The impact of heated tobacco products on biomarkers of potential harm and adverse events: a systematic review and meta-analysis

Supplementary Materials

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Supplementary Appendix 1. Coding of trial affiliation.

Trials were coded as 'Industry-affiliated' if:

• the study sponsor named on the trial registration was a tobacco company or other organisation

directly funded by a tobacco company; or

- funding statements in any of the trial literature indicated the trial was funded in part or in whole by a tobacco company or other organisation directly funded by a tobacco company; or
- author affiliations or conflict of interest statements indicated any author was an employee or funded by a tobacco company or other organisation directly funded by a tobacco company at the time of the trial.

Trials were coded as 'Independent' if:

- the sponsor named on the trial registration had no known ties to the tobacco industry; and
- funding statements in any of the trial literature indicated the trial was not funded by a tobacco company or other organisation funded by a tobacco company; and
- author affiliations and conflict of interest statements indicated authors had no contemporary (i.e., while the study was being conducted, up to and including publication) ties to the tobacco industry.

Trials were coded as 'Unclear' if:

- There was insufficient information to determine affiliation; or
- Reviewers could not reach consensus.

In addition to conflict of interest and funding statements provided in the trial literature, we further investigated known ties and funding using the Tobacco Tactics website (www.tobaccotactics.org), relevant literature published by the Tobacco Control Research Group (University of Bath), and conflict of interest and funding statements in other contemporary work of the authors of included studies.

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Supplementary Table 1. Direction of effect indicative of harm for each biomarker, alongside supporting literature in addition to the reporting in the original study.

	Biomarker	Direction indicating harm	Additional supporting literature
		^	https://doi.org/10.1111/echo.14514;
	A wave velocity		https://doi.org/10.1016/j.jsha.2013.03.003
	Arterial Blood Pressure	1	https://doi.org/10.1093/ntr/ntx273
	Augmentation index	↑	https://doi.org/10.1093/eurheartj/ehq024;
		-	https://doi.org/10.1161/CIRCULATIONAHA.104.482570
	Central pulse pressure	↑	https://www.ncbi.nlm.nih.gov/books/NBK482408/;
	1 1		https://doi.org/10.1093/eurheartj/ehq024
	Diastolic blood pressure	\uparrow	https://doi.org/10.1093/ntr/ntx273
	E wave velocity	Ţ	https://doi.org/10.1111/echo.14514;
		•	https://doi.org/10.1016/j.jsha.2013.03.003
	F wave/A wave ratio	.l.	https://doi.org/10.1111/echo.14514
		¥	https://doi.org/10.1016/j.jsha.2013.03.003
	Heart rate	↑	https://doi.org/10.1093/ntr/ntx273
	Left atrium diameter	1	https://doi.org/10.1111/echo.14514
	Left ventricle early/late		https://doi.org/10.1111/echo.14514
	diastolic mitral annulus		
	tissue Doppler velocities	¥	
	ratio		https://brieflands.com/articles/irgri 132828.pdf
inction	fraction	\downarrow	https://orienands.com/articles/nerj-152626.pdf
	Left ventricle global	1	https://brieflands.com/articles/ircrj-132828.pdf
ar fi	circumferential strain	*	
cul	Left ventricle global	\downarrow	https://doi.org/10.1111/echo.14514
ovas	Left ventricle peak early	1	https://brieflands.com/articles/ircrj-132828.pdf;
rdic	diastolic velocity	\rightarrow	https://doi.org/10.1111/echo.14514
Ca	Left ventricle peak late	↑	https://doi.org/10.1111/echo.14514
	diastolic velocity		https://doi.org/10.1111/echo.1/51/
	mvocardial velocity	↑	https://doi.org/10.1111/ech0.14514
	Left ventricular end-	^	https://doi.org/10.1111/echo.14514
	diastolic diameter	I	
	D.1	^	https://doi.org/10.1016/j.jacc.2007.10.065;
	Pulse wave velocity	I	https://doi.org/10.1161/CIRCULATIONAHA.105.555255,
	Right atrium diameter	1	https://doi.org/10.1111/echo.14514
	Right ventricle diameter	↑ 	https://doi.org/10.1111/echo.14514
	Right ventricle early/late		https://doi.org/10.1111/echo.14514
	diastolic mitral annulus	I	
	tissue Doppler velocities	*	
	ratio Pight ventricle free well		https://doi.org/10.1111/acho.14514
	strain	\downarrow	https://doi.org/10.1111/ecno.14314
	Right ventricle global	I	https://doi.org/10.1111/echo.14514
	longitudinal strain	+	
	Right ventricle peak early	\downarrow	https://doi.org/10.1111/echo.14514
	Dight vontriele mask let-	*	https://doi.org/10.1111/echo.14514
	Right ventricle peak late	I	

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Right ventricle systelic thtps://doi.org/10.1093/ntr/ntx273; Systelic blood pressure 1 https://doi.org/10.1093/ntr/ntx273; Total extracellular 1 https://doi.org/10.1093/ntr/ntx273; Vesicles 1 https://doi.org/10.1093/ntr/ntx273; Total extracellular 1 https://doi.org/10.1016/0.1RCRESAHA.117.310752 Total Peripheral 1 https://doi.org/10.1016/0.1RCRESAHA.117.310752 Tricuspid annular plane 1 https://doi.org/10.1016/0.1RCRESAHA.117.310752 Tricuspid annular plane 1 https://doi.org/10.1016/0.1RCRESAHA.117.310752 Endothelial-derived 1 https://doi.org/10.1016/0.IRCRCMATTONAHA.104.482570; Endothelial-derived 1 https://doi.org/10.1093/ntr/ntx273 Extracellular vesicles 1 https://doi.org/10.1093/ntr/ntx273 Soluble intercellular 1		diastolic velocity		
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Systolic blood pressure https://doi.org/10.1093/uttr/mit2/32 Total extracellular ↑ https://doi.org/10.13389/fcvm.2022.907457; Total extracellular ↑ https://doi.org/10.1161/CIRCRESAHA.117.310752 Total Peripheral ↑ https://doi.org/10.1161/CIRCRESAHA.117.310752 Tricuspid annular plane ↑ https://doi.org/10.1161/CIRCRESAHA.117.310752 Tricuspid annular plane ↓ https://doi.org/10.1161/CIRCRC.11775 Bradothelia-derived ↑ https://doi.org/10.1080/1354750X.2017.1419284 Bradothelia-derived ↑ https://doi.org/10.1093/ntr/mx273 Extracellular vesicles ↑ https://doi.org/10.1093/ntr/mx273 Nitric oxide ↓ https://doi.org/10.1093/ntr/mx273 Soluble intercellular ↑ https://doi.org/10.1093/ntr/mx273 Soluble intercellular ↑ https://doi.org/10.1093/ntr/mx273 Soluble intercellular ↑ https://doi.org/10.1093/ntr/mx273; Bradotnei (C-X-C ↑ https://doi.org/10.1093/ntr/mx273; Chemokine (C-X-C ↑ https://doi.org/10.1080/154750X.2017.1419284 Phys://doi.org/10.1080/1354750X.2017.1419284 https://d		myocardial velocity	I	
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Total extracellular 		Systolic bloba pressure	I	https://doi.org/10.1093/eurheartj/ehq024
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Interferon alpha-2 \uparrow https://doi.org/10.1080/1334/30X.2017.1419284Interferon alpha-2 \uparrow https://doi.org/10.3390/biomedicines12040748Interferon-gamma \downarrow https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.21037/tlcr.2019.03.02Interleukin-1 alpha \uparrow https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 beta \uparrow https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://doi.org/10.2337/dc08-1161Interleukin-10 \downarrow https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Homocysteine	↑	https://doi.org/10.1001/jama.288.10.2013; https://doi.org/10.1080/1254750X.2017.1410284
Interferon alpha-2 \uparrow Inttps://doi.org/10.3390/biointedcines12040/48Interferon-gamma \downarrow https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.21037/tlcr.2019.03.02Interleukin-1 alpha \uparrow https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.5021/ad.2014.26.1.11Interleukin-1 beta \uparrow https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://doi.org/10.2337/dc08-1161Interleukin-10 \downarrow https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;			•	https://doi.org/10.1080/1534/30X.2017.1419284
Interferon-gamma \downarrow https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.21037/tlcr.2019.03.02Interleukin-1 alpha \uparrow https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.5021/ad.2014.26.1.11Interleukin-1 beta \uparrow https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://doi.org/10.1152/ajplung.00074.2015Interleukin-10 \downarrow https://doi.org/10.2337/dc08-1161Interleukin-10 \downarrow https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interferon alpha-2	T	https://doi.org/10.5590/bioinedicines12040748
Interleukin-1 alpha \checkmark https://doi.org/10.21037/tlcr.2019.03.02Interleukin-1 alpha \uparrow https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.5021/ad.2014.26.1.11Interleukin-1 beta \uparrow https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://doi.org/10.1152/ajplung.00074.2015Interleukin-10 \downarrow https://doi.org/10.2337/dc08-1161 https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interferon-gamma	J.	https://doi.org/10.1067/mai.2000.107751;
Interleukin-1 alpha \uparrow https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.5021/ad.2014.26.1.11Interleukin-1 beta \uparrow https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://www.europeanreview.org/article/7005; https://doi.org/10.2337/dc08-1161Interleukin-10 \downarrow https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interferent guinna	¥	https://doi.org/10.21037/tlcr.2019.03.02
Interleukin-1 beta \uparrow https://doi.org/10.5021/ad.2014.26.1.11Interleukin-1 beta \uparrow https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://www.europeanreview.org/article/7005; https://doi.org/10.2337/dc08-1161Interleukin-10 \downarrow https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interleukin-1 alpha	↑	https://doi.org/10.1152/ajplung.00074.2015;
Interleukin-1 beta \uparrow https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015Interleukin-1 receptor antagonist \uparrow https://www.europeanreview.org/article/7005; 		interieuxiii i uipiiu	I	https://doi.org/10.5021/ad.2014.26.1.11
Interleukin-1 beta ↑ https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015 Interleukin-1 receptor antagonist ↑ https://www.europeanreview.org/article/7005; https://doi.org/10.2337/dc08-1161 Interleukin-10 ↓ https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;				https://doi.org/10.3390/molecules27123715;
Interleukin-1 receptor antagonist ↑ https://doi.org/10.1152/ajplung.00074.2015 Interleukin-10 ↑ https://doi.org/10.2337/dc08-1161 Interleukin-10 ↓ https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interleukin-1 beta	Ť	https://doi.org/10.1067/mai.2000.107751;
Interleukin-1 receptor antagonist ↑ https://www.europeanreview.org/article/7005; https://doi.org/10.2337/dc08-1161 Interleukin-10 ↓ https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;				https://doi.org/10.1152/ajplung.00074.2015
antagonist https://doi.org/10.2337/dc08-1161 Interleukin-10 ↓ https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		Interleukin-1 receptor	↑	https://www.europeanreview.org/article/7005;
Interleukin-10 ↓ https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		antagonist		https://doi.org/10.2337//dc08-1161
Interleukin-10 \downarrow https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;		T . 1 11 10		https://doi.org/10.7150/ijms.13800;
https://doi.org/10.1152/ajplung.00074.2015;		Interleukin-10	\downarrow	https://doi.org/10.1155/2014/158530;
				https://doi.org/10.1152/ajplung.00074.2015;

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		https://doi.org/10.1016/j.jaut.2009.12.003
Interdendin 12	*	https://doi.org/10.3109/08958378.2015.1013227;
Interleukin-12		https://doi.org/10.1155/2014/158530
Interleukin-12 beta	J	https://doi.org/10.4049/jimmunol.181.2.1536;
Interiouxin 12 cou	•	https://doi.org/10.1038/s41598-021-91510-x
Interleukin-13	\uparrow	https://doi.org/10.3390/diseases120/0144;
T (1 1: 15	*	http://dx.doi.org/10.1185/fcmb.2009-011/OC
Interleukin-15		https://doi.org/10.2200/diacacac12070144
Interleukin-17	Ϋ́.	https://doi.org/10.5590/diseases120/0144
Interleukin-2	\downarrow	https://doi.org/10.1067/mai.2000.107751;
		https://doi.org/10.1152/ajplung.000/4.2015
Interleukin-3	↑	https://doi.org/10.3389/fimmu.2024.1411047
T (1 1: 4	•	https://doi.org/10.1152/ajplung.00074.2015;
Interleukin-4		https://doi.org/10.1111/j.1365-2249.1994.tb06533.x
Interleukin-5	\uparrow	https://pubmed.ncbi.nlm.nih.gov/24706315/
		https://doi.org/10.1016/j.jaut.2009.12.003;
Interleukin-6	\uparrow	https://doi.org/10.1093/ntr/ntx273;
		https://doi.org/10.1152/ajplung.00074.2015
Interleukin 7		https://doi.org/10.1152/ajplung.000/4.2015; http://dv.doi.org/10.1186/1471.2431.13.57;
Intericukin-7	*	https://doi.org/10.1016/i.sibs 2019 11 001
	•	https://doi.org/10.1016/j.jaut.2009.12.003:
Interleukin-8	T	https://doi.org/10.1038/s41598-020-68753-1
Interleukin_0		https://doi.org/10.3390/biomedicines12040748;
Interieukin-9	*	https://doi.org/10.1183/23120541.00639-2021
Leukocyte-derived	\uparrow	https://doi.org/10.1155/2018/4692081;
extracellular vesicles	•	https://doi.org/10.3390/ijms25010388
Lymphotoxin-alpha	Ϋ́.	
Macrophage	*	https://doi.org/10.1152/ajplung.00074.2015;
alpha		https://doi.org/10.3109/01902149409031733; https://doi.org/10.1007/c00262.006.0140.3
Macrophage		https://doi.org/10.1007/s00262-006-0149-3
inflammatory protein-1	\uparrow	https://doi.org/10.1152/ajplung.00074.2015
beta		
Macrophage-derived		https://doi.org/10.1152/ajplung.00074.2015;
chemokine	Ť	https://doi.org/10.1016/j.clim.2005.03.001;
Matrix		nups://doi.org/10.1058/841598-020-68/53-1 https://doi.org/10.1161/01_ATV_0000100268.27305_4ft
metalloproteinase-1	\uparrow	https://doi.org/10.7150/jims.79889
Matrix	•	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
metalloproteinase-10	1	
Matrix	^	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
metalloproteinase-12		
Matrix	\uparrow	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
Matrix		https://doi.org/10.1161/01.ATV.0000100268.27305.4f
metalloproteinase-8	\uparrow	10000199208.27393.41
Matrix	•	https://doi.org/10.1152/ajplung.00074.2015:
metalloproteinase-9	Ť	https://doi.org/10.4274/MMJ.galenos.2022.45057
Monocyte chemotactic	^	https://doi.org/10.3109/08958378.2015.1013227;
protein-1		https://doi.org/10.4274/MMJ.galenos.2022.45057
Neutrophil-derived	↑	https://doi.org/10.1155/2018/4692081;
extracellular vesicles		https://doi.org/10.3390/1jms25010388
Osteoprotegerin	Ţ	https://doi.org/10.1111/j.1600-051x 2007.01048.x:
	Ť	https://doi.org/10.4103/2277-9175.180992;
		·

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			-
			https://doi.org/10.3390/jcm8030406
	Platalat dariyad growth		https://doi.org/10.1164/rccm.200605-585OC;
	factor isoform A A	\downarrow	https://doi.org/10.1007/s10006-025-01345-3;
	Tactor Isoform AA		https://doi.org/10.3892/etm.2019.8025
	Platelet derived growth		https://doi.org/10.1164/rccm.200605-585OC;
	factor isoform AB/BB	\downarrow	https://doi.org/10.1007/s10006-025-01345-3;
	D		https://doi.org/10.3892/etm.2019.8025
	Receptor activator	\uparrow	https://doi.org/10.1155/2014/731039
	nuclear kappa B ligand		https://doi.org/10.1152/ciplung.00074.2015
	activation normal T-cell	1	https://doi.org/10.1152/ajplung.00074.2015, https://doi.org/10.1093/toysci/kfi147:
	expressed and secreted	I	https://doi.org/10.4049/iimmunol.166.1.552
	Tissue inhibitor of	•	https://doi.org/10.4274/MMJ.galenos.2022.45057
	metalloproteinase-1	T.	
	Transforming growth	^	https://doi.org/10.1002/jat.4469
	factor alpha		
	Tumor necrosis factor		https://doi.org/10.1016/j.jaut.2009.12.003;
	alpha	Ť	https://doi.org/10.1093/ntr/ntx273;
	1		https://doi.org/10.3390/diseases120/0144
	White blood cell count	\uparrow	https://doi.org/10.3109/089583/8.2015.101322/;
	Carbon monovide		https://www.pcbi.plm.pib.gov/pmc/articles/DMC3220853/
	transfer coefficient	\downarrow	https://www.ncbi.nlm.nlm.gov/pnic/articles/1 MC3229835/,
			https://doi.org/10.1016/i.rmed.2003.09.005
	Central obstruction	↑	https://doi.org/10.4103/0970-2113.184875:
			https://doi.org/10.1016/S0140-6736(22)00470-6
	Diffusion Capacity for	I	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/;
	CO	\checkmark	https://www.ncbi.nlm.nih.gov/books/NBK556149/
	Forced expiratory flow at		https://pubmed.ncbi.nlm.nih.gov/12841492/
	25–75% of forced vital	\downarrow	
	capacity		
	Forced expiratory	\downarrow	https://doi.org/10.1093/ntr/ntx2/3;
	Volume		https://doi.org/10.1080/1354/50X.201/.1419284
	volume in the first one		https://pubmed.ncbi.nlm.nin.gov/articles/FWC5229855/,
	second/forced vital	\downarrow	https://publicd.ncol.inin.inii.gov/12641492/
_	capacity		
tior		I	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/;
JUC	Forced vital capacity	\checkmark	https://pubmed.ncbi.nlm.nih.gov/12841492/
y fi			https://doi.org/10.1136/thorax.58.2.175;
utor	Fractional exhaled nitric oxide	J	https://doi.org/10.1080/00039890009604040;
pira		·	https://doi.org/10.5402/2011/832560;
Ses			https://doi.org/10.1183/09031936.06.00113/05
щ	Functional residual	\downarrow	https://pmc.ncbi.nim.nin.gov/articles/PMC3229853/
		1	https://pubmed.nchi.nlm.nih.gov/128/1/02/
	Inspiratory capacity	\checkmark	
		↑	https://doi.org/10.1016/j.rmed.2003.09.005;
	Peripheral obstruction		https://doi.org/10.4103/09/0-2113.1848/5;
			https://doi.org/10.1010/S0140-0750(22)00470-0
	Reactance area	\uparrow	https://doi.org/10.1016/S0140-6736(22)00470-6
	Pasidual volume	1	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/
	Kesidual volullie		http://d-i-c-/10.10/2/-0610085.
	Tidal volume (acute)	\uparrow	https://doi.org/10.1042/cs0610085;
	Tatal lange as 't	1	https://uoi.oig/10.1152/Jappi.1905.36.0.1975
	1 otal lung capacity	4	
	Vital consoit:	I	https://pubmed.ncbi.nlm.nih.gov/12841492/
	v nai capacity	*	
	1		

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	Apolipoprotein A1	\downarrow	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1161/CIRCULATIONAHA.104.482570		
	Apolipoprotein B	↑	https://doi.org/10.1161/CIRCULATIONAHA.104.482570		
	Blood glucose	\uparrow	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008		
ndrome	Hemoglobin glycosylated	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1080/1354750X.2017.1419284		
abolic sy	High-density lipoprotein cholesterol	\downarrow	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1016/j.jacl.2009.10.008		
Met	Low-density lipoprotein cholesterol	Ţ	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1016/j.jacl.2009.10.008		
	Total cholesterol	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008		
	Triglycerides	\uparrow	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008		
	Bleeding on probing	\uparrow	https://doi.org/10.2196/15350		
	Clinical Attachment Loss	\uparrow	https://doi.org/10.2196/15350		
	Periodontal pocket depth	↑	https://doi.org/10.2196/15350		
	Gingival inflammation	1	https://doi.org/10.2196/15350		
	Olaanalla uli	^	https://doi.org/10.1177/0022034515590581;		
ealth	Olsenella uli		https://doi.org/10.1186/s12941-022-00499-2		
	Plaque control record	\uparrow	https://doi.org/10.2196/15350		
Oral h	Porphyromonas gingivalis	\uparrow	https://doi.org/10.1111/omi.12273; https://doi.org/10.1016/j.disamonth.2011.03.008		
	Pseudoramibacter alactolyticus	\uparrow	https://doi.org/10.1177/0022034515590581; https://doi.org/10.1038/ismej.2014.114		
	Tannerella forsythia	\uparrow	https://doi.org/10.1038/s41598-020-80937-3;		
	Tooth mobility	^	https://doi.org/10.2196/15350		
	Treponema denticola	 ↑	https://doi.org/10.1038/s41598-020-80937-3; https://doi.org/10.3389/froh.2021.751099		
	8-epi-prostaglandin F2alpha	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X 2017 1419284		
	8-hydroxy-2'- deoxyguanosine	¢	https://doi.org/10.1080/10590500902885684; https://doi.org/10.1089/ars.2015.6508; https://doi.org/10.1093/carcin/18.9.1763; https://doi.org/10.3390/ijerph6020445		
	8-iso-prostaglandin F2alpha	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284		
tress	H2O2 breakdown activity	\downarrow	https://doi.org/10.3390/antiox11091829		
ve s	H2O2 production	\uparrow	https://doi.org/10.3390/antiox11091829		
dati	Malondialdehyde	↑	https://doi.org/10.7759/cureus.60629		
Oxi	Myeloperoxidase	↑	https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1161/01.ATV.0000163262.83456.6d		
	Protein carbonyls	\uparrow	https://doi.org/10.1089/ars.2009.2887; https://doi.org/10.1016/j.cbi.2024.111008		
	Soluble Nox2-derived peptide	\uparrow	https://doi.org/10.1016/j.chest.2016.04.012		
	Total anti-oxidant capacity	\downarrow	https://doi.org/10.5114/pja.2022.116285; https://doi.org/10.1186/1475-2891-6-39		
	Vitamin E	\downarrow	https://doi.org/10.2147/CIA.S158513		

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	11-dehydrothromboxane	*	https://doi.org/10.3109/08958378.2015.1013227;
	B2	-	https://doi.org/10.1080/1354750X.2017.1419284
	Atheroma-chip, area	^	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
	under the curve		023-09802-9
	Atheroma-chip, time to		https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
	reach 10 kPa	*	023-09802-9
	Atheroma-chip, time to		https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
	reach occlusion pressure	*	023-09802-9
Ę	Fibringgon	*	https://doi.org/10.1093/ntr/ntx273;
atic	Fibiliogen	-	https://doi.org/10.1080/1354750X.2017.1419284
ti vi	Platalat count	*	https://doi.org/10.1093/ntr/ntx273;
ion & ac	r latelet coulit	1	https://doi.org/10.3109/08958378.2015.1013227
	Platelet-chip, area under	^	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
	the curve	-	023-09802-9
nct	Platelet-chip, time to		https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
fu	reach 10 kPa	\rightarrow	023-09802-9
elet	Platelet-chip, time to		https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-
late	reach occlusion pressure	*	023-09802-9
Ч	Platelet-derived	^	https://doi.org/10.1111/jch.14479;
	extracellular vesicles	-	https://doi.org/10.1164/rccm.201012-2061OC
	P-selectin expressing	*	https://doi.org/10.1093/ntr/ntx273
	extracellular vesicles		
	Soluble CD40 ligand	^	https://doi.org/10.1161/CIRCULATIONAHA.104.482570;
	Soluble CD40 ligalid	I	https://doi.org/10.1152/ajplung.00074.2015
			https://doi.org/10.1093/ntr/ntx273;
	Soluble P-selectin	\uparrow	https://doi.org/10.3109/08958378.2015.1013227;
			https://doi.org/10.1080/1354750X.2017.1419284

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Supplementary Figure 1. PRISMA flow diagram for study selection. Abbreviations: HTP = heated tobacco; BoPH = biomarkers of potential harm; AE = adverse events.



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Supplementary Table 2. Risk of bias judgements and support for judgements for each included study.

Bias	Authors' judgements	Support for judgement
Dan da na an ann an an	<u> </u>	"The order of use will be assigned by a pre-
Random sequence	Low	defined computer-generated randomisation
generation		schedule"
		"In ascending order of subject number, enrolled
		participants were assigned to receive the four
Allocation concealment	Unclear	study products in accordance with the pre-defined
		randomisation sequences, with an equal
		proportion of participants in each sequence"
Blinding of participants and	· · · ·	"open-label" (Trial Reg & Poster). One active
personnel	High	(NRT) and one non-active (CC) comparator.
Blinding of outcome	Ŧ	"open-label" (Trial Reg & Poster). Primary
assessment	Low	outcomes were objectively measured.
		Attrition 0% in all study groups. Exclusion: 23%
		of subjects excluded from analysis "Seven
Incomplete outcome data	Low	subjects were excluded from the PK analysis
incomplete outcome duta	Low	population due to major protocol deviations
		(washout problem)"
		All outcomes listed in the study protocol were
Selective reporting	Low	fully reported on in at least one literature source
ISDCTN14201260/UNIT	NAAAA 7 4088	Turry reported on in at least one interature source
Bias	Authors' judgements	Support for judgement
Random sequence	Authors Judgements	"The randomisation will be performed by
canaction	Low	Covance"
generation		"The rendemisation will be norformed by
A 11 +: 1 +	T	Comment and the clinics will even the next investor
Allocation concealment	Low	Covance and the clinics will enrol the participants
		and assign them to interventions
Blinding of participants and	· · · ·	"open-label" (Irial Reg & JA protocol). One
personnel	High	active (Cess) and one non-active (CC)
		comparator.
Blinding of outcome	Low	"open-label". All primary outcomes objectively
assessment	2011	measured.
		Overall attrition = 1.1% . No subjects who
Incomplete outcome data	Low	completed the study were excluded from the
		primary analyses.
		There were several outcomes listed in the
Selective reporting	High	protocol, namely biomarkers of effect and
Selective reporting	Ingn	pharmacokinetic measures, that were not reported
		on.
ISRCTN80651909		
Bias	Authors' judgements	Support for judgement
Random sequence	T	"The randomization will be computer-generated
generation	Low	using SAS Version 9.3"
		"A randomisation scheme was provided for the
Allocation concealment	Low	clinical site to recruit 30 participants for each arm.
		giving a total of 150 participants"
Blinding of participants and		"open-label" (Trial Reg & IA). Two active (Cess
personnel	High	& EC) and one non-active (CC) comparator
Blinding of outcome		"open-label" All primary outcomes objectively
assessment	Low	measured
assessment		Attrition: Glo=6.67% CC=0% EC=6.67%
		Cess= 0% HTP= 3.45% overall= 3.38%
Incomplete outcome data	Low	Evolution: $Clo=6.67\%$ CC=0% EC=6.67%
		$C_{acc} = 0\%$ HTD=N/A $c_{acc} = 1.0\%$ C(= 0.0/%)
Salaatiya namartir -	High	No data reported for an article study and (C
Selective reporting	нıgn	No data reported for an entire study arm (C:

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"switching to a non-BAT commercial product"). No quantitative data reported for two biomarker of effect outcomes (WBC count & 8-epi-PGF2α Type III). No data reported for pharmacokinetic outcomes measured

ISRCTN81075760		
Bias	Authors' judgements	Support for judgement
Random sequence	и сэ Т	"randomised using blocks of computer-generated
generation	Low	random number sequences"
Allocation concealment	Unclear	No information provided.
		"This study will not be blinded" (Protocol
		supplementary file, pg 26)
Blinding of participants and	High	Cigarette and non-smoker arms were non-active
personnel	Ingn	and subjects in the cessation arm received
		additional levels of support and products to aid
		smoking abstinence.
Blinding of outcome	Low	"This study will not be blinded". All primary
assessment	2011	outcomes objectively measured.
		Number of participants randomised/enrolled,
		withdrawn and included in analyses vary between
Incomplete outcome data	Unclear	the 90-day, 180-day and 360-day reports. Entire
		arm (Group C) also removed. It is unclear when
		this group was removed from the study, why or
		how many participants were in the group.
		Several outcomes listed in the trial registration
Selective reporting	High	and protocol have not been reported on in any
1 0	C	publications, including one of the primary
		endpoints, Augmentation index.
Dalrymple, 2022		~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Bias	Authors' judgements	Support for judgement
		Cochrane RoB tools designed to assess trials in
Random sequence		which the unit of randomisation is people, rather
generation	N/A	than multiple sites on one individual, selection
8		bias cannot be fairly assessed using this tool on
	27/4	this study.
Allocation concealment	N/A	
Blinding of participants and	The share	There is insufficient information provided in the
personnel	Unclear	text regarding blinding. One active (EC) and one
		non-active (CC) comparator.
Blinding of outcome	т	No information is provided in the text regarding
assessment	Low	blinding, but all primary outcomes objectively
		All participants completed the study and page
Incomplete outcome data	Low	withdraw
		There was not trial registration or a priori
Selective reporting	Unclear	protocol
		protocol.
Biog	Authors' judgaments	Support for judgement
Dias Bandom sequence	Authors Judgements	Beyond stating the study was 'randomised' no
generation	Unclear	further information provided
Allocation concealment	Unclear	No information provided
Blinding of participants and	oneicaí	"Blinding: Open - no one is blinded" (trial reg.) No
personnel	High	active comparator (CC)
Blinding of outcome		"Blinding: Open-no one is blinded" All primary
assessment	Low	outcomes were objectively measured
ussessment		All subjects randomised completed the study and
Incomplete outcome data	Low	were included in the analyses
Selective reporting	Low	3 safety profile parameters were not reported but

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adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source.

Bias Authors' judgements Support for judgement Random sequence generation Unclear Beyond stating the study was 'randomised', no further information provided. Allocation concealment Unclear No information provided. Blinding of participants and personnel High active comparator (CC) Blinding of outcome assessment Low "Blinding: open-no one is blinded" (trial reg). No active comparator (CC) Blinding of outcome assessment Low All subjects randomised completed the study and were included in the analyses. Selective reporting Low 3 safety profile parameters were not proted, but adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source. UMIN000041539 Support for judgement "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Allocation concealment Low "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Blinding of participants and personnel Low "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the ra	UMIN000025777		
Random sequence generation Unclear Beyond stating the study was randomised', no further information provided. Allocation concealment Unclear No information provided. Blinding of participants and personnel TBinding: Open - no one is blinded" (trial reg). No active comparator (CC) Blinding of outcome assessment Low "Blinding: Open - no one is blinded". All primary outcomes were objectively measured. Incomplete outcome data Low All subjects randomised completed the study and were included in the analyses. Selective reporting Low All subjects randomised completed the study and were included in the analyses. Selective reporting Low Support for judgement Selective reporting Low Support for judgement Random sequence generation Low "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Blinding of outcome assessment High "Open - on one is blinded". Included non-active comparator (cigarettes). Blinding of outcome assessment Low "Open - on one is blinded". Included non-active comparator (cigarettes). Blinding of outcome assessment Low "Subjects will be randomization scheme."	Bias	Authors' judgements	Support for judgement
generation Concating Allocation concealment Unclear No information provided. Binding of participants and personnel High "Binding: Open -no one is blinded" (trial reg). No active comparator (CC) Incomplete outcome data Low "Binding: Open -no one is blinded". All primary outcomes were objectively measured. Incomplete outcome data Low All subjects randomised completed the study and were included in the analyses. Selective reporting Low Stafety profile parameters were not reported, but adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source. UMIN000041539 Bias Authors' judgements Support for judgement Random sequence generation Low "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Allocation concealment Low "Open -no one is blinded". Included non-active comparator (cigarettes). Incomplete outcome data Low "Open -no one is blinded". Included non-active comparator (cigarettes). Incomplete outcome data Low "Open -no one is blinded". Included non-active comparator (cigarettes). Incomplete outcome data <	Random sequence	Unclear	Beyond stating the study was 'randomised', no
Allocation concealment Unclear No information provided. Blinding of participants and personnel High "Blinding: Open -no one is blinded" (trial reg). No active comparator (CC) Blinding of outcome assessment Low "Blinding: Open -no one is blinded". All primary outcomes were objectively measured. Incomplete outcome data Low All subjects randomised completed the study and were included in the analyses. Selective reporting Low 3 safety profile parameters were not reported, but adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source. UMIN000041539 Bias Authors' judgements "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Allocation concealment Low "Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme." Blinding of outcome assessment Low "Open -no one is blinded". All primary outcomes objectively measured. Selective reporting Low "Open -no one is blinded". All primary outcomes objectively measured. Selective reporting Low "Open -no one is blinded". All primary outcomes objectively	generation	Ulicieal	further information provided.
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Incomplete outcome data Low Exclusion: IQOS=3% CC=2.5%, overall=4.1%. Incomplete outcome data Low Exclusion: IQOS=3.75% CC=12.5%, overall=6.6%. Selective reporting High "Samples for 4-HNE analysis have been collected but will not be analyzed due to the failure to develop a selective and quantitative assay." QSU, Intent to Use of CHTP 1.2, Prochaska Value of CHTP 1.2, Prochaska	assessment		outcomes objectively measured.
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Selective reporting High "Samples for 4-HNE analysis have been collected but will not be analyzed due to the failure to develop a selective and quantitative assay." QSU, Intent to Use of CHTP 1.2, Prochaska	incomplete outcome data	Low	Exclusion: $IQUS=3.75\%$ CC=12.5%,
Selective reporting High Selective reporting High Samples for 4-HNE analysis nave been collected but will not be analyzed due to the failure to develop a selective and quantitative assay."			Uverall=0.0%.
Selective reporting High Gevelop a selective and quantitative assay." QSU, Intent to Use of CHTP 1.2, Prochaska			Samples for 4-HINE analysis have been collected but will not be analyzed due to the failure to
Selective reporting High QSU, Intent to Use of CHTP 1.2, Prochaska			develop a selective and quantitative assay "
	Selective reporting	High	OSU Intent to Use of CHTP 1.2 Prochaska
"Stage of Change" Questionnaire MCFO and			"Stage of Change" Ouestionnaire MCEO and
pre- and post-bronchodilator FVC. FEV1/FVC.			pre- and post-bronchodilator FVC. FEV1/FVC.

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		FEF 25-75 were not reported in any literature
NCTAINERCOT		sources.
NC101959607		~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Bias	Authors' judgements	Support for judgement
Random sequence	_	"Randomization to each product exposure
generation	Low	sequence was done through an Interactive
generation		Telephone and Web Response System."
		"Randomization to each product exposure
Allocation concealment	Low	sequence was done through an Interactive
		Telephone and Web Response System."
		"This was an open-label study; therefore the
		subjects and investigators were unblinded to
Blinding of participants and		subjects' sequence." No supportive products or
personnel	High	behavioural support were provided to any
personner		participants during the trial, but in one arm the
		comparator intervention was non-active
		(cigarettes).
Blinding of outcome	Low	"This was an open-label study". All primary
assessment	Low	outcomes objectively measured.
		Attrition: IQOS-CC=5%, IQOS-NRT=0%. No
Incomplete outcome data	Low	participants who completed the trial were
		excluded from the analyses.
	т	All outcomes reported in at least one literature
Selective reporting	Low	source.
NCT02503254		
Bias	Authors' judgements	Support for judgement
Random sequence	Judgements	"subjects were randomized by an interactive web
generation	Low	and voice response system"
generation		"subjects were randomized by an interactive web
Allocation concealment	Low	and voice response system"
Blinding of participants and		"Masking: None (Open Label)" (Trial reg) No
personnel	High	active comparator (CC)
Blinding of outcome		"Masking: None (Open Label)" All primary
assessment	Low	outcomes objectively measured
Incomplete outcome data	Low	Attrition and evaluation both 0%
incomplete outcome data	Low	Several outcomes listed in the study protocol were
Selective reporting	High	several outcomes listed in the study protocol were
Selective reporting	nigii	one was reported on in a poster instead
NCT010(7710		one was reported on in a poster instead.
NC 101967719		
Bias	Authors' judgements	Support for judgement
Random sequence		"Randomization to each product exposure
generation	Low	sequence was done through an Interactive
generation		Telephone and Web Response System"
		"Randomization to each product exposure
Allocation concealment	Low	sequence was done through an Interactive
		Telephone and Web Response System"
Blinding of participants and		"Masking: None (Open Label)" (Trial Reg). One
personnel	High	active (NRT) and one non-active (CC)
personner		comparator.
Blinding of outcome	Low	"Masking: None (Open Label)". All primary
assessment	Low	outcomes objectively measured.
		Attrition: IQOS/CC=4.55% IQOS/NRT=0%,
Incomplete outcome data	Low	overall=3.23%. No subjects who completed the
		study were excluded from the analysis.
Salactive reporting	Low	All outcomes reported in at least one literature
Selective reporting	LUW	source.
NCT01989156		
Bias	Authors' judgements	Support for judgement

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Random sequence generation	Low	"randomization was done through the Interactive Web and Voice Response System (IWRS)"
Allocation concealment	Low	"randomization was done through the Interactive Web and Voice Response System (IWRS)"
Blinding of participants and personnel	High	"This is an open-label study; therefore, the subjects and Investigators will be unblinded to subject's arm" (Study protocol) The level of support given to each arm differed: "All subjects in the SA arm will receive smoking cessation counselling and will be able to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject"
Blinding of outcome assessment	Low	"This is an open-label study". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=9%, CC=15%, SA=21%. Although the primary analysis used per-protocol populations, results data for the full analysis set were also provided in the clinical study report.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01970982		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Low	"randomization was performed through an Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was performed through an Interactive Web and Voice Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=0% CC=0% Cess=5%, overall=1.25%. All subjects who completed the study were included in the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01959932		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Low	"randomization was done through an Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was done through an Interactive Web and Voice Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=1.25% CC=0% Cess=0%, overall=0.62%. All subjects who completed the
	Low	study were included in the analysis.
Selective reporting	Low	study were included in the analysis. All outcomes reported in at least one literature source.
Selective reporting NCT01780714	Low	study were included in the analysis. All outcomes reported in at least one literature source.
Selective reporting NCT01780714 Bias	Low Low Authors' judgements	study were included in the analysis. All outcomes reported in at least one literature source. Support for judgement
Selective reporting NCT01780714 Bias Random sequence generation	Low Low Authors' judgements Unclear	study were included in the analysis. All outcomes reported in at least one literature source. Support for judgement Beyond stating the study was 'randomised', no further information provided.

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Blinding of outcome assessment	Low	"Masking None (Open Labal)" All asima
	LOW	outcomes objectively measured.
		All participants randomised completed the trial
Incomplete outcome data	Low	and no participants were excluded from the analysis.
Selective reporting	High	Data for 4 outcomes listed in the protocol (Cytochrome P450 2A6 activity, Questionnaire of Smoking Urges, Minnesota Nicotine Withdrawal Scale, Respiratory symptoms) were not reported
NCT02396381		Source, respiratory symptoms, were not reported
Bias	Authors' judgements	Support for judgement
Random sequence	Low	"Randomization was done through the interactive voice and web response system (IXRS)"
Allocation concealment	Low	"Randomization was done through the interactive voice and web response system (IXRS)"
Blinding of participants and	High	"Masking: None (Open Label)" (Trial reg). No
Blinding of outcome	T	"Masking: None (Open Label)". All primary
assessment	Low	outcomes objectively measured
		Attrition: IQOS=15.16% CC=10.69%,
T 1, , 1,	т	overall=2.91%. Although not the main analysis
Incomplete outcome data	Low	population, full analysis set (as randomised)
		literature
<u> </u>		All outcomes reported on in at least one literature
Selective reporting	Low	source.
NCT01970995		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Low	"randomization was performed through the Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was performed through the Interactive Web and Voice Response System"
Blinding of participants and		"Masking: None (Open Label)" (Trial Reg). One
personnel	High	active (Cess) and one non-active (CC)
Dlinding of outcome		comparator.
assessment	Low	outcomes objectively measured
ussessment		Attrition: IOOS=2.56% CC=2.38% Cess=5%.
Incomplete outcome data	Low	overall=3.12%. Exclusion: IQOS=10.26%
-		CC=2.4% Cess=7.5%, overall=7.5%.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT02466412		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Low	"Randomization to product exposure sequence will be done through IxRS"
Allocation concealment	Low	"Randomization to product exposure sequence will be done through IxRS"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome	Low	"Masking: None (Open Label)". All primary
assessment	LO W	outcomes were objectively measured.
Incomplete outcome data	Low	Attrition was 0%. Exclusion: mCHTP- mCC=4.16% mCC-mCHTP=0%, overall=2.1%
		Only results data for the two primary outcomes
assessment Incomplete outcome data Selective reporting NCT02466412 Bias Random sequence generation Allocation concealment Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low Low Authors' judgements Low Low High Low Low	outcomes objectively measured. Attrition: IQOS=2.56% CC=2.38% Cess=5%, overall=3.12%. Exclusion: IQOS=10.26% CC=2.4% Cess=7.5%, overall=7.5%. All outcomes reported in at least one literature source. Support for judgement "Randomization to product exposure sequence will be done through IxRS" "Randomization to product exposure sequence will be done through IxRS" "Randomization to product exposure sequence will be done through IxRS" "Masking: None (Open Label)" (Trial reg). No active comparator (CC) "Masking: None (Open Label)". All primary outcomes were objectively measured. Attrition was 0%. Exclusion: mCHTP- mCC=4.16% mCC-mCHTP=0%, overall=2.1% Only results data for the two primary outcomes

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NCT02649556		
Bias	Authors' judgements	Support for judgement
Pandom sequence		"Randomization was done during the original
generation	Low	study at V4 through the interactive voice and web
generation		response system (IXRS)."
		"Randomization was done during the original
Allocation concealment	Low	study at V4 through the interactive voice and web
		response system (IXRS)."
Blinding of participants and	High	"Masking: None (Open Label)" (Trial reg). No
personnel	Ingn	active comparator (CC)
Blinding of outcome	Low	"Masking: None (Open Label)". All primary
assessment	Low	outcomes objectively measured.
		Attrition rates in all arms were <50% (IQOS=8%,
		CC=9%) and differed by <20%. However results
Incomplete outcome data	High	data reported are based on participant product use
		not randomisation. True ITT or FAS sets were not
		provided
Salaatiya raparting	High	Several outcomes listed in the study protocol have
Selective reporting	nigii	not been reported on in any publications.
Other	High	Only reported data grouped by participant product
Other	High	use not randomisation.
NCT01967732		
Bias	Authors' judgements	Support for judgement
	J	"Randomization to product exposure sequence
Random sequence	Low	was performed through an Interactive Telephone
generation	20.0	and Web Response System"
		"Randomization to product exposure sequence
Allocation concealment	Low	was performed through an Interactive Telephone
	Low	and Web Response System"
		"Masking: None (Open Label)" (Trial Reg) One
Blinding of participants and	High	active (NRT) and one non-active (CC)
personnel	mgn	comparator
Blinding of outcome		"Masking: None (Open Label)" All primary
assessment	Low	outcomes objectively measured.
		Attrition: IOOS/CC=4.55% IOOS/NRT=5.56%
Incomplete outcome data	Low	overall=4.84% Exclusion: IOOS/CC=6.81%
meompiete outcome autu	Low	IOOS/NRT=5.5% overall=6.45%
		All outcomes reported in at least one literature
Selective reporting	Low	source
NCT01780688		source.
Biog	Authors' judgements	Sunnart for judgement
Dias Dandam aaguanaa	Authors Judgements	"Dendemization was performed using an
concretion	Low	Internative Web Despanse System"
generation		"Dendemization was performed using on
Allocation concealment	Low	Kandonnization was performed using an
		"Mashing: Naga (Open Label)" (Trial and) Na
Blinding of participants and	High	Masking: None (Open Label)" (Trial reg). No
Diadia of externa	-	"Mashing Naga (Open Label)" All primary
Blinding of outcome	Low	Masking: None (Open Label)". All primary
assessment		All sections objectively measured.
T 14 4 14	т	All participants randomised completed the trial
Incomplete outcome data	Low	and no participants were excluded from the
		anaiysis.
Selective reporting	Low	All outcomes reported on in at least one literature
		source.
NCT01967706		
Bias	Authors' judgements	Support for judgement
Random sequence	Low	"Randomization to product exposure sequence
generation	2011	was done through an Interactive Telephone and

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		Web Response System"
		"Randomization to product exposure sequence
Allocation concealment	Low	was done through an Interactive Telephone and
		Web Response System"
Blinding of participants and	TT' 1	"Masking: None (Open Label)" (Trial reg). 1
personnel	High	active (NRT) and 1 non-active (CC) comparator
Blinding of outcome		"Masking: None (Open Label)" All primary
assessment	Low	outcomes objectively measured
		Attrition: IOOS-CC=2 27% IOOS-NRT=0%
Incomplete outcome data	Low	overall-1.61% No subjects who completed the
meomplete outcome data	Low	study were excluded from the analysis
		All outcomes reported on in at least one literature
Selective reporting	Low	All outcomes reported on in at least one interature
NCT022(4751		source.
NC103304751		
Bias	Authors' judgements	Support for judgement
Random sequence		"Randomization will be done through the
generation	Low	Interactive Web and Voice Response System
generation		(IXRS)"
		"Randomization will be done through the
Allocation concealment	Low	Interactive Web and Voice Response System
		(IXRS)"
Blinding of participants and	TT: 1	"Masking: Single (Investigator)" (trial reg). No
personnel	High	active comparator (CC)
Blinding of outcome		"Masking: Single (Investigator)" Primary
assessment	Low	outcome objectively assessed
assessment		Attrition: IOOS-1 15% CC-1 18%
Incomplete outcome data	Low	$\alpha_{1111011110011100000000000000000000000$
incomplete outcome data	Low	CC = 1.18% overall = 1.74%
		CC=1.18%, overall=1.74%.
		Results data from "Full transcriptomics profile
Selective reporting	High	assessment of buccal swabs derived from the right
	C	and left buccal mucosa (3 and 6 months)" has not
		been reported
Other	High	Only reported data grouped by participant product
	8	use not randomisation.
DRKS00012919		
DRKS00012919 Bias	Authors' judgements	Support for judgement
DRKS00012919 Bias Random sequence	Authors' judgements	Support for judgement Beyond stating the study was 'randomised', no
DRKS00012919 Bias Random sequence generation	Authors' judgements Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided.
DRKS00012919 Bias Random sequence generation Allocation concealment	Authors' judgements Unclear Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided.
DRKS00012919 Bias Random sequence generation Allocation concealment	Authors' judgements Unclear Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and	Authors' judgements Unclear Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel	Authors' judgements Unclear Unclear High	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC)
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel	Authors' judgements Unclear Unclear High	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome	Authors' judgements Unclear Unclear High	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the excitograptic arms were blinded. All
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Authors' judgements Unclear Unclear High Low	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Authors' judgements Unclear Unclear High Low	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the armsteach the tract for enrolment was 55. It
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Authors' judgements Unclear Unclear High Low	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unspecified after the set of
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Authors' judgements Unclear Unclear High Low Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and the s
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Authors' judgements Unclear Unclear High Low Unclear	Support for judgementBeyond stating the study was 'randomised', no further information provided.No information provided."partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.Only the e-cigarette arms were blinded. All primary outcomes objectively measured.In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Authors' judgements Unclear Unclear High Low Unclear	Support for judgementBeyond stating the study was 'randomised', no further information provided.No information provided."partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.Only the e-cigarette arms were blinded. All primary outcomes objectively measured.In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.In the trial registration, the authors state outcomes
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DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Authors' judgements Unclear Unclear High Low Unclear High	Support for judgementBeyond stating the study was 'randomised', no further information provided.No information provided."partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.Only the e-cigarette arms were blinded. All primary outcomes objectively measured.In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Authors' judgements Unclear Unclear High Low Unclear High	Support for judgementBeyond stating the study was 'randomised', no further information provided.No information provided."partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.Only the e-cigarette arms were blinded. All primary outcomes objectively measured.In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Authors' judgements Unclear Unclear High Low Unclear High	Support for judgementBeyond stating the study was 'randomised', no further information provided.No information provided."partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.Only the e-cigarette arms were blinded. All primary outcomes objectively measured.In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported.
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT03301129	Authors' judgements Unclear Unclear High Low Unclear High	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses. In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported.
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT03301129 Bias	Authors' judgements Unclear Unclear High Low Unclear High Authors' judgements	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses. In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported. Support for judgement
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT03301129 Bias Random sequence	Authors' judgements Unclear Unclear High Low Unclear High Low Unclear Low Unclear High Low Low Low Unclear High Low Hops Low Low Low Low Low Low Low	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses. In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported. Support for judgement
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT03301129 Bias Random sequence generation	Authors' judgements Unclear Unclear High Low Unclear High Low High Low	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses. In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported. Support for judgement "The randomization list was computer generated"
DRKS00012919 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT03301129 Bias Random sequence generation Allocation concealment	Authors' judgements Unclear Unclear High Low Unclear Authors' judgements Low Unclear High Unclear Unclear	Support for judgement Beyond stating the study was 'randomised', no further information provided. No information provided. "partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator. Only the e-cigarette arms were blinded. All primary outcomes objectively measured. In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses. In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported. Support for judgement "The randomization list was computer generated" No information provided.

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Blinding of participants and personnel	Unclear	Despite describing the trial as "Double" blinded on the trial registration, only "Investigator" and "Outcome Assessor" are noted as being masked, not participants.
Blinding of outcome assessment	Low	"Masking: Double (Investigator, Outcomes Assessor)". Primary outcomes were objectively measured
Incomplete outcome data	Low	The 30 subjects excluded were excluded pre- randomisation. No subjects who were randomised withdrew or were excluded from the final analysis population.
Selective reporting	Low	All outcomes reported on in at least one literature source.
NCT03435562		
Bias	Authors' judgements	Support for judgement
Random sequence	I and	"Order of the products used in each session will
generation	Low	be assigned using Latin-square order procedure"
Allocation concealment	Unclear	No information provided.
Blinding of participants and	TT' 1	Masking: None (Open Label) (trial reg). 1 active
personnel	High	(EC) and 1 non-active (CC) comparators
Blinding of outcome	-	"Masking: None (Open Label)". Primary outcome
assessment	Low	objectively measured.
	_	Overall attrition = 18.18% . All participants who
Incomplete outcome data	Low	completed the study were included in the analysis.
		Results data for heart rate and blood pressure have
Selective reporting	High	not been reported
NCT03452124		F
Riog	Authors' judgements	Sunnart for judgement
Dias	Authors Judgements	"Dendemization was performed by an attending
		Randomization was performed by an attending
Random sequence generation	Low	research nurse using a table of random numbers as reproduced from the online randomization software
Random sequence generation	Low	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm"
Random sequence generation Allocation concealment	Low Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed
Random sequence generation Allocation concealment	Low Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple
Random sequence generation Allocation concealment Dlinding of participants and	Low Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator,
Random sequence generation Allocation concealment Blinding of participants and personnel	Low Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors.
Random sequence generation Allocation concealment Blinding of participants and personnel	Low Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single,
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome	Low Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low Unclear Low	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were
Random sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcome assessment	Low Unclear Low Low	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures.
Random sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcome assessmentIncomplete outcome data	Low Unclear Unclear Low Low	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Low Unclear Unclear Low Low High	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Ioakeimidis, 2021	Low Unclear Unclear Low Low High	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Ioakeimidis, 2021 Bias	Low Unclear Unclear Low Low High Authors' judgements	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Ioakeimidis, 2021 Bias Random sequence generation	Low Unclear Unclear Low Low Low Low High Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on. Support for judgement Whether or how participants were randomised is unclear.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Ioakeimidis, 2021 Bias Random sequence generation Allocation concealment	Low Unclear Unclear Low Low Low Unclear Unclear Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on. Support for judgement Whether or how participants were randomised is unclear. How interventions were allocated is not described.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Ioakeimidis, 2021 Bias Random sequence generation Allocation concealment Blinding of participants and personnel	Low Unclear Unclear Low Low Unclear Unclear Unclear Unclear Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on. Support for judgement Whether or how participants were randomised is unclear. How interventions were allocated is not described. No information is provided in the text regarding blinding. Non-active (CC) comparator.
Random sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcome assessmentIncomplete outcome dataSelective reporting Ioakeimidis, 2021Bias Random sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcomeBlinding of participants and personnelBlinding of outcome assessment	Low Unclear Unclear Low Low Low Unclear Unclear Unclear Unclear Unclear Unclear Unclear Unclear Unclear	research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm" There is insufficient information provided to determine whether intervention allocation was concealed Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors. "examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures. All participants completed the study and none withdrew. Not all outcomes measured were reported on. Support for judgement Whether or how participants were randomised is unclear. How interventions were allocated is not described. No information is provided in the text regarding blinding. Non-active (CC) comparator. Outcomes were physiological measures.

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Incomplete outcome data	Unclear	The authors state they "studied 22 current smokers" but it is unclear whether more than 22 were initially randomised or enrolled.
Selective reporting	Unclear	There was not trial registration or a priori
Lopez, 2016		protovon
Bias	Authors' judgements	Support for judgement
Random sequence generation	Low	"Participants completed each of the three, Latin- square ordered, ~2.5-h sessions" (JA)
Allocation concealment	Unclear	There is no information provided to determine the presence or level of intervention allocation concealment
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. One active (EC) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	No information is provided in the text regarding blinding. Primary outcomes were objectively measured.
Incomplete outcome data	Low	Overall attrition = 37.5%. No subjects who completed the study were excluded form the analysis.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
Yaman, 2021		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Unclear	Participants were already IQOS users. It is unclear how participants were randomised to CC or HTP.
Allocation concealment	Unclear	Staff asked participants to use products, ie. They were aware. It is not clear if the order of interventions was randomised.
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. Non-active (CC) comparator.
Blinding of outcome assessment	Low	Outcomes were physiological measures.
Incomplete outcome data	Low	Reasons for withdrawal are clearly described.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
NCT06093659		
Bias	Authors' judgements	Support for judgement
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC).
Blinding of outcome assessment	Low	"Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured.
Incomplete outcome data	Unclear	Number of participants lost to attrition and/or excluded from analyses not reported.
Selective reporting	High	Puff count not reported.
<u>Yuki, 2023</u>		~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Bias	Authors' judgements	Support for judgement
Random sequence generation	Unclear	method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and	Unclear	There is insufficient information provided in the

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		There is insufficient information provided in the
Blinding of outcome	Low	text regarding blinding. Primary outcomes
assessment	Low	objectively measured
		Attriction notes in all annual (500% (high act
		Altrition rates in all arms were $<50\%$ (nignest
Incomplete outcome data	High	47.1% - Conort H) but there was a 30.9%
	0	difference between the highest and lowest cohorts
		(Conort F vs Conort H).
Selective reporting	Unclear	There was not trial registration or a priori
		protocol.
UMIN000045304		
Bias	Authors' judgements	Support for judgement
		"The subjects were randomly assigned into the
Random sequence generation	Low	study groups by using the electronic data capture
Random sequence generation	Low	system, and the investigators and site staff were
		blinded to the randomization scheme."
		"The subjects were randomly assigned into the
Allocation concealment	Low	study groups by using the electronic data capture
Anotation conceannent	LOW	system, and the investigators and site staff were
		blinded to the randomization scheme."
Blinding of participants and	II:-h	"open-label". Both active and non-active
personnel	підп	comparators.
Blinding of outcome	T	"open-label". However all primary outcomes were
assessment	Low	objectively measured.
	-	Attrition 2% overall, and no participants excluded
Incomplete outcome data	Low	from analyses.
Selective reporting	Low	All outcomes were reported on.
NCT05459857		
D iag	Authors' independents	Sunnant for judgement
Dias	Authors judgements	Support for judgement
		Subjects who completed the study coreening
		Subjects who completed the study screening
		assessments were assigned a unique
	Ţ	assessments were assigned a unique randomisation identification number.
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the
Random sequence generation	Low	subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product
Random sequence generation	Low	subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc.
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number.
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the
Random sequence generation Allocation concealment	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the
Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product
Random sequence generation Allocation concealment	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc.
Random sequence generation Allocation concealment Blinding of participants and	Low Low High	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No
Random sequence generation Allocation concealment Blinding of participants and personnel	Low Low High	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC).
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome	Low Low High	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg).
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low Low High Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low Low High Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low Low High Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low Low High Low Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low Low Low Low Low Low	 Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Low Low High Low Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863	Low Low Low Low Low Low Low Low	 Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863 Bias	Low Low High Low Low Low Low Low Low Low Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863 Bias	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863 Bias	Low Low High Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on.
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863 Bias Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on. Support for judgement The study statistician at the contract research organization generated the random allocation sequence and is implementation
Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting NCT05114863 Bias Random sequence generation	Low	assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc. Masking: None (Open Label) (Trial reg). No active comparator (CC). "Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured. All participants randomised completed the trial and no participants were excluded from the analysis. All outcomes were reported on. Support for judgement The study statistician at the contract research organization generated the random allocation sequence and its implementation.

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		organization generated the random allocation
		sequence and its implementation.
Blinding of participants and	High	By necessity, this study was unblinded due to the
personnel	mgn	different visual appearances of the study products.
Blinding of outcome	Low	"Masking: None (Open Label)" (Trial reg).
assessment	Low	Primary outcomes were objectively measured.
Incomplete outcome dete	Low	Attrition 8% overall, and no participants excluded
Incomplete outcome data	Low	from analyses.
Selective reporting	Low	All outcomes were reported on.
DRKS00020446		k
Bios	Authors' judgements	Support for judgement
Dias	Authors Judgements	Darticipanta "randomized" hut no details of
Random sequence generation	Low	method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and	Unclear	No details provided regarding blinding. Both
Diadia e efecte en e		Ne deteile annu det de comparators.
assessment	Low	outcomes were objectively measured.
Incomplete outcome dete	Unalaan	17 participants included, but details of how many
Incomplete outcome data	Unclear	were recruited was not reported.
		The outcomes listed on the trial registration were
Selective reporting	Unclear	not reported on in the publication. It appears the
		registration may have been for a different study.
ChiCTR2200065055		
Bias	Authors' judgements	Support for judgement
Dius	Tutnors judgements	"Fligible participants were randomized through a
Pandom sequence generation	Low	computer generated sequence utilizing a simple
Kandolli sequence generation	Low	randomization algorithm in SAS version 9.4."
		"Eligible participants were rendomized through a
		Engible participants were randomized unough a
Allocation concealment	Low	computer generated sequence utilizing a simple
Allocation concealment	Low	computer-generated sequence utilizing a simple
Allocation concealment	Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4."
Allocation concealment	Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants upon acquirement of
Allocation concealment Blinding of participants and	Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of
Allocation concealment Blinding of participants and personnel	Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical
Allocation concealment Blinding of participants and personnel	Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non-
Allocation concealment Blinding of participants and personnel	Low High	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC)
Allocation concealment Blinding of participants and personnel Blinding of outcome	Low High Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low High Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low High Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%,
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low High Low Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low High Low Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting	Low High Low Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024	Low High Low Low Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias	Low High Low Low Low Low Authors' judgements	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Bandom accuracy concertion	Low High Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation	Low High Low Low Low Low Low Unclear	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation	Low High Low Low Low Low Unclear Unclear	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment	Low High Low Low Low Low Low Unclear Unclear Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of method.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Duit the context of the second se	Low High Low Low Low Low Unclear Unclear	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. No details provided regarding blinding. One
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and	Low High Low Low Low Low Low Unclear Unclear Unclear	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel	Low High Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity.
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome	Low High Low Low Low Low Low Unclear Unclear Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low High Low Low Low Low Low Unclear Unclear Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However outcomes were objectively measured
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low High Low Low Low Low Low Unclear Low Low Low Low Loce Low Loce Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However outcomes were objectively measured. The authors note that due to a loss of data they
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment	Low High Low Low Low Low Low Unclear Low Low Low Low Low Loce Low Loce Low	computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non- active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However outcomes were objectively measured. The authors note that due to a loss of data, they had to recruit an additional 8 individuals All but
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low High Low Low Low Low Unclear Unclear Low Low Low	 computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non-active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However outcomes were objectively measured. The authors note that due to a loss of data, they had to recruit an additional 8 individuals. All but one of the 32 (original 24 + 8) participants
Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Lyytinen, 2024 Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data	Low High Low Low Low Low Low Unclear Low	 computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4." "Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non-active comparator (CC) "open-label". However all primary outcomes were objectively measured. Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses All outcomes were reported on. Support for judgement Participants "randomised" but no details of method. Participants "randomised" but no details of method. No details provided regarding blinding. One active comparator (no exposure), but not similar intensity. No details provided regarding blinding. However outcomes were objectively measured. The authors note that due to a loss of data, they had to recruit an additional 8 individuals. All but one of the 32 (original 24 + 8) participants

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		"23 individuals completed the arterial stiffness analysis and 22 the T-TAS analysis" (exclusion
		<30%).
Selective reporting	Unclear	There was not trial registration or a priori protocol.
Bias	Authors' judgements	Support for judgement
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	Unclear	"All statistical analyses were conducted by an investigator who was blinded to the group allocations." But otherwise no further details given regarding blinding. One active comparator (no exposure), but not similar intensity.
Blinding of outcome assessment	Low	Insufficient details provided regarding blinding. However outcomes were objectively measured.
Incomplete outcome data	High	24 enrolled & randomised. 23 included in analyses, unclear if missing one was due to withdrawal or exclusion. A further participant was also excluded from analyses due to being an "outlier".
Selective reporting	Unclear	The outcomes listed on the trial registration were not reported on in the publication. It appears the registration may have been for a different study.

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Supplementary Figure 2. Summary plot showing risk of bias judgements across studies.



Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome assessment Incomplete outcome data Selective reporting Other sources of bias **Overall**

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Risk of bias



Supplementary Figure 3. Risk of bias traffic light plot: review authors' judgments about risk of bias items for each included study.

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Supplementary Figure 4. Direction of effect between baseline and last follow-up in HTP arms in confined studies.





Supplementary Figure 5. Direction of effect between baseline and last follow-up in HTP arms in ambulatory studies.

Abbreviations: BDR = bronchodilator response.





Study	Extracted data
NCT01959607	Format: n (%) subjects; [n] AEs
	THS-CC:
	AEs = 3 (13.6%) [3]
	Mild AEs= $2 (9.1\%) [2]$
	Moderate $AEs = 1 (4.5\%)[1]$
	Severe $AEs=0$ (0%)
	SAEs = 0 [0]
	AEs related to $IP = 0$ [0]
	Also related to $NKT = 0$ [0]
	CC-THS:
	$AF_{s} = 3(13.6\%)[5]$
	Mild $AEs= 2 (9.1\%) [4]$
	Moderate AEs= 1 (5.4%) [1]
	Severe $AEs=0[0]$
	SAEs= 0 [0]
	AEs related to IP= 2 (9.1%) [2]
	Dysphoria= 1 (4.5%)
	Hepatic function $abnormal = 1$ (4.5%)
	AEs related to NRT= 0 $[0]$
	AEs related to study procedures= $1 (4.5\%) [3]$
	$AES = 4 (44.4\%) [5]$ Mild $AE_{2-} 2 (22.2\%) [4]$
	Milu AES= $5(55.5\%)$ [4] Moderate AEs= $1(11.1\%)$ [1]
	Nodelate ALS= $1(11.170)[1]$ Severe $\Delta F_{S}=0[0]$
	SAFs = 0 [0]
	AEs related to IP= 1 (11.1%) [1]
	Dysphoria= $1(11.1\%)$
	AEs related to NRT= 0 $[0]$
	AEs related to study procedures= 2 (2.2%) [2]
	NRT-THS:
	AEs = 1 (11.1%) [1]
	Mild $AEs = 1 (11.1\%) [1]$
	Moderate $AEs=0$ [0]
	Severe $AEs=0[0]$
	SAEs = $0 [0]$ A Es related to ID= $0 [0]$
	Also related to NPT- $0[0]$
	AEs related to study procedures= 0 [0]
NCT01967719	Format: n (%) subjects: [n] AEs
	THS2.2-CC:
	AEs=7 (31.8%) [10]
	SAEs = 0[0]
	Severe $AEs=0$ [0]
	AEs related to IP= $2(9,1\%)$ [3]
	Headache= 1 (4 5%)
	Vomiting= $1(4.5\%)$
	Nausea $= 1 (4.5\%)$
	AEs related to NNS= 1 (4 5%)
	Sneezing=1 (4.5%)
	AFs related to study procedures= $2(91\%)$ [4]
	CC-THS2 2.
	$AE_{s} = 7 (31.8\%) [9]$
	$S\Delta F_{s} = 0.001$
	5AL9- 0 [0]

Supplementary Table 3. Serious and non-serious adverse event data from crossover trials.

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Supplemental material

	Severe $AEs = 0$ [0]
	AEs related to IP= $1 (4.5\%) [1]$
	Vomiting= $1 (4.5\%)$
	AEs related to study procedures= $2(9.1\%)$ [2]
	THS2.2-NNS:
	AEs = 3 (3.33%) [7]
	SAFs = 0[0]
	Severe $AFs = 1$ (11.1%) [2]
	AFs related to $IP = 1 (11.1\%) [1]$
	Nausea $= 1 (1111\%)$
	A Es related to study procedures $-1(11.1\%)$ [3]
	NNS THS2 2.
	$AE_{s} = 2(22.2\%)$ [2]
	AES = 2(22.2%)[2] SAEs = 0[0]
	SAES = 0 [0]
	Severe $AES = 0$ [0]
	AEs related to $IP = 0$ [0]
NCT010(7722	All strated to study procedures= $0[0]$
INC10190//32	TUS2 2 CC.
	THS2.2-CC:
	AEs = 10 (45.5%) [21]
	SAEs=0
	AE related to $IP = 4 (18.2\%) [4]$
	AE related to study procedure= $3(13.6\%)[7]$
	Mild $AE= 7 (31.8\%) [18]$
	Moderate $AE=3 (13.6\%) [3]$
	Severe $AE = 0$
	Discontinuation due to $AE = 0$
	Dizziness= $5(22.7\%)$ [6]
	Headache= $3(13.6\%)[3]$
	Presyncope= 1 (4.5%) [1]
	Nausea= $2(9.1\%)[3]$
	Vomiting= 1 (4.5%) [1]
	Muscle spasms= 1 (4.5%) [1]
	Pallor= 1 (4.5%) [1]
	Constipation= $1 (4.5\%) [1]$
	Dysgeusia= 1 (4.5%) [1]
	СС-ТНS2.2:
	AEs= 7 (31.8%) [10]
	SAEs=0
	AE related to IP= 4 (18.2%) [6]
	AE related to study procedure= 0
	Mild AE= 3 (13.6%) [5]
	Moderate $AE = 4 (18.2\%) [5]$
	Severe $AE=0$
	Discontinuation due to $AE=0$
	Dizziness= 1 (4.5%) [1]
	Headache= $2(9.1\%)[2]$
	Presyncope= 3 (13.6%) [3]
	Nausea= 1 (4.5%) [1]
	Vomiting= 2 (9.1%) [2]
	Dysmenorrhoea= 1 (4.5%) [1]
	THS2.2-NNS:
	AEs = 4 (44.4%) [4]
	SAEs=0
	AE related to IP= 3 (33.3%) [3]

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Supplemental material

	AE related to NNS=0
	AE related to study procedure= 0
	Mild $AF = 2(22.2\%)$ [2]
	Moderate $AF = 2(22.2\%)[2]$
	Noderate $AE = 2(22.270)[2]$ Severe $AE = 0$
	Discontinuation due to $\Delta E = 0$
	$U_{\text{readeaba}} = 1 (11 10^{\circ}) [1]$
	Headache= $1(11.1\%)[1]$
	Presyncope= 2 (22.2%) [2]
	Pallor= $1(11.1\%)[1]$
	NNS-THS2.2:
	AEs= 2 (22.2%) [4]
	SAEs=0
	AE related to $IP=1 (11.1\%) [1]$
	AE related to NNS= 0
	AE related to study procedure= 0
	Mild $AE= 1 (11.1\%) [3]$
	Moderate $AE=1 (11.1\%) [1]$
	Severe $AE=0$
	Discontinuation due to $AE=0$
	Dizziness= 1 (11.1%) [1]
	Muscle spasms= $1 (11.1\%) [1]$
	Cough= $1(11.1\%)[1]$
NCT01967706	Format: n (%) subjects; [n] AEs
	THS-CC:
	AEs = 1 (4.5%) [1]
	SAEs = 0[0]
	AEs related to $IP = 0[0]$
	AEs related to study procedure= 0 [0]
	All AEs were mild.
	CC-THS:
	AEs=2(9.1%)[2]
	$SAE_{s} = 0 [0]$
	AFs related to $IP = 0$ [0]
	AFs related to study procedure 0 [0]
	All AFs were mild
	THS-NRT.
	$\Delta \mathbf{F}_{\mathbf{s}} = 0 [0]$
	$\mathbf{A}\mathbf{E}\mathbf{S} = 0 \begin{bmatrix} 0 \end{bmatrix}$
	$\Delta E_{\rm S}$ related to ID= 0 [0]
	Also related to $II = 0$ [0] Also related to study procedure= 0 [0]
	All AEs ware mild
	$NK1-1\Pi S;$ $AE_{2} = 1 (11 10/2) [1]$
	AES = 1 (11.1%) [1] SAEs = 0 [0]
	SAEs = $0[0]$
	Also related to $P = 0 \begin{bmatrix} 0 \end{bmatrix}$
	AEs related to study procedure= 0 [0]
	All AES were mild.
ISRCTN13439529	8 exposure period adverse events (AEs)[3 mild, 5 moderate] were reported by
	6 of the 32 subjects (18.8%). One exposure period AE was related to cigarette
	use (cough with mild severity). The were no severe AEs.
	6/23 participants (18.8%) reported 8 mild events (3 mild, 5 moderate). 1
	events was related to CC use (cough with mild severity). There were no
	severe adverse events.
NCT01780688	HTP exposure: 14 participants experienced AEs. Most frequent AEs: nausea

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	(4 participants), headache (5), dizziness (4), presyncope (1).
	CC exposure: 10 participants experienced AEs. Most frequent AEs: nausea (5
	participants), headache (2), dizziness (2), presyncope (4), and abdominal pain
	(2).
	Most AEs were mild. No AEs were reported by the investigator based on
	coughing symptoms. No notable changes in spirometry parameters were
	observed from baseline to the end of the study in either exposure group.
UMIN000017297	HTP arm: 1 participant experienced an AE (vasovagal reaction) after PNTV
	product use.
	CC arm: no AE was reported after CC1 smoking.
	There were no serious AEs reported during the entire study.
NCT05114863	"All product-related adverse events were categorised as mild in severity (e.g.,
	dizziness, nausea and headache)" "No serious product-related adverse events
	observed following the use of PULZE 2.0 and iD/iSENZIA sticks"
NCT05459857	"During the product trial period on Day -1, during which subjects were
	allowed to use a single iD of their choice with the Pulze HTS, one mild AE
	(dizziness) was reported by one (4%) subject. The Investigator considered this
	event unrelated to study product use. Overall, AEs were infrequently reported
	in this study, with six AEs reported by five (21%) subjects after study product
	randomisation. Catheter site pain was reported three times by three (13%)
	subjects, and the remaining AEs (constipation, dizziness, and neck pain) were
	reported by one (4%) subject each. The constipation and dizziness events
	were moderate in severity, and the catheter site pain and neck pain events
	were mild. The Investigator considered all AEs to be unlikely related or
	unrelated to study product."
NCT06093659	"Overall, 15 AEs were reported, including eight AEs among six subjects
	(15.4%) in the non-menthol group and seven AEs among five subjects
	(13.9%) in the menthol group.

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Supplementary Figure 6. Effect of heated tobacco product use compared with cigarette use (A), smoking abstinence (B) and e-cigarette use (C) on rate of participants reporting adverse events.

	Heated Tobacco P	Heated Tobacco Products				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 Confined						A* 18	
ISRCTN14301360/UMIN00002498	8 4	90	4	60	1.1%	0.67 [0.17, 2.56]	· · · · · · · · · · · · · · · · · · ·
NCT01970982	6	80	3	40	1.1%	1.00 [0.26, 3.79]	
NCT01780714	4	20	10	20	2.0%	0.40 [0.15, 1.07]	2
ISRCTN80651909	13	56	14	30	4.5%	0.50 [0.27, 0.92]	
NCT02503254	31	41	20	39	9.6%	1.47 [1.04, 2.10]	
NCT01959932	50	80	29	41	12.9%	0.88 [0.68, 1.15]	
Subtotal (95% CI)		367		230	31.1%	0.82 [0.54, 1.24]	•
Total events	108		80				
Heterogeneity: Tau ² = 0.14; Chi ² = 1	14.30, df = 5 (P = 0.01); P	= 65%					
Test for overall effect: Z = 0.95 (P =	0.34)						
1.1.2 Ambulatory							
ChiCTR2200065055	10	25	5	25	2.2%	2.00 [0.80, 5.02]	
NCT01970995	32	78	14	42	6.0%	1.23 [0.74, 2.04]	
NCT03364751	25	70	29	91	7.4%	1.12 [0.73, 1.73]	
NCT01989156	52	80	20	41	9.5%	1.33 [0.94, 1.90]	
NCT02649556	40	241	87	434	9.9%	0.83 [0.59, 1.16]	
NCT02641587	64	80	31	40	15.5%	1.03 [0.85, 1.26]	+
NCT02396381	214	477	228	483	18.4%	0.95 [0.83, 1.09]	+
Subtotal (95% CI)		1051		1156	68.9%	1.03 [0.91, 1.16]	•
Total events	437		414				
Heterogeneity: Tau ² = 0.01; Chi ² = 3	7.45, df = 6 (P = 0.28); I ² =	= 19%					
Test for overall effect: Z = 0.47 (P =	0.64)						
Total (95% CI)		1418		1386	100.0%	1.01 [0.87, 1.16]	•
Total events	545		494				
Heterogeneity: Tau ² = 0.02; Chi ² = 3	21.86, df = 12 (P = 0.04);	² = 45%					there are a start and a start
Test for overall effect: Z = 0.11 (P =	0.92)						U.U1 U.1 1 10 11
Test for subgroup differences: Chi ^a	= 1.09, df = 1 (P = 0.30)	I ² = 8.3%					ravouis min ravouis cigarette

B

	Heated Tobacco Pr	oducts	Smoking Abst	linence		Risk Ratio	Rist	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ran	dom, 95% Cl		
2.1.1 Confined								7		
NCT01970982	6	80	1	40	0.8%	3.00 [0.37, 24.08]		· · ·		
ISRCTN14301360/UMIN000024988	4	90	2	30	1.3%	0.67 [0.13, 3.46]	·			
ISRCTN80651909	13	56	10	29	7.4%	0.67 [0.34, 1.34]				
NCT01959932	50	80	24	39	39.0%	1.02 [0.75, 1.37]		-		
Subtotal (95% CI)		306		138	48.5%	0.96 [0.73, 1.26]		•		
Total events	73		37							
Heterogeneity: Tau ² = 0.00; Chi ² = 2.48	8, df = 3 (P = 0.48); l ² =	= 0%								
Test for overall effect: Z = 0.29 (P = 0.7	7)									
2.1.2 Ambulatory										
NCT01970995	32	78	14	40	14.2%	1.17 [0.71, 1.93]	-			
NCT01989156	52	80	23	39	37.4%	1.10 [0.81, 1.50]		-		
Subtotal (95% CI)		158		79	51.5%	1.12 [0.86, 1.46]		٠		
Total events	84		37							
Heterogeneity: Tau ² = 0.00; Chi ² = 0.04	1, df = 1 (P = 0.83); I ² =	= 0%								
Test for overall effect: Z = 0.86 (P = 0.3	9)									
Total (95% CI)		464		217	100.0%	1.04 [0.86, 1.26]		•		
Total events	157		74					2007		
Heterogeneity: Tau ² = 0.00; Chi ² = 3.17	7, df = 5 (P = 0.67); I ² =	= 0%					tot de	1 10	100	
Test for overall effect: Z = 0.41 (P = 0.6	8)						0.01 0.1 Eavoure LITE	1 10 Envoure obstino	100	
Test for subgroup differences: Chi ² = 0).65, df=1 (P=0.42),	l ² = 0%					ravouismir	r avours absurre	100	

С

, ,	Heated Tobacco Products		Electronic Cigarettes			Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
ISRCTN80651909	13	56	8	28	100.0%	0.81 [0.38, 1.73]			-	
Total (95% CI)		56		28	100.0%	0.81 [0.38, 1.73]				
Total events	13		8							
Heterogeneity: Not a Test for overall effec	pplicable t: Z = 0.54 (P = 0.59)						L 0.01	0.1 Favours HTP	1 10 Favours e-ciga	100 irette

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Supplementary Figure 7. Effect of heated tobacco product use compared with cigarette use (A), smoking abstinence (B) and e-cigarette use (C) on rate of participants reporting serious adverse events.

	Heated Tobacco Pro	Cigaret	tes		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events Total		Weight	M-H, Random, 95% Cl		M-H, Rando	m, 95% Cl	
4.1.1 Confined										
ISRCTN80651909 Subtotal (95% CI)	1	59 59	0	30 30	3.3% 3.3 %	1.55 [0.07, 36.94] 1.55 [0.07, 36.94]				-
Total events	1		0							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.27 (P = 0.79)									
4.1.2 Ambulatory										
NCT02396381	6	477	7	483	27.9%	0.87 [0.29, 2.56]			<u> </u>	
NCT02641587	2	80	1	40	5.8%	1.00 [0.09, 10.70]				
NCT02649556	12	241	15	434	59.4%	1.44 [0.69, 3.03]				
NCT03364751	0	70	2	91	3.6%	0.26 [0.01, 5.31]				
Subtotal (95% CI)		868		1048	96.7%	1.14 [0.64, 2.04]				
Total events	20		25							
Heterogeneity: Tau ² =	0.00; Chi ² = 1.57, df =	3 (P = 0.	67); I ² = 0	96						
Test for overall effect:	Z = 0.45 (P = 0.65)	2								
Total (95% CI)		927		1078	100.0%	1.15 [0.65, 2.05]			•	
Total events	21		25							
Heterogeneity: Tau ² =	0.00; Chi ² = 1.61, df =	4 (P = 0.	81); I ² = 0	%						
Test for overall effect:	Z = 0.49 (P = 0.62)						0.01	U.1 1	1U Foucuro signarat	100
Test for subaroup diff	erences: Chi ² = 0.03. d	f=1 (P=	= 0.85), I ²	= 0%				Favours HIF	Favours cigaret	le

B		Heated Tobacco Pr	oducts	Smoking Abs	inence		Risk Ratio		Risk	Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rando	om, 95% Cl	
	ISRCTN80651909	1	59	0	29	100.0%	1.50 [0.06, 35.73]				-
	Total (95% CI)		59		29	100.0%	1.50 [0.06, 35.73]				-
	Total events	1		0							2
	Heterogeneity: Not ap	plicable						0.01	01 1	10	100
	Test for overall effect:	Z = 0.25 (P = 0.80)						0.01	Favours HTP	Favours abstine	nce

	Heated Tobacco P	Electronic Cig	arettes		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
ISRCTN80651909	1	59	0	30	100.0%	1.55 [0.07, 36.94]				
Total (95% CI)		59		30	100.0%	1.55 [0.07, 36.94]				-
Total events	1		0							
Heterogeneity: Not a Test for overall effect	pplicable : Z = 0.27 (P = 0.79)						L.01	0.1 Favours HTP	1 10 Favours e-cigan	100 ette

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