	-2.4	-4.5 to 0.3	0.024	Lifestyle modification and medication	-3.2	-6.8 to 0.4	0.085	
				Lifestyle modification only	-1.4	-4.4 to 1.5	0.33	
				All	-1.0	-2.4 to 0.4	0.17	
24-hour DBP	-0.6	-1.8 to 0.7	0.36	Lifestyle modification and medication	-1.6	-4.0 to 0.7	0.17	
				Lifestyle modification only	-1.0	-2.8 to 0.7	0.25	
				All	-0.9	-2.2 to 0.4	0.19	
24-hour HR	-0.7	-1.9 to 0.6	0.29	Lifestyle modification and medication	1.0	-1.0 to 3.0	0.31	
				Lifestyle modification only	-2.1	-3.9 to -0.4	0.019	

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table S4. Differences in change from baseline to 12 and 24 weeks between the digital
therapeutics and control groups in home systolic and diastolic blood pressure (mmHg), and
heart rate (beats/min).

At 12 weeks				At 24 weeks					
	Difference	95% CI	p-value	Medication-use evaluation at 12 weeks	Difference	95% CI	p-value		
M				All	-4.9	-7.8 to -2.0	0.001		
Morning home SBP	-4.3	-6.7 to -1.9	< 0.001	Lifestyle modification and medication	-7.3	-11.4 to -3.1	< 0.001		
nome SDr				Lifestyle modification only	-3.7	-7.7 to 0.3	0.067		
Maurina				All	-1.6	-3.6 to 0.3	0.10		
Morning home DBP	-1.7	-3.3 to -0.2	0.031	Lifestyle modification and medication	-1.6	-4.4 to 1.2	0.26		
nome DD1				Lifestyle modification only	-1.9	-4.5 to 0.6	0.14		
Manaina				All	-1.6	-2.9 to -0.2	0.023		
Morning home HR	-1.1	-2.3 to 0.1	0.061	Lifestyle modification and medication	-0.8	-2.7 to 1.2	0.42		
nome mx				Lifestyle modification only	-1.8	-3.7 to 0.1	0.065		
Evening				All	-3.0	-5.8 to -0.2	0.038		
Evening home SBP	-3.3	-5.8 to -0.7	0.013	Lifestyle modification and medication	-6.6	-11.2 to -2.0	0.006		
nome SDI				Lifestyle modification only	-2.1	-5.5 to 1.4	0.24		
F				All	-0.9	-2.9 to 1.1	0.36		
Evening home DBP	-0.9	-2.8 to 1.0	0.34	Lifestyle modification and medication	-2.4	-5.5 to 0.6	0.12		
nome DBr				Lifestyle modification only	-0.8	-3.4 to 1.8	0.55		
Evoning				All	-2.3	-4.1 to -0.6	0.010		
Evening home HR	-2.3	-3.9 to -0.8	0.003	Lifestyle modification and medication	-1.9	-4.5 to 0.8	0.16		
				Lifestyle modification only	-2.1	-4.7 to 0.4	0.10		

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table S5. Differences in change from baseline to 12 and 24 weeks between the digital therapeutics and control groups in office systolic and diastolic blood pressure (mmHg), and heart rate (beats/min).

	At 12 w	veeks		At 24 weeks					
	Difference	95% CI	p-value	Medication-use evaluation at 12 weeks	Difference	95% CI	p-value		
				All	-1.4	-4.1 to 1.4	0.33		
Office SBP	-3.6	-6.2 to -1.0	0.006	Lifestyle modification and medication	-2.9	-6.9 to 1.0	0.15		
				Lifestyle modification only	-1.4	-5.3 to 2.4	0.47		
				All	-0.7	-2.5 to 1.0	0.41		
Office DBP	-0.9	-2.6 to 0.7	0.27	Lifestyle modification and medication	-0.4	-2.9 to 2.2	0.78		
				Lifestyle modification only	-1.8	-4.2 to 0.6	0.14		
				All	-0.1	-2.2 to 1.9	0.91		
Office HR	-0.4	-2.5 to 1.6	0.69	Lifestyle modification and medication	0.1	-3.2 to 3.4	0.95		
				Lifestyle modification only	-0.6	-3.3 to 2.0	0.63		

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table S6. Proportion of	patients achieving target BP contr	ol criteria at 12 and 24 weeks.

	At 12 weeks		At 24 weeks			
% Patients	Digital therapeutics		Medication-use evaluation at 12 weeks	Digital therapeutics	Controls	
>5 mmHg decrease			All	72.2%	66.3%	
in ambulatory BP	59.0%	50.6%	Lifestyle modification and medication	82.9%	82.9%	
from baseline			Lifestyle modification only	65.1%	51.2%	
Mouning home DD			All	35.1%	19.0%	
Morning home BP <135/85 mmHg	22.2%	10.4%	Lifestyle modification and medication Lifestyle modification only	37.7% 33.3%	17.9% 20.3%	

		Baseline	12 weeks		24 weeks		
		Dasenne	12 weeks	All	LM + MED	LM only	
T (1 1 1 (1	DTx	213.9 ± 37.5	217.3 ± 37.0	215.1 ± 34.6	217.6 ± 35.7	213.3 ± 33.8	
Total cholesterol	Control	213.8 ± 33.5	218.0 ± 36.7	214.4 ± 33.4	211.6 ± 33.3	217.3 ± 33.5	
(mg/dL)	p for difference	-	0.81	0.64	0.46	0.37	
	DTx	137.0 ± 107	150.2 ± 110	144.0 ± 120	149.9 ± 106	139.8 ± 123	
Triglycerides	Courteral					$138.60\pm$	
(mg/dL)	Control	131.5 ± 102	156.0 ± 160	139.7 ± 92.2	140.70 ± 93.4	91.6	
	p for difference	-	0.42	0.96	0.57	0.50	
UDL -h-lt1	DTx	60.3 ± 16	59.9 ± 17	61.0 ± 18	61.4 ± 17	60.7 ± 19	
HDL cholesterol	Control	59.6 ± 15	58.7 ± 15	58.7 ± 15	57.5 ± 13	59.8 ± 16	
(mg/dL)	p for difference	-	0.88	0.43	0.13	0.09	
E	DTx	98.0 ± 19	96.8 ± 17	96.4 ± 14	99.7 ± 25	95.9 ± 13	
Fasting plasma	Control	99.7 ± 23	99.8 ± 24	101.6 ± 25	101.9 ± 29	100.8 ± 28	
glucose (mg/dL)	p for difference	-	0.45	0.045	0.31	0.02	
	DTx	6.13 ± 1.3	6.27 ± 1.3	6.13 ± 1.2	6.13 ± 1.3	6.14 ± 1.2	
Uric acid (mg/dL)	Control	5.99 ± 1.2	6.10 ± 1.2	6.04 ± 1.2	6.25 ± 1.2	5.82 ± 1.3	
	p for difference	-	0.63	0.70	0.79	0.73	
	DTx	25.3 ± 11	24.7 ± 12	24.8 ± 12	25.8 ± 13	24.2 ± 11	
AST (IU/L)	Control	25.9 ± 12	26.1 ± 11	27.3 ± 18	26.9 ± 12	27.7 ± 22	
	p for difference	-	0.72	0.30	0.63	0.39	
	DTx	28.5 ± 21	27.4 ± 19	27.6 ± 21	31.2 ± 23	25.1 ± 19	
ALT (IU/L)	Control	28.4 ± 18	29.5 ± 20	31.6 ± 24	33.4 ± 24	29.7 ± 24	
	p for difference	-	0.72	0.30	0.63	0.39	
	DTx	46.5 ± 45	46.7 ± 50	47.2 ± 57	57.3 ± 77	40.2 ± 35	
γ-GTP (IU/L)	Control	53.0 ± 72	54.9 ± 85	56.0 ± 71	60.1 ± 86	51.8 ± 52	
	p for difference	-	0.47	0.46	0.41	0.21	

Table S7. Changes in obesity-related metabolic risk factors and measures of fatty liver from baseline to 24 weeks in the digital therapeutics (DTx) and control groups.

Values are mean \pm standard deviation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; HDL, highdensity lipoprotein; LM, lifestyle modification; MED, medication.

	Baseline 24-hour	• ambulatory SBP	
	<145 mmHg	≥145 mmHg	p-value
	(n=213)	(n=177)	
Age, years	51.7 ± 8.6	52.7 ± 6.7	0.21
Male, n (%)	170 (80%)	142 (80%)	0.92
Body mass index, kg/m ²	25.0 ± 3.7	26.6 ± 4.2	< 0.0001
Waist circumference, cm	87.5 ± 10	91.0 ± 11	0.0012
Current smoking, n (%)	28 (13%)	34 (19%)	0.10
Previous antihypertensive drug treatment, n (%)	22 (10%)	35 (20%)	0.0086
Comorbidities, n (%)			
Dyslipidaemia	102 (48%)	93 (53%)	0.36
Diabetes	13 (6%)	13 (7%)	0.62
Proteinuria	11 (5%)	16 (9%)	0.13
Non-valvular atrial fibrillation	1 (1%)	2 (1%)	0.46
Blood pressure, mmHg			
24-hour ambulatory SBP	136.8 ± 4.3	153.9 ± 7.6	< 0.0001
24-hour ambulatory DBP	90.8 ± 5.9	99.2 ± 7.0	< 0.0001
Morning home SBP	142.8 ± 11	154.9 ± 12	< 0.0001
Morning home DBP	92.3 ± 7.8	98.0 ± 10	< 0.0001
Evening home SBP	136.7 ± 12	148.9 ± 13	< 0.0001
Evening home DBP	87.0 ± 9.5	91.5 ± 11	< 0.0001
Office SBP	151.4 ± 9.7	156.4 ± 10	< 0.0001
Office DBP	97.2 ± 7.3	99.7 ± 6.6	0.0007

Table S8. Baseline characteristics in patient subgroups based on baseline 24-hour ambulatory SBP (\geq 145 versus <145 mmHg); p-values were calculated using unpaired *t*-test for continuous variables and Chi-square test for categorical variables.

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table S9. Morning and evening home blood pressure (BP) measurement rates in the digital therapeutics and control groups. Home BP measurement rate was calculated as the number patients with successful home BP monitoring for \geq 5 days in the week (7 days) immediately prior to a study visit divided by the number of patients completed their follow-up at each visit.

	Dagalina	4	8 weeks	12 weeks _	24 weeks			
	Baseline	4 weeks			All	LM + MED	LM only	
Digital therapeutics group								
N completed follow-up at each visit	199	197	196	192	191	78	113	
N with morning BP measured	167	187	191	187	181	76	105	
Morning BP measurement rates (%)	83.9	94.9	97.4	97.4	94.8	97.4	92.9	
N with evening BP measured	160	181	180	180	171	70	101	
Evening BP measurement rates (%)	80.4	91.9	91.8	93.8	89.5	89.7	89.4	
Control group								
N completed follow-up at each visit	191	190	186	180	175	87	88	
N with morning BP measured	158	170	177	178	168	85	83	
Morning BP measurement rates (%)	82.7	89.5	95.2	98.9	96.0	97.7	94.3	
N with evening BP measured	159	162	172	174	166	85	81	
Evening BP measurement rates (%)	83.2	85.3	92.5	96.7	94.9	97.7	92.0	

LM, lifestyle modification; MED, medication.

faematological or lymphatic0 (0%)1 (0.5%)Anaemia01ardiovascular0 (0%)2 (1.0%)Angina01Cardiovascular disease01Ophthalmologic2 (1.0%)1 (0.5%)Chalazion01Conjunctival bleeding10Visual impairment10Abdominal distention01Abdominal pain13Constipation01Diarrhoea10Gastroitis10Gastroitis10Impaired dental development10Impaired dental development10Impaired dental development01Impaired dental development01Impaired dental development01Impaired dental development01Impaired dental development01Impaired dental development01Itakhaustion01Extanation04Ever04Fever04Fever04Fever04Fever04Fever04Fever04Fever04Fever04Fever04Fever00Anaphylactic reaction01Seasonal allergy01	Patients (%)	Control (n=194)	Digital therapeutics (n=200)
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Angina0 (0%)2 (1.0%)Angina01Cardiovascular disease01Ophthalmologic2 (1.0%)1 (0.5%)Chalazion01Conjunctival bleeding10Visual impairment01Abdominal distention01Abdominal pain13Constipation01Caries11Upper abdominal pain13Constipation01Caries11Diarrhoea19Gastriftis10Gastro-escophageal reflux11Bloody stool10Oral ulcer01Impaired dental development10Deverlessness10Chest pain02Fatigue04Fever04Reparitirary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Faty liver10Numunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Haematological or lymphatic	0 (0%)	1 (0.5%)
Angina O 1 Cardiovascular disease 0 1 Opthalmologic 2 (1.0%) 1 (0.5%) Chalazion 0 1 Conjunctival bleeding 1 0 Visual impairment 1 0 astrointestinal 9 (4.6%) 21 (10.5%) Abdominal distention 0 1 Abdominal pain 1 5 Upper abdominal pain 1 3 Constipation 0 1 Caries 1 1 Gastroites 1 0 Gastroites 1 1 Bloody stool 0 1 Impaired dental development 1 0 Oral ulcer 0 1 Powerlessness 1 0 Chest pain 0 1 Evated hepatic enzyme levels 3 3 Fatigue 0 4 Fever 0 4 <tr tr=""> Up tertingical</tr>	Anaemia	0	1
Cardiovascular disease01bpthalmologic2 (1.0%)1 (0.5%)Chalazion01Conjunctival bleeding10Visual impairment10Sastrointestinal9 (4.6%)21 (10.5%)Abdominal distention01Abdominal pain13Constipation01Constipation01Constipation01Constipation01Caries11Diarrhoea19Gastritis10Gastroitis10Gastroitis10Oral ulcer01Impaired dental development10Dental pain01Impaired dental development01Impaired dental development01Everal10.05%)8 (4.0%)Powerlessness10Chest pain01Etyabeiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Faty liver01Ournunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Cardiovascular	0 (0%)	2 (1.0%)
phthalmologic2 (1.0%)1 (0.5%)Chalazion01Conjunctival bleeding10Visual impairment10astrointestinal9 (4.6%)21 (10.5%)Abdominal distention01Abdominal pain15Upper abdominal pain13Constipation01Caries11Diarrhoea19Gastritis10Gastro-oesophageal reflux11Bloody stool01Uper aldevelopment10Impaired development10Impaired development10Iterare10Powerlessness10Chest pain01Evated hepatic enzyme levels33Fatigue04Ievared hepatic enzyme levels33Faty liver10Anaphylactic reaction01Seasonal allergy01	Angina	0	1
Chalazion 0 1 Conjunctival bleeding 1 0 Visual impairment 1 0 astrointestinal 9 (4.6%) 21 (10.5%) Abdominal distention 0 1 Abdominal pain 1 5 Upper abdominal pain 1 3 Constipation 0 1 Diarrhoea 1 9 Gastriis 1 0 Gastroinescophageal reflux 1 1 Bloody stool 0 1 Oral ucer 0 1 0 Oral ucer 0 1 1 Impaired dental development 1 0 1 Dental pain 1 2 Vomiting 0 1 Powerlessness 1 0 1 1 1 Evated hepatic enzyme levels 3 3 1 0 Chest pain 0 4 4 1 0 Evated hepatobilary	Cardiovascular disease	0	1
Conjunctival bleeding10Visual impairment10iastrointestinal9 (4.6%)21 (10.5%)Abdominal distention01Abdominal pain15Upper abdominal pain13Constipation01Caries11Diarrhoea19Gastriis10Gastroincesophageal reflux10Bloody stool01Impaired dental development10Dental pain12Vomiting01Impaired dental development10Dental pain10Powerlessness10Powerlessness10Chest pain01Evated hepatic enzyme levels33Fatigue04Iseared10Innuological0(0%)2(1.0%)Anaphylactic reaction01Seasonal allergy01	Ophthalmologic	2 (1.0%)	1 (0.5%)
Visual impairment I 0 astrointestinal 9 (4.6%) 21 (10.5%) Abdominal distention 0 1 Abdominal pain 1 5 Upper abdominal pain 1 3 Constipation 0 1 Diarrhoea 1 1 Diarrhoea 1 9 Gastritis 1 0 Gastroopeosophageal reflux 1 1 Bloody stool 0 1 Oral ulcer 0 1 Oral ulcer 1 0 Oral ulcer 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 0 Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Upper 1 0	Chalazion	0	1
Bastrointestinal 9 (4.6%) 21 (10.5%) Abdominal distention 0 1 Abdominal pain 1 5 Upper abdominal pain 1 3 Constipation 0 1 Caries 1 1 Diarrhoea 1 9 Gastritis 1 0 Gastro-oesophageal reflux 1 1 Bloody stool 0 1 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 1 Powerlessness 1 0 1 Exhaustion 0 2 1 Exhaustion 0 2 1 Fatype 0 4 1 Iepatobiliary 4 (2.1%) 3 (1.5%) 3 Fatype 1 0 1 Imparted depatic enzyme levels 3 3 3	Conjunctival bleeding	1	0
Abdominal distention 0 1 Abdominal pain 1 5 Upper abdominal pain 1 3 Constipation 0 1 Caries 1 1 Diarrhoea 1 9 Gastritis 1 0 Gastro-oesophageal reflux 1 1 Bloody stool 0 1 Maemorrhoid 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 0 Powerlessness 1 0 1 Ethaustion 0 2 1 Ethaustion 0 4 2 Fever 0 4 1 Elevated hepatic enzyme levels 3 3 3 Fatty liver 1 0 1 munological 0(0%) 2(1.0%) 1 <td>Visual impairment</td> <td>1</td> <td>0</td>	Visual impairment	1	0
Abdominal pain15Upper abdominal pain13Constipation01Caries11Diarrhoea19Gastritis10Gastro-oesophageal reflux11Bloody stool01Haemorrhoid10Oral ulcer01Impaired dental development10Dental pain12Vomiting01Evereral10.5%)8 (4.0%)Powerlessness10Evated hepatic enzyme levels33Faty liver10Inmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Gastrointestinal	9 (4.6%)	21 (10.5%)
Upper abdominal pain 1 3 Constipation 0 1 Caries 1 1 Diarrboea 1 9 Gastritis 1 0 Gastro-oesophageal reflux 1 1 Bloody stool 0 1 Haemorrhoid 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 0 Powerlessness 1 0 Fetreral 0 1 Exhaustion 0 2 Fatigue 0 4 Ievarde hepatic enzyme levels 3 3 Fatty liver 1 0 munological 0(0%) 2(1.0%) Anaphylactic reaction 0 1	Abdominal distention	0	1
Constipation 0 1 Carsies 1 1 Diarrhoea 1 9 Gastritis 1 0 Gastro-oesophageal reflux 1 1 Bloody stool 0 1 Haemorrhoid 0 1 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 1 Reneral 1 (0.5%) 8 (4.0%) 1 Exhaustion 0 1 0 1 Exhaustion 0 1 2 1 0 1	Abdominal pain	1	5
Caries 1 1 Diarrhoea 1 9 Gastritis 1 0 Gastro-oesophageal reflux 1 1 Bloody stool 0 1 Haemorrhoid 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 ieneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 rever 0 4 Itepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 munological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1	Upper abdominal pain	1	3
Diarhoea19Gastriis10Gastro-oesophageal reflux11Bloody stool01Haemorrhoid01Oral ulcer01Oral ulcer01Impaired dental development10Dental pain12Vomiting01ieneral1 (0.5%)8 (4.0%)Powerlessness10Chest pain01Exhaustion02Fatigue04teqatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Constipation	0	1
Gastriis10Gastro-oesophageal reflux11Bloody stool01Haemorthoid10Oral ulcer01Impaired dental development10Dental pain12Vomiting01eneral1 (0.5%)8 (4.0%)Powerlessness10Chest pain01Exhaustion02Fatigue04Fever04Lepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10munuological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Caries	1	1
Gastro-oesophageal reflux11Bloody stool01Haemorrhoid10Oral ulcer01Impaired dental development10Dental pain12Vomiting01ieneral1 (0.5%)8 (4.0%)Powerlessness10Chest pain01Exhaustion02Fatigue04Fever04Iepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Diarrhoea	1	9
Bloody stool 0 1 Haemorrhoid 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 Beneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Iepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 munological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Gastritis	1	0
Haemorthoid 1 0 Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 ieneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Iepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 munological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Gastro-oesophageal reflux	1	1
Oral ulcer 0 1 Impaired dental development 1 0 Dental pain 1 2 Vomiting 0 1 Beneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Bepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 mmunological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Bloody stool	0	1
Impaired dental development10Dental pain12Vomiting01ieneral1 (0.5%)8 (4.0%)Powerlessness10Chest pain01Exhaustion02Fatigue04Fever04Uepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Haemorrhoid	1	0
Dental pain 1 2 Vomiting 0 1 Seneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Repatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 mmunological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Oral ulcer	0	1
Voniting 0 1 Seneral 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Lepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 mmunological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Impaired dental development	1	0
initial 1 (0.5%) 8 (4.0%) Powerlessness 1 0 Chest pain 0 1 Exhaustion 0 2 Fatigue 0 4 Fever 0 4 Iepatobiliary 4 (2.1%) 3 (1.5%) Elevated hepatic enzyme levels 3 3 Fatty liver 1 0 mmunological 0 (0%) 2 (1.0%) Anaphylactic reaction 0 1 Seasonal allergy 0 1	Dental pain	1	2
Powerlessness10Chest pain01Exhaustion02Fatigue04Fever04Lepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Vomiting	0	1
Chest pain01Exhaustion02Fatigue04Fever04Iepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	General	1 (0.5%)	8 (4.0%)
Exhaustion02Fatigue04Fever04Lepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Powerlessness	1	0
Fatigue04Fever04Lepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Chest pain	0	1
Fever04Lepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Exhaustion	0	2
Iepatobiliary4 (2.1%)3 (1.5%)Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Fatigue	0	4
Elevated hepatic enzyme levels33Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Fever	0	4
Fatty liver10mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Hepatobiliary	4 (2.1%)	3 (1.5%)
mmunological0 (0%)2 (1.0%)Anaphylactic reaction01Seasonal allergy01	Elevated hepatic enzyme levels	3	3
Anaphylactic reaction01Seasonal allergy01	Fatty liver	1	0
Seasonal allergy 0 1	Immunological	0 (0%)	2 (1.0%)
	Anaphylactic reaction	0	1
nfectious diseases 15 (7.7%) 33 (16.5%)	Seasonal allergy	0	1
	Infectious diseases	15 (7.7%)	33 (16.5%)

Table S10. Safety outcomes and adverse events by patients during the trial period.	Table S10	. Safety	outcomes	and a	dverse	events	by	patients	during	the trial	period.
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Cellulitis	0	1
Cystitis	0	1
Gastroenteritis	1	2
Viral gastroenteritis	0	1
Gingivitis	2	0
Shingles	1	0
Hordeolum	1	0
Influenza virus infection	1	0
Nasopharyngitis	6	24
Periodontitis	0	2
Pharyngitis	2	2
Rhinitis	1	1
Sinusitis	1	0
Dental infection	0	1
Injuries	3 (1.5%)	12 (6.0%)
Arthropod bite	0	2
Leg bone fracture	1	1
Skin damage	0	1
Sprain	1	1
Bruise	1	2
Scratch	1	0
Heatstroke	0	4
Foreign body in airway	0	1
Laboratory data	1 (0.5%)	5 (2.5%)
Aspartate aminotransferase elevation	0	1
Gamma glutamyl-transferase elevation	0	1
Positive for urine glucose	0	1
Positive for occult haematuria	0	1
White blood cell count elevation	0	1
Hepatic enzyme elevation	1	0
Metabolic	6 (3.1%)	7 (3.5%)
Diabetes	1	1
Gout	1	2
Hyperuricaemia	1	3
Dyslipidaemia	2	0
Hyperlipidaemia	1	1
Musculoskeletal	8 (4.1%)	28 (14.0%)
Joint pain	0	7
Arthritis	0	1
Back pain	2	10

Joint effusion10Cramp11Musculoskeletal pain01Myalgia27Neck pain01Nodal osteoarthritis01Osteoarthritis01Costeoarthritis01Snapping finger01Fibromyalgia10Neurological pain syndrome01Neurological10Sinapping finger01Neurological10Sinapping finger01Neurological10Sinapping finger32Dysgeusia10Myofascial pain syndrome01Neurological10Sin papilloma10Neurological32Dysgeusia10Head discomfort11Intracranial ancurysm10Migraine03Presyncope01Genital2(10%)3(15%)Joynnorthoea10Ingerinativi10Oropharyngeal pain10Cough210Ipper respiratory tract inflammation01Oropharyngeal pain11Notei11Skin01Notei11Oropharyngeal pain11Skin01Norei	Fasciitis	0	1
Musculoskeletal pain01Myalgia27Neck pain01Nock pain01Osteoarthritis01Limb pain11Arthritis deformans01Snapping finger01Fibromyalgia10Noeplasms10.05%)10.05%)Lymphoma10Skin papilloma01Neurological6(3.1%)21 (10.5%)Dizziness32Dysgeusia10Head discomfort11Head discomfort11Head discomfort11Genital aneurysm10Migraine03Postatitis10Renal and urinary tract2 (1.0%)3 (1.5%)Dysnenorrhoea10Respiratory3 (1.5%)42.0%)Asthra10Cough21Voice impairment01Upypnoca01Upypnoca01Upypnoca01Upypnoca01Upyproca01Upyproca01Upyproca01Upper respiratory tract inflammation01Upper respiratory tract inflammation01Upper respiratory tract inflammation01Upper respiratory tract inflammation01Upper	Joint effusion	1	0
Musculoskeletal pain 0 1 Myalgia 2 7 Neck pain 0 1 Nodal osteoarthritis 0 1 Osteoarthritis 0 1 Limb pain 1 1 Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head che 3 16 Intracranial aneurysm 1 0 Migrainie 0 3 Presyncope 0 1 Haenal dysfunction 1 1 Renal and urinary tract 2 (1.0%) 3 (1.5%) Dysmenorrhoca 1 3 Prostatitis 1	Cramp	1	1
Neck pain 0 1 Nodal osteoarthritis 0 1 Osteoarthritis 0 1 Linb pain 1 1 Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 0 1 Myofascial pain syndrome 0 1 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 1 0 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgcusia 1 0 Head discomfort 1 1 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Genital 1 0 Renal and urinary tract 2 (1.0%) 3 (1.5%) Jysneotrhoea 1 0 Postatitis <t< td=""><td></td><td>0</td><td>1</td></t<>		0	1
Nodal osteoarthritis 0 1 Osteoarthritis 0 1 Limb pain 1 1 Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Necolasmi 1 0 Myofascial pain syndrome 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Headache 3 16 Intractnial ancurysm 1 0 Migraine 0 1 Question 1 1 Meadache 1 0 Itaematuria 1 0 Renal and urinary tract 2 (1.0%) 1 (0.5%) Ideenturia 1 0 Renal dysfunction 1 1 Ideenturia 1 0 Respiratory 3 (1.5%)	-	2	7
Osteoarthritis 0 1 Limb pain 1 1 Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Posyncope 0 1 Renal and urinary tract 2 (1.0%) 3 (1.5%) Migraine 1 0 Renal and urinary tract 2 (1.0%) 3 (1.5%) Mespiratory 3 (1.5%) 4 (2.0%) Dysmenorrhoea 1 0 Respiratory 3 (1.5%) 4 (2.0%)		0	1
Linb pain 1 1 Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1(0.5%) 1(0.5%) Lymphoma 1 0 Skin papilloma 0 1 Neurological 6(3.1%) 21(10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2(1.0%) 3(1.5%) Mysmenorthoca 1 0 Respiratory 3(1.5%) 4(2.0%) Asthma 1 0 Cogh 2 1 Voice impairment 0 1 Outprinoary embolism 0	Nodal osteoarthritis	0	1
Arthritis deformans 0 1 Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 1 0 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Asthma 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 0 1 Opphoca 0 1	Osteoarthritis	0	1
Snapping finger 0 1 Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 1 0 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Mysmenorrhoea 1 0 Respiratory 3 (1.5%) 4 (2.0%) Astima 1 0 Cough 2 1 Voice inpairment 0 1 Opspnoca 0<	Limb pain	1	1
Fibromyalgia 1 0 Myofascial pain syndrome 0 1 Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 1 0 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Meematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmeorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Astma 1 0 Cough 2 1 Voice impairment 1	Arthritis deformans	0	1
Myofascial pain syndrome 0 1 Necoplasms 1 (0.5%) 1 (0.5%) Lymphoma 0 1 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (10.0%) 3 (1.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Postatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Oropharyngeal pain 1<	Snapping finger	0	1
Neoplasms 1 (0.5%) 1 (0.5%) Lymphoma 0 1 Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Voice impairment 1 0 Dyspnoca 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Upphang	Fibromyalgia	1	0
Lymphoma 1 0 Skin papilloma 0 1 Neurological 6(3.1%) 21(10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2(1.0%) 1(0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2(1.0%) 3(1.5%) Prostatitis 1 0 Respiratory 3(1.5%) 4(2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoca 0 1 Pulmonary embolism 0 1 Oropharyngeal pain 1 1	Myofascial pain syndrome	0	1
Skin papilloma 0 1 Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Head discomfort 1 1 Head discomfort 1 0 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoca 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoca 0 1 Pulmonary embolism 0 1 Oropharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Neoplasms	1 (0.5%)	1 (0.5%)
Neurological 6 (3.1%) 21 (10.5%) Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Head discomfort 1 1 Head discomfort 1 0 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1	Lymphoma	1	0
Dizziness 3 2 Dysgeusia 1 0 Head discomfort 1 1 Head discomfort 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoca 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Skin papilloma	0	1
Dysgeusia 1 0 Head discomfort 1 1 Head discomfort 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Qup 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Neurological	6 (3.1%)	21 (10.5%)
Head discomfort 1 1 Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspneea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1	Dizziness	3	2
Headache 3 16 Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoca 0 1 Pulmonary embolism 0 1 Orpharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Dysgeusia	1	0
Intracranial aneurysm 1 0 Migraine 0 3 Presyncope 0 1 Remal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Ge-nital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 pyspnoea 0 1 Pulmonary embolism 0 1 Qipper respiratory tract inflammation 0 1 Kir 4 (2.1%) 12 (6.0%)	Head discomfort	1	1
Migraine 0 3 Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 psynoea 0 1 Pulnonary embolism 0 1 Orpharyngeal pain 1 1 Skir 4 (2.1%) 12 (6.0%)	Headache	3	16
Presyncope 0 1 Renal and urinary tract 2 (1.0%) 1 (0.5%) Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 pyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Kir 4 (2.1%) 12 (6.0%)	Intracranial aneurysm	1	0
Renal and urinary tract $2 (1.0\%)$ $1 (0.5\%)$ Haematuria10Renal dysfunction11Genital $2 (1.0\%)$ $3 (1.5\%)$ Dysmenorrhoea13Prostatitis10Respiratory $3 (1.5\%)$ $4 (2.0\%)$ Asthma10Cough21Voice impairment10Dyspnoea01Pulmonary embolism01Upper respiratory tract inflammation01Skin $4 (2.1\%)$ $12 (6.0\%)$	Migraine	0	3
Haematuria 1 0 Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 0 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Noice impairment 1 1 Upper respiratory tract inflammation 0 1 Kir 4 (2.1%) 12 (6.0%)	Presyncope	0	1
Renal dysfunction 1 1 Genital 2 (1.0%) 3 (1.5%) Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1 Skir 4 (2.1%) 12 (6.0%)	Renal and urinary tract	2 (1.0%)	1 (0.5%)
Genital 2 (1.0%) 3 (1.5%) Dysmenorhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1	Haematuria	1	0
Dysmenorrhoea 1 3 Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Renal dysfunction	1	1
Prostatitis 1 0 Respiratory 3 (1.5%) 4 (2.0%) Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Opper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1	Genital	2 (1.0%)	3 (1.5%)
Respiratory $3(1.5\%)$ $4(2.0\%)$ Asthma 1 0 Cough 2 1 Voice impairment 1 0 Dyspnoea 0 1 Pulmonary embolism 0 1 Upper respiratory tract inflammation 0 1 Oropharyngeal pain 1 1 Skir $4(2.1\%)$ $12(6.0\%)$	Dysmenorrhoea	1	3
Asthma10Cough21Voice impairment10Dyspnoea01Pulmonary embolism01Upper respiratory tract inflammation01Oropharyngeal pain11KI4(2.1%)12 (6.0%)	Prostatitis	1	0
Cough21Voice impairment10Dyspnoea01Pulmonary embolism01Upper respiratory tract inflammation01Oropharyngeal pain11Skir4(2.1%)12 (6.0%)	Respiratory	3 (1.5%)	4 (2.0%)
Voice impairment10Dyspnoea01Pulmonary embolism01Upper respiratory tract inflammation01Oropharyngeal pain11Skin4 (2.1%)12 (6.0%)	Asthma	1	0
Dyspnoea01Pulmonary embolism01Upper respiratory tract inflammation01Oropharyngeal pain11Skir4 (2.1%)12 (6.0%)	Cough	2	1
Pulmonary embolism01Upper respiratory tract inflammation01Oropharyngeal pain11Skin4 (2.1%)12 (6.0%)	Voice impairment	1	0
Upper respiratory tract inflammation01Oropharyngeal pain11Skin4 (2.1%)12 (6.0%)	Dyspnoea	0	1
Oropharyngeal pain 1 1 Skin 4 (2.1%) 12 (6.0%)	Pulmonary embolism	0	1
Skin 4 (2.1%) 12 (6.0%)	Upper respiratory tract inflammation	0	1
	Oropharyngeal pain	1	1
Blister 0 1	Skin	4 (2.1%)	12 (6.0%)
	Blister	0	1

Dermatocyst	0	1
Dermatitis	0	1
Allergic dermatitis	1	0
Contact dermatitis	2	2
Eczema	0	1
Miliaria	0	1
Pityriasis rosea	0	1
Pruritus	2	1
Skin rush	0	2
Hives	0	1
Blood vessels	1 (0.5%)	1 (0.5%)
Orthostatic hypotension	1	0
Hot flash	0	1